ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ
ΙΑΤΡΙΚΗ ΣΧΟΛΗ

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«ΣΑΚΧΑΡΩΔΗΣ ΔΙΑΒΗΤΗΣ ΚΑΙ ΠΑΧΥΣΑΡΚΙΑ»

ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

«ΔΙΑΤΡΟΦΙΚΑ ΠΡΟΤΥΠΑ ΚΑΙ ΚΑΡΚΙΝΟΣ ΤΟΥ ΜΑΣΤΟΥ ΣΤΙΣ ΓΥΝΑΙΚΕΣ»

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ABSTRACT

Breast cancer is the most diagnosed cancer worldwide, with a significant increase in incidence. It poses a global health concern, as survivors continue to face challenges long after their initial diagnosis, being at a heightened risk of cancer recurrence and susceptible to developing other health issues such as cardiovascular diseases or metabolic disorders. The development of breast cancer is often influenced by complex interactions among genetic predisposition, hormonal factors, environmental exposures, and lifestyle choices. One important lifestyle factor, as shown by numerous studies, is the maintenance of a healthy body weight. The purpose of this review is to examine the impact of interventions promoting healthy dietary patterns, single nutrients, and supplements. The goal is to identify any gaps or inconsistencies in existing studies and provide a basis for clearer further investigation so that it could be possible to propose the optimal and most effective intervention for breast cancer survivors within the scope of secondary prevention.

Keywords: breast cancer (BC), dietary patterns, obesity.

INTRODUCTION

1. Epidemiology

Breast cancer (BC) represents the most globally diagnosed cancer, with over 2 million new cases reported in 2020. Over the last twenty years, there has been a significant increase in the global cancer diagnosis rate, nearly doubling from approximately 10 million cases in 2000 to 19.3 million cases in 2020, which stands as the primary cause of mortality among women aged 20 to 50 years [1]. It is estimated that one out of every five individuals worldwide will experience a cancer diagnosis at some point in their life. Predictions indicate that this trend will continue, with the number of cancer diagnoses expected to rise by almost 50% by the year 2040 compared to 2020 [2]. BC is a global health concern, yet its occurrence, death rates, and chances of survival differ significantly across regions. These variations are influenced by demographics, lifestyle choices, genetic predisposition, and environmental conditions. Alterations in these risk factors have contributed to the growing prevalence of breast cancer, a trend that continues to rise steadily [3, 4].

While BC rates have historically been elevated in Western Europe and North America, there is a noticeable upward trend in developing nations. This rise can be attributed to factors like longer life expectancy, urbanization, and the adoption of Western habits [5]. According to data from the American Cancer Society, the five-year survival rate has significantly progressed from 63% in 1960 to 90% as of 2019 thanks to earlier diagnosis with mammogram screening, and improved surgery and adjuvant treatment [6].

However, survivors face ongoing challenges even long after their initial diagnosis. Specifically, they are at a heightened risk of cancer recurrence, which can occur for up to two decades following their initial diagnosis. Additionally, breast cancer survivors

are at risk of weight gain and are more susceptible to developing other health issues such as cardiovascular diseases or metabolic disorders. These risks highlight the importance of ongoing checking and complete healthcare support for BC survivors to address their long-term health needs [7].

BC is more prevalent in Western European countries compared to regions like West Africa, having a five times higher incidence. The incidence rates of BC in Central and Eastern Europe are reported to be similar. In the year 2020, nearly half (45.4%) of all BC diagnoses worldwide occurred in Asia [7, 8].

There are differences in the age at which BC typically occurs in Asian women compared to Western women. In Asian countries, the peak age for BC diagnosis is typically between 40 and 50 years old, while in Western countries, it tends to occur later, between 60 and 70 years old. One explanation could be that younger generations in Asian countries may be exposed to risk factors associated with BC at an earlier age than those in Western countries. Also, Western countries generally have longer average lifespans compared to many Asian countries. As a result, women in Western countries may have more years of life during which they are at risk of developing BC, leading to a later peak age of diagnosis [8, 9].

The mortality-to-incidence ratio (M/I) is calculated by dividing the number of deaths from a particular cancer by the number of new cases (incidence) of that cancer within a given period, usually one year. It provides insight into the proportion of diagnosed cases that result in death. This ratio is higher in Asia (0.32) than the global average (0.28), suggesting relatively poorer outcomes in terms of BC mortality compared to incidence. Oceania, Northern America, Europe, Latin America, and the Caribbean have lower M/I ratios for breast cancer, ranging from 0.15 to 0.26 [10].

The variation in BC incidence rates across regions reflects disparities in healthcare

infrastructure, access to screening and diagnostic services, as well as socio-economic factors such as income levels and education. Regions with higher income levels, such as North America, report higher incidence rates of BC, with 92 cases per 100,000 women, in contrast to Middle Africa and Eastern Asia which have incidence rates of 27 cases per 100,000 women. The highest percentage of BC diagnoses in the US occurs in the 55–64 age group, highlighting the significance of age as a risk factor for BC development [11, 12].

2. Risk factors

Differences in lifestyle and dietary habits are believed to contribute to the observed gradient distribution of BC in Europe, with higher prevalence documented in Northern countries compared to Southern regions. For instance, Northern European countries may have distinct dietary patterns and lifestyle behaviors that could potentially increase BC risk, while Southern European countries, historically following a Mediterranean-style diet characterized by high consumption of fruits, vegetables, and olive oil, may experience lower incidence rates. Approximately 30% of cancers are believed by The World Cancer Research Fund (WCRF) to be preventable through lifestyle changes, including adopting a healthy diet, maintaining a healthy weight, regular physical activity, and avoiding tobacco and alcohol consumption [13, 14].

The development of BC is often influenced by complex interactions among genetic predisposition, for instance, certain genes, such as BRCA1 and BRCA2, can increase the risk of developing BC if inherited, hormonal factors, environmental exposures, and lifestyle choices. These interactions can vary widely among individuals and may contribute to differences in BC risk. Both endogenous (produced within the body) and exogenous (from external sources) hormones can impact BC risk. For example, higher

levels of estrogen over a prolonged period, whether naturally produced or obtained through hormone therapy, may increase the risk of BC [15, 16]. Various environmental factors, such as radiation exposure and dietary patterns, can influence BC risk. For instance, exposure to ionizing radiation, particularly at a young age, is a known risk factor for BC [17, 18]. Exposure to ionizing radiation and genetic factors both play significant roles in BC development. Ionizing radiation can cause DNA mutations in breast cells, increasing the risk of cancer, while genetic variations may determine an individual's sensitivity to environmental carcinogens, influencing their likelihood of developing BC upon exposure to substances like exogenous estrogens and alcohol [19].

BC is described as heterogeneous, meaning it exhibits diversity in its biological features and behavior. Gene-expression profiling has identified two main groups of breast tumors based on the presence or absence of estrogen receptor expression. Tumors that express estrogen receptor (ER+) are more influenced by hormone-related factors compared to tumors that do not express it (ER-). BC is also classified based on the types of cells from which it originates, specifically luminal cells or basal/myoepithelial cells. This classification divides BC into two main subtypes: basal-like and non-basal-like. Basal-like BC is sometimes referred to as "triple-negative" BC. This subtype constitutes approximately 10% of all breast cancers. It is characterized by the absence of three hormonal receptors: estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (Her2). Additionally, basal-like BC typically exhibits high expression of basal cytokeratins, which are proteins found in the basal cells of the breast epithelium. Understanding of BC subtypes is crucial for treatment approaches and predicting patient outcomes [20, 21]. While BC can occur in men, it is significantly more common in women accounting for

less than 1% of all cancer cases in men. The incidence of BC increases significantly with age, peaking around the time of menopause. After menopause, the incidence may either decrease or remain relatively stable. Tumors in younger women are often larger, diagnosed at more advanced stages, have positive lymph node involvement, and may be associated with poorer survival outcomes [22, 23]. The likelihood of developing BC reduces with higher parity, particularly when childbirth occurs at a younger age and is full-term. Conversely, the use of oral contraceptive pills is linked to an elevated risk of BC [24]. Also, breastfeeding lowers the likelihood of developing BC in women and is a significant behavior that can be changed to reduce risk. The longer a woman breastfeeds, the more her risk of BC decreases [25]. Furthermore, around 40% of hereditary BC cases are linked to mutations in the BRCA1 and BRCA2 genes, which are inherited in a dominant autosomal manner. This means that a mutation in only one copy of the gene (inherited from either parent) is enough to increase the risk of developing BC. However, it should also be noted that even women without mutations in these genes can be at high risk if there is a strong family history of BC [26]. This suggests that other genetic factors beyond BRCA mutations may also play a role in increasing the risk in some individuals [27]. Breast density also stands out as a significant risk factor. The use of combined hormone therapy tends to increase mammographic breast density [28].

Lifestyle factors and their effects on weight management play significant roles in both the development and management of BC. Obesity, lack of physical activity, and excessive alcohol consumption have been established as significant risk factors for both the incidence and mortality of BC.

Alcohol consumption is associated with an increased risk, and this relationship tends to follow a linear dose-response pattern. One potential biological mechanism

underlying this association is alcohol's influence on circulating estrogen levels, which are known to be involved in breast cancer pathogenesis[29]. Smoking increases the risk too, particularly among postmenopausal women, as well as smoking during pregnancy[30, 31].

3. BC and excess body weight

After being diagnosed with BC, having obesity o overweight is associated with a higher risk of various adverse outcomes, including cancer recurrence, death, or the development of a second primary contralateral breast cancer. Many women undergoing treatment for BC experience weight gain [32]. This weight gain is often attributed to changes in hormone levels and body composition resulting from the treatment process. On average, women may gain between 2 to 6 kilograms in the first year following diagnosis, although some may experience greater weight gains. [33, 34]. Figure 1 illustrates the interaction of breast cancer risk factors and the impact of weight loss[35].

Chemotherapy can lead to a decrease in metabolism. This reduction in metabolism may occur due to various reasons, including the impact of chemotherapy drugs on metabolic processes in the body. Chemotherapy can induce menopause in women who have not yet reached this stage or accelerate menopause in those who are already peri-menopausal. Menopause is associated with hormonal changes, particularly a decline in estrogen levels. These hormonal changes can affect metabolism, fat distribution, and energy balance in the body, making weight gain more likely. High BMI is associated with increased production of hormones such as estrogens, insulin, and leptin. Estrogenic stimulation plays a significant role in promoting the development and growth of breast cancer cells. Insulin and leptin also

contribute to tumor progression by exerting proliferative, mitogenic, and anti-apoptotic effects on mammary cells, further supporting tumor growth and survival. Together, these factors contribute to weight gain during chemotherapy treatment, posing challenges for individuals undergoing cancer therapy [36, 37].

Several factors can influence weight gain and body composition changes during cancer treatment. The side effects of cancer treatments, such as chemotherapy, radiation therapy, and hormonal therapy, can impact appetite, digestion, and taste perception. These effects may lead to changes in dietary habits and physical activity levels, ultimately affecting energy balance and potentially promoting weight gain. The length of cancer treatments can vary depending on the type and stage of cancer. Prolonged treatment durations may exacerbate treatment-related side effects on diet and physical activity, further affecting energy balance and contributing to weight gain. Dealing with a cancer diagnosis and undergoing treatment can lead to psychological distress, including anxiety, depression, and stress. These psychological factors may influence eating behaviors and physical activity levels, potentially leading to changes in energy balance and weight gain [33, 38, 39].

Obesity triggers systemic and local changes in the body, particularly in adipose tissue, that are thought to support cancer growth. Excessive calorie intake linked with obesity can raise blood sugar and insulin levels, along with fat accumulation [40].

4. Pathogenesis

The growth of fat cells requires the development of new blood vessels, a process known as angiogenesis, facilitated by factors like vascular endothelial growth factor (VEGF). While the exact mechanisms linking obesity and cancer are not fully understood, hormones like estrogen and insulin are elevated in individuals with

obesity, potentially fostering a tumor-friendly environment characterized by inflammation and increased blood vessel formation. Interestingly, while obesity and hypoxia (low oxygen) in fat cells activate VEGF production, they also trigger fibrotic and inflammatory responses, indicating a complex relationship between VEGF regulation and adipose tissue dynamics [41, 42]. When fat cells experience low oxygen levels, they release substances called chemokines, like monocyte chemoattractant protein 1 (MCP1), which attract immune cells such as macrophages. These immune cells then produce inflammatory molecules. High levels of inflammatory markers such as C-reactive protein (CRP), serum amyloid A (SAA), IL-6, and prostaglandin E2 (PGE2) in the blood have been associated with an increased risk of BC, as well as higher chances of cancer recurrence and mortality. Additionally, dysfunctional fat cells release other substances like leptin, CCL2, IL-1b, IL-6, and TNF-a, which also contribute to inflammation and attract and transform immune cells [43, 44]. Chronic inflammation has been implicated in various stages of cancer development, including metastasis [45].

Another explanation of the pathogenesis of BC and the contribution of excessive weight is that excessive fat tissue contributes to oxidative stress, which occurs when there's an imbalance between oxidants (like reactive oxygen species or ROS) and antioxidants in the body [46]. This imbalance can lead to damage to lipids, proteins, and DNA. DNA damage is thought to be a significant factor in the development of cancer. Oxidative stress also activates signalling pathways in cells, promoting tumor cell growth, migration, and the development of new blood vessels to nourish the tumor (angiogenesis) [47]. Additionally, oxidative stress plays a role in programmed cell death (apoptosis), impacting cancer progression and spread. Some cancer treatments, including certain chemotherapy drugs and radiotherapy, work by inducing oxidative

stress to kill cancer cells [48, 49].

Intentional weight loss achieved through increased physical activity and caloric restriction can improve hormonal balance. Hormonal imbalances, such as elevated levels of estrogen, have been associated with an increased risk of BC recurrence. Estrogen promotes cell proliferation in breast tissue and can stimulate the growth of hormone-sensitive tumors. By promoting weight loss, these interventions may help restore hormonal balance, reducing the risk of cancer recurrence [34]. Weight loss interventions can also contribute to improvements in quality of life among breast cancer survivors. Achieving a healthier weight and engaging in regular physical activity can enhance overall well-being, alleviate symptoms of fatigue and discomfort, and improve psychological outlook and self-esteem. There is also an improvement in physical functioning and mobility among breast cancer survivors who have obesity or overweight. This may include improvements in cardiovascular fitness, strength, flexibility, and endurance, leading to enhanced functional capacity and independence in daily activities. Despite the potential benefits, there have been relatively few intervention trials specifically targeting weight loss and lifestyle modification among breast cancer survivors. This highlights the need for further research to explore the efficacy and feasibility of integrating physical activity and dietary interventions as part of care plans for breast cancer survivors. [35].

5. Treatment

As for treatment modalities, they include chemotherapy, radiation therapy, surgery (mastectomy or lumpectomy), and hormonal therapies, depending on the stage of the cancer. For BC at stages I to III, surgery and radiation therapy are commonly used, often in combination with chemotherapy or other drug therapies before or after surgery.

Stage IV BC and distant recurrence typically require systemic therapy, which may include chemotherapy, hormone therapy, and antibody therapy. Chemotherapy regimens commonly used include CMF (cyclophosphamide, methotrexate, 5-fluorouracil) or anthracyclines (epirubicin or doxorubicin), which have been shown to reduce mortality by 35%. Chemotherapy typically lasts for 3 to 6 months and can lead to side effects such as nausea, vomiting, loss of appetite, dry mouth, and changes in taste or smell perception. These treatment options aim to effectively manage BC but can also pose risks and side effects that need to be carefully managed [50].

6. The aim

Breast cancer survivors (BCS) represent a significant portion of cancer survivors worldwide, and it's crucial to find lifestyle changes that can lower the risk of cancer returning and reduce the chances of developing other health issues after surviving cancer. Dietary interventions are primarily aimed at weight loss or management due to the association of excess weight and body fat with disease recurrence as well as various other complications such as cardiovascular disease. However, as reported by Zahebi et al., several studies have highlighted the correlation between diets exacerbating inflammation and the risk of developing BC, whereas an anti-inflammatory diet has been associated with a lower risk of cardiovascular events, thus creating the need for various dietary patterns that could act supportively in reducing the risk of recurrence [7, 51].

So far, few clinical studies have focused on the association between different types of diets and BC [19]. Most have concentrated on weight loss diets without sufficient clinical outcomes. The present literature review aims to search for clinical studies published in a specific time frame from 2000 to 2024 that have examined various types

of diets or food groups or some modifiable lifestyle factors applied to BCS, their impact on disease progression, to identify potential gaps and create prospects for new clinical studies and data.

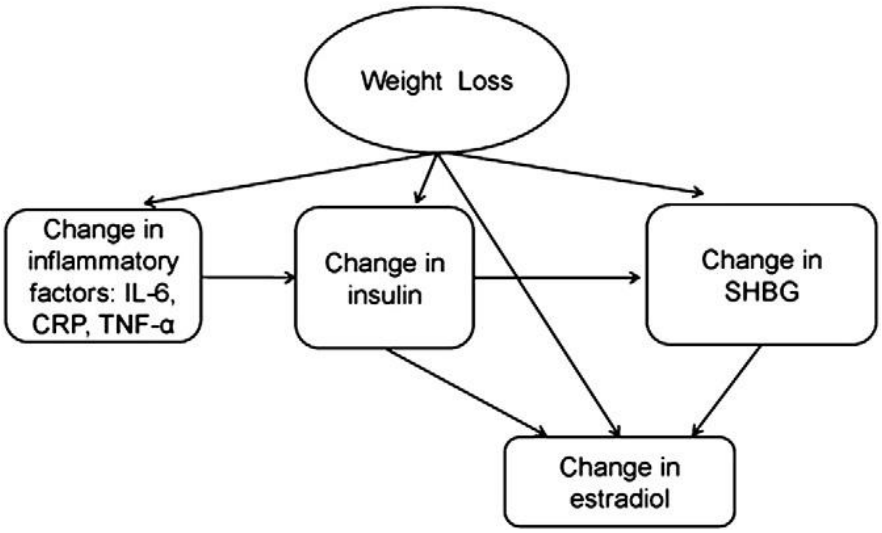

Figure 1 The interaction of breast cancer risk factors and the impact of weight loss (IL-6, interleukin-6; CRP, C-reactive protein; TNF-α, tumor necrosis factor-α; SHBG, sex hormone binding globulin). Adapted from " Reducing breast cancer recurrence with weight loss, a vanguard trial: the Exercise and Nutrition to Enhance Recovery and Good Health for You (ENERGY) Trial" by Rock CL, Byers TE, Colditz GA, Demark-Wahnefried W, Ganz PA, Wolin KY, et al., 2013

METHODS

The literature was searched using PubMed, Google Scholar, and SCOPUS databases. The combinations of keywords were “breast cancer” and “dietary patterns” (i.e. alcohol, fruits, vegetables, meat, Mediterranean diet) or “lifestyle factors” (i.e. BMI, inactivity, obesity) and “incidence” or “survival” or “recurrence” or “chemotherapy”. We have included randomized controlled trials and clinical trials between 1 January 2000 and 31 March 2024. Only studies published in English and conducted with humans (females) have been considered. The evaluation of the studies was carried out through a structured method, beginning with the title and then with the abstract, and the entire manuscript. References from the extracted articles were also used as well as meta-analyses, systematic reviews, and other epidemiological studies were utilized for additional information.

We included studies referring to breast cancer incidence, recurrence, survival, or studies focusing on women at high risk for breast cancer. Studies referring to the postmenopausal period or lifestyle interventions, such as physical activity, were not excluded. However, studies discussing metastasis were excluded. In all, 2085 studies were found. Out of these studies, 86 were duplicates, and several ultimately did not meet the criteria for clinical studies with the result of the decrease of their number to 19 studies.

RESULTS

a/a	Ref.	Dietary pattern	Design	Biomarker	Effect
1	[52]	DER [liquid diet, 3,656 kJ/d (864 kcal/d)	randomized, placebo-controlled 2 subequal menstrual cycles, 19 premenopausal, parous, 35-45 y, sedentary lifestyle, BMI 28-40 kg/m^2	Body weight, body fat % (BIA), resting metabolic rate, waist, hip & bust measurements, breast and abdominal epithelial cells, genes involved in glycolytic & lipid synthesis, (insulin, leptin, total and low-density lipoprotein cholesterol, and triglycerides)	↓
2	[53]	intermittent energy restriction (IER) (2 consecutive days 650–1000 kcal, low- 50 g carbohydrate, 50–70 g protein, 30–40 g fat) (vs continuous energy restriction (CER) Mediterranean diet (30%fat, 25% pr, 45% carbohydrates)	During chemotherapy cycles, randomized, controlled two-arm, adjuvant or neoadjuvant chemotherapy, stages 1–3, ≥18 years, haemoglobin >110 g/L, 172 participants (non-insulin or non-Sus therapy, BMI 19≥ kg/m^2) The ability of diet & PA to lead to weight loss, pre-/peri- or post-menopausal	Fasting glucose, fasting insulin, HOMA-IR, Metabolic biomarkers Body weight, FFM, body fat, waist & hip circumference, trunk fat, blood pressure, fasting insulin, exploratory metabolic (adiponectin, receptors for IGF-I, insulin & leptin, CRP, oxidative markers	↓ ↔
3	[54]	i)Caloric restriction 1200-2000 kcal/day, <30% Kcal from fat ii) exercise 45' moderate to vigorous 5 d/week iii) diet+exercise iv)control	12 months, randomized-four-armed trial, post-menopausal 438 overweight or obese, sedentary women aged 50-75 years (no >100 min/week moderate, diabetes or other medical conditions)	Body weight, BMI, body composition (VO2max) Glucose, insulin, and c-peptide glucose, insulin and HbA1c Blood lipid profile estradiol & testosterone, IL-6, CRP inflammation-related biomarkers (IL-1β, IL-4, TNF-α), serum amyloid protein A [SAA], ghrelin, leptin, angiogenesis markers, VEGF	↓ ↔ ↓

4	[55]	Diet increased in vegetables, fruit, fiber & decreased in fat (5 vegetable servings +16 oz of vegetable juice; 3 fruit servings; 30 g of fiber; & 15% to 20% of energy intake) from fat.	3088 previously treated for BC, 18-70 y.o. women, randomized-controlled, stages I to IIIA 4 years, treatment with axillary dissection and total mastectomy or lumpectomy followed by primary breast radiation	risk of developing additional breast cancer events	↔
5	[56]	total fat to20%, fruit + vegetables at least 5 servings & grains 6 servings min.	9 years, randomized controlled, 48835 postmenopausal women, 50-79 y.o.	BMI, anthropometric measurements, blood pressure, glucose, insulin, LDL Chol. Total, HDL, TGA, α-carotene, β-carotene, total carotenoids, α-tocopherol, γ-tocopherol, _-cryptoxanthin, lycopene, circulating hormones	↓ ↔
6	[57]	high fat, low carbohydrate versus low fat, high carbohydrate	6 months, nonrandomized, controlled study,142 obese or overweight participants	fasting glucose, LDL, Chol total, TGA BMI, Weight, % Fat mass	↔ ↓ ↓
7	[58]	Low-Fat (15% of energy from fat), and/or High Fruit-and-Vegetable Diets (9 servings/d)	randomized controlled 122 premenopausal women, 12 mo	8-isoprostane-F2 in plasma, BMI Chol. Total, HDL, LDL, TGA	↓ ↔
8	[59]	8 servings of fruit and vegetables, 30 g fiber, ≤20% total energy from fat/day	48 months, randomized, controlled, 52 postmenopausal women From Arizona site (WHEL study)	Body weight, waist:hip ratio (WHR), body mass index (BMI) and body composition	↔
9	[60]	5 vegetable servings, 16 ounces of vegetable juice, 3 fruit servings, 30 g of fiber (18 g/1000 kcal) and 15–20% energy from fat	12 months, randomized Controlled, 3088 postmenopausal women (WHEL study)	carotenoid concentrations	↑

10	[61]	Soy protein intake with 99 mg isoflavones daily vs of milk protein (placebo)	double-blind, randomized, controlled trial, 1 year, 126 Dutch, postmenopausal women, 60-75 y.o.	Mammographic density	↔
11	[62]	phase 1, an isocaloric low-fat, high-fiber (LFHF) vs. usual diet, phase 2, a soy supplement either with or without isoflavones (soy+IF vs. soy–IF)	sequential, 2-phase randomized trial, 154 premenopausal women 20–40 years	IGF-I, IGFBP1 and IGFBP3 IGF-I, IGFBP1 IGFBP3 IGF-I:BP3	↔ (phase 1) ↔ ↓ (phase 2) ↑ (phase 2)
12	[63]	4 six servings of canned/pouched fish per week (1.68 g _1.68 g per day of EPA + DHA)	3 months, randomized, controlled, 26 adult women at high risk of BC	EPA & DHA in breast adipose tissue, plasma and erythrocyte membrane BMI waist hip circumference ratio Breast adipose tissue samples	↑
13	[64]	habitual diets plus 0, 5, or 10 g of ground flaxseed	randomized, crossover trial, three seven-week feeding periods, 28 postmenopausal women 52-82 yo	estrone sulfate, 17-estradiol, sex hormone-binding globulin, progesterone, dehydroepiandrosterone sulfate, dehydroepiandrosterone, androstenedione, testosterone, and free testosterone prolactin	↓ ↔ ↑
14	[65]	2 tablespoons (15 g) of ground flaxseed daily for 7 weeks	7 week two-arm, parallel, randomized controlled trial (RCT), 99 postmenopausal women, 57-64 yo, Canada	Sex hormones 2-hydroxy-estrone	↔ ↑
15	[66]	(1) isocaloric dietary intervention mainly based on plant foods (2) moderate-intensity PA intervention (3) both interventions (4) general recommendations	24-month four-arm randomized control trial, 234 healthy postmenopausal women with high breast density, 50-69 yo	Leptin, resistin, IL-1α, IL-6 Adiponectin Leptin, resistin, adiponectin	↓ (arms 2 & 3) ↔ ↔ (in diet intervention)

				Interleukins (IL)-1α, -1β, -6, tumor necrosis factor-α and C-reactive protein Body weight	↔
16	[67]	(1) eating five servings of fruit and vegetables daily; (2) eating wholemeal bread and cereals; and (3) limiting the amount of animal fats	12 months, double-blind randomized controlled trial, three-arm, 492 women	BMI	↔
17	[68]	Anti-inflammatory diet (multiple spices and herbs, increased marine fish intake, cruciferous and colorful vegetables and fruit, olive oil, and green and black tea)	two-arm randomized controlled trial (RCT)153 overweight and obese (BMI ≥ 25 kg/m2), 12 months, ≥ 18 yo	Anthropometric measures C-reactive protein (CRP) Interleukins -3, -6, and -8 (IL-3, IL-6, IL-8), and Tumor Necrosis Factor (TNF)–α fraction)	↓ ↔
18	[69]	aerobic and resistance exercise (EX) (3 times/week)	16-week randomized pilot trial, 20 obese (BMI ≥ 30 kg/m2), postmenopausal breast cancer survivors	Body composition blood glucose, insulin, HOMA-IR, total cholesterol, LDL, triglycerides, HgA1c, and increased HDL-C, CRP, leptin, IL-6, IL-8 adipose tissue macrophages (ATMs) adiponectin pro-inflammatory cytokines IL-6 and TNF- α	↓
19	[70]	water-based exercise and/or oral ginger supplement	6 week-Randomized controlled, 40 women	malondialdehyde (MDA), nitric oxide (NO), glutathione peroxidase (GPx),adiponectin	↓ ↑

Table 1 Selection of trials that examined the impact of dietary patterns and lifestyle interventions on breast cancer

↓ lowering effect; ↑ increasing effect, ↔ no change

PA: physical activity SUs: sulfonylureas VEGF: vascular endothelial growth factor, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, FFM: fat-free mass, IGF-1: Insulin-like growth factor 1, CRP: C-reactive protein, TNF- α : Tumor necrosis factor α, EPA & DHA: eicosapentaenoic & docosahexaenoic acid, IGFBP: insulin-like growth factor binding protein, WHR: waist:hip ratio, BMI: body mass index

DISCUSSION

Excessive weight and adiposity upon BC diagnosis, as well as weight gain during treatment, have been correlated with unfavorable prognoses. Many women diagnosed with BC experience weight gain and an increase in body fat, coupled with a loss of lean body mass. These alterations are linked to heightened chemotherapy toxicity, often leading to dose reductions, which may exacerbate treatment outcomes [6].

Some clinical studies have examined the impact of reduced energy intake on body weight and anthropometric indices, extending the analysis to other parameters directly linked to breast cancer and its potential recurrence.

The randomized study by Kai et al., [52] investigated the effect of dietary energy restriction through a liquid diet over two menstrual cycles. Nineteen premenopausal women, meeting the criteria for overweight or obesity, aged 35 to 45 years, and parous, participated in the study. Before the intervention, biopsies were conducted on both the breast and abdomen, and blood and urine samples were collected to study markers associated with cancer risk such as insulin, leptin, total cholesterol, low-density cholesterol, and triglycerides, along with anthropometric measurements. Genes involved in the glycolytic pathway and lipid synthesis pathways were studied from abdominal and breast cancer tissues, as well as from breast epithelial cells. The control group followed their usual dietary and physical activity habits, while the intervention group received 4 cans of 325 mL fortified beverages and supplemented with 2-3 L of other clear fluids providing adequate electrolyte intake but low in calories (tea, coffee, and others), resulting in a daily energy intake of 846 Kcal. The clinical intervention was well tolerated with constipation being the main side effect. The intervention group showed a reduction in body weight as well as other anthropometric data, as well as biochemical markers such as cholesterol, leptin, and triglycerides. An increase in

certain markers such as urea and ketone bodies indicates a state of ketosis, attributed to low calorie intake. Regarding gene expression, no difference was observed between the baseline and repeat biopsy in the control group. However, in the intervention group, DER resulted in changes in gene expression primarily related to metabolism and energy pathways, and these changes were observed in both breast and abdominal tissues, indicating a systemic response to the dietary intervention. In general, gene expression changes observed in breast and abdominal tissues following DER may provide insights into how short-term energy restriction could potentially impact BC risk through molecular mechanisms.

The study conducted by Michelle Harvie et al., [53], investigated the effect of reduced energy intake on weight management and toxicity during chemotherapy. Weight gain during diagnosis and chemotherapy has been associated with increased chances of disease recurrence and treatment toxicity. Energy restriction was implemented in two ways, in a randomized two-armed clinical trial, with one group undergoing intermittent energy restriction (IER) and the other continuous energy restriction (CER). Inclusion criteria were women aged >18, with hemoglobin>110 g/L and body mass index (BMI) > 19 kg/m2, allowing for weight loss in healthy volunteers through a combination of diet and exercise. Diabetic women were not excluded from the intervention unless their medication included insulin or sulfonylureas due to the risk of hypoglycemia. The IER group received 650-1000 kcal, 50g carbohydrates, 50-70g protein, and 30-40g fat, with an emphasis on monounsaturated (MUFA) and polyunsaturated fat (PUFA) with 5 servings of vegetables and 1 fruit. This dietary pattern was followed for 2 consecutive days per week, with the remaining days consisting of a Mediterranean diet tailored to each patient's needs for weight loss or maintenance. The low-energy days occurred just before chemotherapy, while on the day of treatment, patients were instructed to

return to the Mediterranean diet. In the CER group, patients followed a Mediterranean diet according to their energy needs for weight loss or maintenance. In addition to diet, emphasis was placed on physical activity. Measurements of the studied biomarkers were taken before the start of chemotherapy and 3 weeks after completion. Various indicators were studied, such as anthropometric, metabolic, inflammation, and oxidative stress markers such as CRP. Additionally, specific biomarkers related to epithelial and bone marrow toxicity were assessed, including serum cytokeratin 18 (CK18) and plasma FMS-like tyrosine kinase 3 ligand (FLT3 ligand) measured respectively.

Toxicity from previous chemotherapy cycles was recorded. The study involved 86 volunteers in each intervention group. Both the IER and CER groups experienced similar reductions in waist circumference, hip circumference, and trunk fat assessed by DXA (dual-energy X-ray absorptiometry) and increased lean mass in appendages. There were no changes in HOMA or total and LDL cholesterol levels in either group, but both groups saw a decrease in HDL cholesterol. Serum triglyceride levels increased in the CER group but remained stable in the IER group. The mean change in triglyceride levels between IER and CER was slightly negative but not statistically significant. Both groups showed reductions in systolic blood pressure and forced vital capacity (FVC) while maintaining forced expiratory volume in one second (FEV1) and hand-grip strength. There was no significant difference in the change in the distance walked in six minutes between the two groups. Regarding the outcomes assessed by FACT-TOI-ES, TOI-F, and TOI-BC, the intervention had a similar effect on both groups. FACT-TOI-ES (Functional Assessment of Cancer Therapy - Treatment Outcome Index - Endocrine Symptoms) is a questionnaire designed to assess the impact of cancer treatment on patients' quality of life and symptoms specifically related

to endocrine cancers, while TOI-F (Trial Outcome Index – Fatigue) refers to a questionnaire used to assess fatigue levels and TOI-BC to the "Trial Outcome Index - Breast Cancer" questionnaire. The IER group adhered well to the prescribed low-energy days and exhibited specific dietary changes compared to the CER group. Hormonal and receptor changes occurred in both groups, but there were no significant changes in markers of inflammation, oxidative stress, or antioxidant capacity. Both groups showed comparable increases in serum CK18 levels and plasma FLT3 ligands. IER is feasible but did not demonstrate significant reductions in weight and body fat compared to CER. There were no differences in grade 3/4 toxicity overall. The greater reductions in weight and body fat with IER likely indicate this group achieved an overall greater energy restriction through better dietary adherence compared to CER over the 5-month chemotherapy period. FLT3 levels remained relatively stable before the sixth cycle of chemotherapy in the IER group, which was not reflected in the self-reported clinical data on side effects. This discrepancy could suggest that the observed FLT3 levels were incidental or, alternatively, that IER helped preserve healthy bone marrow stem cells during chemotherapy.

In the study of Duggan C., et. al. [54] The Dietary Inflammatory Index (DII) and its energy-adjusted counterpart (E-DIITM) scores were computed based on responses from food frequency questionnaires (FFQ). The biomarkers that were examined are: 1) markers related to inflammation (such as CRP, IL-6, TNF-α, and serum amyloid protein A [SAA]), 2) sex hormones (including estradiol, estrone, testosterone, and androstenedione), hormones and proteins involved in metabolism (insulin, glucose, and HOMA), hormones associated with obesity and satiety (ghrelin and leptin), and markers of angiogenesis (such as pigment epithelium-derived factor [PEDF], vascular endothelial growth factor [VEGF], and plasminogen activator inhibitor type-1 [PAI-1]).

This study suggests that weight change has a stronger influence on biomarkers compared to changes in the dietary inflammatory index (E-DII). Specifically, changes in E-DII after 12 months were inversely correlated with variations in ghrelin levels, a hormone involved in appetite regulation, and positively correlated with levels of vascular endothelial growth factor (VEGF) and red blood cell counts. However, no significant relationships were observed between changes in E-DII and levels of C-reactive protein (CRP) or Interleukin (IL)-6, which are markers of inflammation. Adopting a low-calorie, low-fat diet appears to diminish the inflammatory potential of the diet, thereby influencing biomarkers associated with tumorigenesis, such as VEGF, while not significantly affecting CRP or IL-6 levels.

As some studies specifically focus on reduced energy intake by decreasing the amount of fat consumed, it is of interest to examine whether this reduction in fat intake affects the intake of other nutrients and its impact.

A study that examined this is the one by Winters BL et. al. [71], which analyzed the data from the WINS randomized clinical trial. The Women's Intervention Nutrition Study (WINS) was conducted in the 1990s, with recruitment starting in 1994 and the study concluding in 2001. The WINS study showed that a low-fat diet can reduce the risk of breast cancer recurrence in postmenopausal women who have been diagnosed with early-stage breast cancer. The study found that women who followed a low-fat diet experienced a lower rate of breast cancer recurrence compared to those who did not change their diet [72]. So, what Winters BL et. al. analyzed is that in the 12-month study, women were divided into two groups, where in the first intervention group, the percentage of fat in daily energy intake should be around 15%, specifically up to 20%, while in the second group, it should be above 20%. Indeed, a reduction in fat intake was observed in the first group; however, no difference was observed in the adequacy

of other nutrients. It is noteworthy, however, that only 40% of the participants managed to adhere to a low-fat diet.

The first study that examined the benefits of fat reduction in the diet was the WHI (Women's Health Initiative) [56], where fat restriction up to 20% was also implemented along with an increase in the consumption of fruits and vegetables. Ross L. Prentice et al. describe the study conducted, focusing on cancer incidence risk relative to prior studies. Unlike previously referred studies, this clinical trial did not aim to reduce energy intake or promote weight loss. Some participants continued hormone therapy concurrently with dietary study. Regarding dietary intervention, a marginal decrease in energy consumption was noted in the intervention group compared to the control group. Overall, minimal changes were observed in the blood concentration levels of biomarkers such as cholesterol, carotenoids, tocopherols, and circulating hormones. . The intervention group exhibited a more significant decline in γ-tocopherol levels and slight positive variances in α-carotene, β-carotene, and β-cryptoxanthin levels. LDL cholesterol levels modestly decreased in the intervention group compared to the control group, while differences in levels of HDL cholesterol, triglycerides, insulin, and glucose were not statistically significant between the two groups. Comparable biomarker shifts were observed at other assessment points (year 1 and year 6), with disparities between groups slightly more pronounced at year 1. After an approximately 8-year follow-up, BC incidence was 9% lower among women in the dietary intervention group compared to those in the control group, although overall incidence rates did not diverge significantly. One interpretation of these findings is that the difference in fat energy percentage between intervention and control groups was only approximately 70% of the intended target, with few women meeting the dietary fat goal of 20% energy intake. In conclusion, among postmenopausal women, adherence to a low-fat dietary

pattern did not yield a statistically significant reduction in the risk of invasive BC over an average 8.1-year follow-up period.

Motivated by the fact that excess body fat increases inflammatory response in the body and maintaining a healthy body weight is a significant factor in preventing disease recurrence, Thomson et al. [57] aimed to investigate the role of dietary design targeting weight loss. Thus, the study involved two intervention groups in addition to the control group. Both groups had the same protein ratio, with differences in fat and carbohydrate percentages. One intervention group had a higher proportion of carbohydrates, while the other intervention group had a higher proportion of fat. Both groups showed a decrease in total cholesterol and LDL, with a more significant reduction observed in the low-fat diet group, while a decrease in triglycerides and an increase in HDL were observed in the other intervention group with a low carbohydrate percentage. The percentage of body fat loss did not appear to differ significantly between the two intervention groups. It was observed that the decrease in fasting glucose was relative to weight loss and not to the type of diet, although the results were not statistically significant.

The study by Chen G. et al. [58] examined the effect of dietary plans on levels of 8-isoprostane-F2α, which is a product of lipid oxidation, with dietary plans including low-fat and/or high-fiber content. The intervention that showed a reduction in 8-isoprostane-F2α levels was the low-fat one, which was also the only intervention where weight loss was observed. However, neither in this intervention group nor in the others was there a decrease in lipid levels such as LDL, total cholesterol or triglycerides. In conclusion, it appeared that its levels were not positively affected by a low-fat dietary plan or by one with a high fiber content.

Pierce et al. also analyzed the levels of carotenoids in the blood from the WHEL study.

As this clinical trial investigates a diet rich in fruits and vegetables and low in fat, carotenoids serve as a biomarker indicative of fruit and vegetable consumption, and their potential anticancer properties have been reported in other studies [60, 73]. The analysis of results, following a 12-month intervention, revealed an increase in the levels of carotenoids that are more associated with reduced risk of disease recurrence like α-carotene, β-carotene and lutein. These outcomes were primarily attributed to the consumption of vegetable juice, without diminishing the importance of consuming vegetable servings.

So far, the impact of reduced energy intake has been analyzed, focusing on the outcome of weight loss resulting from it. In addition to low-calorie dietary plans, some studies have attempted to examine the effect of increased dietary fiber from fruits and vegetables, sometimes in combination with reduced fat and sometimes without. Few studies have been found to investigate various other nutritional components as a means of prevention or adjunctive factors in the management of BC.

In the study by Verheus M. et al. [61], the effect of daily supplementation with soy products on breast density which is one of the main indicators of BC risk was investigated. This study was based on the observation of higher soy product consumption in Asian countries and the lower incidence of the disease compared to Western countries [74]. For isoflavones in soy, which are a type of phytoestrogens, there are no clear conclusions yet. Phytoestrogens, on the one hand, compete with estrogens for binding to specific receptors, potentially increasing the risk of disease development; on the other hand, this competition against endogenous estrogens could be considered a protective factor [75].

This study utilized data from another double-blind, randomized study, initially aiming to investigate the effect of soy supplementation on bone density and other factors such

as cardiovascular disease. The intervention group received soy supplements, containing a certain amount of specific isoflavones, while the control group received another protein supplement with similar physicochemical characteristics. Both types of supplements were enriched with vitamins and trace elements. The intervention took place between two mammography examinations, a period corresponding to 2 years. Overall, no differences were observed in tissue density between the two groups. The slight decrease in density observed in both groups, with a slightly greater reduction in the intervention group, was attributed to aging, as tissue density tends to decrease over time. The intervention had a long duration, the volunteers received a significant amount of supplementation, and compliance was evident in blood tests as well. However, the long interval between the end of the intervention and the examination may not provide clear data.

The second study examining the effect of soy on disease risk was conducted by Gann PH et al.[62], in a two-phase study. Initially, the volunteers followed a low-fat, high-fiber diet for 12 months, followed by 3 months of either receiving a full soy protein supplement containing all isoflavones or a soy supplement lacking two isoflavones, genistein and daidzein. The biomarkers that were studied were IGF-1 and two proteins binding to it, IGFBP1 and IGFBP3, aiming to understand if IGF-1 could be a marker that could be altered by dietary modification as it has been associated in some way with the risk of certain types of cancer, although nothing is clear yet. This study, as the previous one, assumed that the lower BC incidence in some parts of Asia may be due to diets low in fat and more soy protein enriched. It is worth noting that calorie intake and body weight remained stable in both phases, from the beginning to the end of the study. In the intervention group, as expected, there was an increase in protein intake in both the first and second phases. The weight stability suggests that it is due to

reduced fat intake, despite the protein increase, thus emphasizing the importance of the energy balance in weight fluctuations.

Regarding the biomarkers studied, in the first phase, the IGF-1, IGFBP1, and IGFBP3 did not show any change from baseline. No statistically significant change was observed in the second phase either, except for IGFBP3, where the decrease was very small (2.3%) but statistically significant. In individuals who followed a regular diet in phase 1 and received the soy supplement in phase 2, an increase in IGF-1 was observed, which was correlated with increased protein intake from plant sources and increased calcium intake, suggesting that an increase in soy or calcium intake from the diet could increase bioavailable IGF-1 levels by suppressing its binding protein, IGFBP3.

This study showed that a low-fat, high-fiber diet through increased fruit and vegetable intake and whole-grain foods did not cause any change in IGF-1 levels after one year of intervention. However, what could cause its variation is the soy supplement through the effect of protein or calcium intake and not so much the soy isoflavones. This provides an opportunity for further and more detailed study of the action of individual nutrients such as calcium or protein or food groups such as dairy products.

Among the few dietary components that have been subject to clinical studies are omega-3 fatty acids (EPA and DHA). For the timeframe covered by this literature review, just one clinical trial was found investigating the effect of omega-3 fatty acids on various parameters potentially related to the disease.

The omega-3 fatty acids, known as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been shown to exert some effect on cancer. Omega-3 fatty acids appear to modulate various biological processes involved in cancer development and treatment, potentially offering benefits such as reducing

inflammation, slowing tumor growth, and improving treatment outcomes [76, 77].

EPA and DHA have been shown to possess properties that reduce inflammation in the body by influencing the production of eicosanoids, which are signalling molecules involved in inflammation and immune response. EPA and DHA can change the composition of lipids (fats) in cell membranes. This alteration affects the structure and function of the cell membrane, influencing its interactions with other molecules and signalling pathways leading to downstream effects on cellular functions related to inflammation. Furthermore, they can influence the expression of genes involved in inflammation. By altering gene expression, they can regulate the production of proteins and other molecules involved in the inflammatory response [78].

The clinical trial of Straka et. Al. [63] was designed to compare the effects of n-3 fatty acids consuming fish versus n-3 fatty acid supplements on EPA + DHA composition of breast adipose tissue. 25 women were randomly assigned to one of two intervention groups. One arm of the study received 4 six-ounce servings of canned or pouched fish per week and the second one received two capsules per day of an n-3 fatty acid supplement. The n-3 fatty acid supplement provided a daily dose of at least 1.68 grams of EPA + DHA combined. Breast adipose tissue samples and fasting blood samples were collected, and total lipids were extracted from plasma and breast adipose samples. Additionally, tissue samples were collected for RNA-level analysis. After the intervention, an increase in EPA and DHA levels was observed in both plasma and erythrocyte membranes, with a more significant increase in EPA in the supplement group. Changes in EPA levels were also correlated with weight and BMI, with smaller changes observed in higher weights. Increased BMI and weight also correlated with smaller changes in EPA-DHA levels in breast adipose tissue. Statistically significant changes were observed in both intervention groups. Furthermore, the analysis of

breast tissues focused on genes associated with inflammation, namely IL-6, CD68, and COX-2. The findings indicated that there were no significant differences observed in gene expression over time or between the study arms. The small sample size, short intervention duration, and perhaps the dosage of fatty acids may not be sufficient to induce changes in gene expression levels.

One of the few foods studied for their contribution to the outcome or prevention of BC is flaxseed, and specifically, for the period from 2000 to 2024, two clinical studies examined its association with sex hormone concentrations.

Postmenopausal women have less fluctuation in hormone levels compared to those who are premenopausal. High estrogen levels in the bloodstream are closely linked to an increased risk of BC, particularly when looking at the portion of estradiol that is not bound to sex hormone-binding globulin (SHBG). This unbound fraction is believed to be the most potent form of estrogen [79].

This trial [64] aimed to assess the impact of consuming a plant-based food rich in lignans (flaxseed) on the levels of various hormones and a binding protein in the bloodstream of postmenopausal women. Lignans are thought to have a similar structure to endogenous steroid sex hormones. Hormones that were studied included estrone, estrone sulfate, 17β-estradiol, SHBG, progesterone, prolactin, dehydroepiandrosterone sulfate (DHEAS), dehydroepiandrosterone (DHEA), androstenedione, testosterone, and free testosterone.

The volunteers received an additional 5g of flaxseed in their usual diet for 7 weeks, followed by a wash-out period, and then received an additional 10g of flaxseed in their usual diet. It is worth noting that they were asked to maintain their weight stable. Moreover, no statistically significant changes were observed in energy or macronutrient composition in the diet between the baseline and the end of the

intervention.

Heightened concentrations of estrone sulphate, the primary form of estrogen found in postmenopausal women, and 17-estradiol, which is acknowledged as the most potent estrogen in both pre-and postmenopausal women, may elevate the risk of BC onset in women [80].

The intake of either 5 or 10 g of flaxseed daily for seven weeks affected the levels of estrogen and prolactin but did not impact androgen or binding protein levels in this study. The reductions observed in 17-estradiol and estrone sulphate levels indicate a potential protective effect of flaxseed consumption against BC. Consequently, a decrease in estrogen levels, as observed with 17-estradiol and estrone sulphate in this trial, would logically lead to a decline in prolactin production. However, the rise in prolactin levels might counteract the beneficial outcomes associated with flaxseed consumption concerning BC, especially if prolactin is identified as a promoter of the disease.

The three significant clinical trials were the following, upon which additional studies relied to analyze specific outcomes.

The WHEL (Women's Healthy Eating and Living) study was a clinical trial that examined the effects of a plant-based, low-fat diet on the recurrence of BC among women who had previously been treated for early-stage BC. It aimed to determine whether dietary changes, specifically reducing fat intake and increasing fruit and vegetable consumption, could lower the risk of cancer recurrence and improve overall health outcomes. The trial took place between 1995 and 2006. [17].

The clinical trial WINS (Women's Intervention Nutrition Study) was another study focusing on dietary interventions among women with BC. The WINS clinical trial also included postmenopausal women with a similar aim to the WHEL study. The trial was

conducted in the late 1980s and early 1990s.

And the third one in this area is the Women's Health Initiative Dietary Modification Trial (WHI-DMT). This trial also examined the effects of dietary interventions, including reducing fat intake and increasing fruit and vegetable consumption, on various health outcomes among postmenopausal women, including BC risk. The Women's Health Initiative Dietary Modification Trial (WHI-DMT) was conducted between 1993 and 2005.

Few clinical studies have focused on investigating the contribution of individual foods, components, or food groups. Among the various dietary elements investigated were soy, which assesses the influence of isoflavones, omega-3 fatty acids derived from fish or flaxseed consumption, and an "anti-inflammatory" diet. Additionally, what has been observed is that most studies examined in this literature review placed significant emphasis on qualitative measures. There were studies, but not enough, that included inflammation-related biomarkers in their intervention assessments.

In general, notable observations were made in interventions where significant weight loss was achieved. In those studies, changes in inflammation markers were evident, as seen in the study by Duggan et al. [54], where reductions in anthropometric measurements and improvements in lipid profiles were associated with improvements in various inflammation markers such as interleukins and vascular endothelial growth factor (VEGF).

Furthermore, conflicting results were noted. Contradictory results regarding the previously mentioned study are highlighted in the trial conducted by Ramirez AG et al. [68]. Here improvements in anthropometric indices and CRP levels following an anti-inflammatory dietary intervention did not appear to affect inflammation markers. Additionally, the age group exhibited heterogeneity. Some interventions were applied

to premenopausal women, others to postmenopausal women, while certain studies did not specify such criteria, such as the study by Michelle Harvie et al. [53].

Among the limitations identified, it was noted that not all clinical trials identified were both double-blinded and randomized, potentially affecting the generalizability of the results. Additionally, the study population consists of individuals living independently, which introduces challenges related to compliance and accurately quantifying dietary intake and physical activity.

Most of them provided grounds for further investigation. This was the purpose of the present literature review. To shed light on what has been implemented as a dietary intervention in the last 24 years, to identify any gaps or inconsistencies in existing studies, and to provide a basis for a clearer further investigation.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA: a cancer journal for clinicians. 2019;69(1):7-34.
2. Breast cancer: World Health Organization; [cited 2024. Available from: https://www.who.int/news-room/fact-sheets/detail/breast-cancer.
3. Momenimovahed Z, Salehiniya H. Epidemiological characteristics of and risk factors for breast cancer in the world. Breast Cancer: Targets and Therapy. 2019;11(null):151-64.
4. Parkin DM, Fernández LM. Use of statistics to assess the global burden of breast cancer. The breast journal. 2006;12 Suppl 1:S70-80.
5. Soerjomataram I, Louwman WJ, Lemmens VE, de Vries E, Klokman WJ, Coebergh JW. Risks of second primary breast and urogenital cancer following female breast cancer in the south of The Netherlands, 1972-2001. European journal of cancer (Oxford, England : 1990). 2005;41(15):2331-7.
6. De Cicco P, Catani MV, Gasperi V, Sibilano M, Quaglietta M, Savini I. Nutrition and Breast Cancer: A Literature Review on Prevention, Treatment and Recurrence. Nutrients. 2019;11(7).
7. Makari-Judson G, Braun B, Jerry DJ, Mertens WC. Weight gain following breast cancer diagnosis: Implication and proposed mechanisms. World journal of clinical oncology. 2014;5(3):272-82.
8. Lim YX, Lim ZL, Ho PJ, Li J. Breast Cancer in Asia: Incidence, Mortality, Early Detection, Mammography Programs, and Risk-Based Screening Initiatives. Cancers. 2022;14(17).
9. Fan L, Goss PE, Strasser-Weippl K. Current Status and Future Projections of Breast Cancer in Asia. Breast care (Basel, Switzerland). 2015;10(6):372-8.
10. World Health Organisation (WHO). Estimated Age-Standardized Incidence Rates (World) in 2020 B, Females, All Ages, Asia. 2020. Available online: https://gco.iarc.fr/today/home (accessed on 3 February 2022). [
11. Ginsburg O, Bray F, Coleman MP, Vanderpuye V, Eniu A, Kotha SR, et al. The global burden of women's cancers: a grand challenge in global health. Lancet (London, England). 2017;389(10071):847-60.
12. Winters S, Martin C, Murphy D, Shokar NK. Breast Cancer Epidemiology, Prevention, and Screening. Progress in molecular biology and translational science. 2017;151:1-32.
13. Grasgruber P, Hrazdira E, Sebera M, Kalina T. Cancer Incidence in Europe: An Ecological Analysis of Nutritional and Other Environmental Factors. Frontiers in oncology. 2018;8:151.
14. Buckland G, Travier N, Cottet V, González CA, Luján-Barroso L, Agudo A, et al. Adherence to the mediterranean diet and risk of breast cancer in the European prospective investigation into cancer and nutrition cohort study. International journal of cancer. 2013;132(12):2918-27.
15. Eliassen AH, Colditz GA, Rosner B, Willett WC, Hankinson SE. Adult weight change and risk of postmenopausal breast cancer. Jama. 2006;296(2):193-201.
16. Key T, Appleby P, Barnes I, Reeves G. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. Journal of the National Cancer Institute. 2002;94(8):606-16.
17. Pierce JP, Faerber S, Wright FA, Rock CL, Newman V, Flatt SW, et al. A randomized trial of the effect of a plant-based dietary pattern on additional breast cancer events and survival: the Women's Healthy Eating and Living (WHEL) Study. Controlled clinical trials. 2002;23(6):728-56.
18. Rebbeck TR. Inherited genetic predisposition in breast cancer. A population-based perspective. Cancer. 1999;86(11 Suppl):2493-501.
19. Zhang B, Beeghly-Fadiel A, Long J, Zheng W. Genetic variants associated with breast-

cancer risk: comprehensive research synopsis, meta-analysis, and epidemiological evidence. The Lancet Oncology. 2011;12(5):477-88.
20. Althuis MD, Fergenbaum JH, Garcia-Closas M, Brinton LA, Madigan MP, Sherman ME. Etiology of hormone receptor-defined breast cancer: a systematic review of the literature. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2004;13(10):1558-68.
21. Clusan L, Le Goff P, Flouriot G, Pakdel F. A Closer Look at Estrogen Receptor Mutations in Breast Cancer and Their Implications for Estrogen and Antiestrogen Responses. International journal of molecular sciences. 2021;22(2).
22. Kim Y, Yoo KY, Goodman MT. Differences in incidence, mortality and survival of breast cancer by regions and countries in Asia and contributing factors. Asian Pacific journal of cancer prevention : APJCP. 2015;16(7):2857-70.
23. Assi HA, Khoury KE, Dbouk H, Khalil LE, Mouhieddine TH, El Saghir NS. Epidemiology and prognosis of breast cancer in young women. Journal of thoracic disease. 2013;5 Suppl 1(Suppl 1):S2-8.
24. Bhadoria AS, Kapil U, Sareen N, Singh P. Reproductive factors and breast cancer: a case-control study in tertiary care hospital of North India. Indian journal of cancer. 2013;50(4):316-21.
25. Palmer JR, Boggs DA, Wise LA, Ambrosone CB, Adams-Campbell LL, Rosenberg L. Parity and lactation in relation to estrogen receptor negative breast cancer in African American women. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2011;20(9):1883-91.
26. Couch FJ, Hart SN, Sharma P, Toland AE, Wang X, Miron P, et al. Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2015;33(4):304-11.
27. Cobain EF, Milliron KJ, Merajver SD. Updates on breast cancer genetics: Clinical implications of detecting syndromes of inherited increased susceptibility to breast cancer. Seminars in oncology. 2016;43(5):528-35.
28. Boyd NF, Martin LJ, Yaffe MJ, Minkin S. Mammographic density and breast cancer risk: current understanding and future prospects. Breast cancer research : BCR. 2011;13(6):223.
29. Baer HJ, Tworoger SS, Hankinson SE, Willett WC. Body fatness at young ages and risk of breast cancer throughout life. American journal of epidemiology. 2010;171(11):1183-94.
30. Luo J, Margolis KL, Wactawski-Wende J, Horn K, Messina C, Stefanick ML, et al. Association of active and passive smoking with risk of breast cancer among postmenopausal women: a prospective cohort study. BMJ (Clinical research ed). 2011;342:d1016.
31. Shin S, Fu J, Shin WK, Huang D, Min S, Kang D. Association of food groups and dietary pattern with breast cancer risk: A systematic review and meta-analysis. Clinical nutrition (Edinburgh, Scotland). 2023;42(3):282-97.
32. Nissen MJ, Shapiro A, Swenson KK. Changes in weight and body composition in women receiving chemotherapy for breast cancer. Clinical breast cancer. 2011;11(1):52-60.
33. Vance V, Mourtzakis M, McCargar L, Hanning R. Weight gain in breast cancer survivors: prevalence, pattern and health consequences. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2011;12(4):282-94.
34. Gnagnarella P, Dragà D, Baggi F, Simoncini MC, Sabbatini A, Mazzocco K, et al. Promoting weight loss through diet and exercise in overweight or obese breast cancer survivors (InForma): study protocol for a randomized controlled trial. Trials. 2016;17:363.
35. Rock CL, Byers TE, Colditz GA, Demark-Wahnefried W, Ganz PA, Wolin KY, et al.

Reducing breast cancer recurrence with weight loss, a vanguard trial: the Exercise and Nutrition to Enhance Recovery and Good Health for You (ENERGY) Trial. Contemporary clinical trials. 2013;34(2):282-95.
36. Vegunta S, Lester SP, Pruthi S, Mussallem DM. Effects of Major Lifestyle Factors on Breast Cancer Risk: Impact of Weight, Nutrition, Physical Activity, Alcohol and Tobacco. Breast Cancer Management. 2020;9(4):BMT51.
37. Warner ET, Hu R, Collins LC, Beck AH, Schnitt S, Rosner B, et al. Height and Body Size in Childhood, Adolescence, and Young Adulthood and Breast Cancer Risk According to Molecular Subtype in the Nurses' Health Studies. Cancer prevention research (Philadelphia, Pa). 2016;9(9):732-8.
38. Carmichael AR. Obesity and prognosis of breast cancer. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2006;7(4):333-40.
39. Stephenson GD, Rose DP. Breast cancer and obesity: an update. Nutrition and cancer. 2003;45(1):1-16.
40. Ray A. Adipokine leptin in obesity-related pathology of breast cancer. Journal of biosciences. 2012;37(2):289-94.
41. Sun K, Kusminski CM, Scherer PE. Adipose tissue remodeling and obesity. The Journal of clinical investigation. 2011;121(6):2094-101.
42. Brown KA. Metabolic pathways in obesity-related breast cancer. Nature reviews Endocrinology. 2021;17(6):350-63.
43. Engin A. The Pathogenesis of Obesity-Associated Adipose Tissue Inflammation. Advances in experimental medicine and biology. 2017;960:221-45.
44. Crespi E, Bottai G, Santarpia L. Role of inflammation in obesity-related breast cancer. Current opinion in pharmacology. 2016;31:114-22.
45. Rock CL, Flatt SW, Laughlin GA, Gold EB, Thomson CA, Natarajan L, et al. Reproductive steroid hormones and recurrence-free survival in women with a history of breast cancer. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2008;17(3):614-20.
46. Walter KR, Ford ME, Gregoski MJ, Kramer RM, Knight KD, Spruill L, et al. Advanced glycation end products are elevated in estrogen receptor-positive breast cancer patients, alter response to therapy, and can be targeted by lifestyle intervention. Breast cancer research and treatment. 2019;173(3):559-71.
47. Manna P, Jain SK. Obesity, Oxidative Stress, Adipose Tissue Dysfunction, and the Associated Health Risks: Causes and Therapeutic Strategies. Metabolic syndrome and related disorders. 2015;13(10):423-44.
48. Lee JD, Cai Q, Shu XO, Nechuta SJ. The Role of Biomarkers of Oxidative Stress in Breast Cancer Risk and Prognosis: A Systematic Review of the Epidemiologic Literature. Journal of women's health (2002). 2017;26(5):467-82.
49. Lawenda BD, Kelly KM, Ladas EJ, Sagar SM, Vickers A, Blumberg JB. Should supplemental antioxidant administration be avoided during chemotherapy and radiation therapy? Journal of the National Cancer Institute. 2008;100(11):773-83.
50. Anampa J, Makower D, Sparano JA. Progress in adjuvant chemotherapy for breast cancer: an overview. BMC medicine. 2015;13:195.
51. Zuniga KE, Parma DL, Muñoz E, Spaniol M, Wargovich M, Ramirez AG. Dietary intervention among breast cancer survivors increased adherence to a Mediterranean-style, anti-inflammatory dietary pattern: the Rx for Better Breast Health Randomized Controlled Trial. Breast cancer research and treatment. 2019;173(1):145-54.
52. Ong KR, Sims AH, Harvie M, Chapman M, Dunn WB, Broadhurst D, et al. Biomarkers of dietary energy restriction in women at increased risk of breast cancer. Cancer prevention research (Philadelphia, Pa). 2009;2(8):720-31.
53. Harvie M, Pegington M, Howell SJ, Bundred N, Foden P, Adams J, et al. Randomised

controlled trial of intermittent vs continuous energy restriction during chemotherapy for early breast cancer. British journal of cancer. 2022;126(8):1157-67.
54. Duggan C, Tapsoba JD, Shivappa N, Harris HR, Hébert JR, Wang CY, et al. Changes in Dietary Inflammatory Index Patterns with Weight Loss in Women: A Randomized Controlled Trial. Cancer prevention research (Philadelphia, Pa). 2021;14(1):85-94.
55. Pierce JP, Natarajan L, Caan BJ, Parker BA, Greenberg ER, Flatt SW, et al. Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast cancer: the Women's Healthy Eating and Living (WHEL) randomized trial. Jama. 2007;298(3):289-98.
56. Prentice RL, Caan B, Chlebowski RT, Patterson R, Kuller LH, Ockene JK, et al. Low-fat dietary pattern and risk of invasive breast cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. Jama. 2006;295(6):629-42.
57. Thompson HJ, Sedlacek SM, Paul D, Wolfe P, McGinley JN, Playdon MC, et al. Effect of dietary patterns differing in carbohydrate and fat content on blood lipid and glucose profiles based on weight-loss success of breast-cancer survivors. Breast cancer research : BCR. 2012;14(1):R1.
58. Chen G, Heilbrun LK, Venkatramanamoorthy R, Maranci V, Redd JN, Klurfeld DM, et al. Effects of low-fat and/or high-fruit-and-vegetable diets on plasma levels of 8-isoprostane-F2alpha in the Nutrition and Breast Health study. Nutrition and cancer. 2004;50(2):155-60.
59. Thomson CA, Rock CL, Giuliano AR, Newton TR, Cui H, Reid PM, et al. Longitudinal changes in body weight and body composition among women previously treated for breast cancer consuming a high-vegetable, fruit and fiber, low-fat diet. European journal of nutrition. 2005;44(1):18-25.
60. Pierce JP, Natarajan L, Sun S, Al-Delaimy W, Flatt SW, Kealey S, et al. Increases in plasma carotenoid concentrations in response to a major dietary change in the women's healthy eating and living study. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2006;15(10):1886-92.
61. Verheus M, van Gils CH, Kreijkamp-Kaspers S, Kok L, Peeters PH, Grobbee DE, et al. Soy protein containing isoflavones and mammographic density in a randomized controlled trial in postmenopausal women. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2008;17(10):2632-8.
62. Gann PH, Kazer R, Chatterton R, Gapstur S, Thedford K, Helenowski I, et al. Sequential, randomized trial of a low-fat, high-fiber diet and soy supplementation: effects on circulating IGF-I and its binding proteins in premenopausal women. International journal of cancer. 2005;116(2):297-303.
63. Straka S, Lester JL, Cole RM, Andridge RR, Puchala S, Rose AM, et al. Incorporation of eicosapentaenioic and docosahexaenoic acids into breast adipose tissue of women at high risk of breast cancer: a randomized clinical trial of dietary fish and n-3 fatty acid capsules. Molecular nutrition & food research. 2015;59(9):1780-90.
64. Hutchins AM, Martini MC, Olson BA, Thomas W, Slavin JL. Flaxseed consumption influences endogenous hormone concentrations in postmenopausal women. Nutrition and cancer. 2001;39(1):58-65.
65. Chang VC, Cotterchio M, Boucher BA, Jenkins DJA, Mirea L, McCann SE, et al. Effect of Dietary Flaxseed Intake on Circulating Sex Hormone Levels among Postmenopausal Women: A Randomized Controlled Intervention Trial. Nutrition and cancer. 2019;71(3):385-98.
66. Bendinelli B, Masala G, Bella CD, Assedi M, Benagiano M, Pratesi S, et al. Adipocytokine plasma level changes in a 24-month dietary and physical activity randomised intervention trial in postmenopausal women. European journal of nutrition. 2023;62(3):1185-94.

67. Del Valle MO, Martín-Payo R, Cuesta-Briand B, Lana A. Impact of two nurse-led interventions targeting diet among breast cancer survivors: Results from a randomized controlled trial. European journal of cancer care. 2018;27(4):e12854.
68. Ramirez AG, Parma DL, Muñoz E, Mendoza KD, Harb C, Holden AEC, et al. An anti-inflammatory dietary intervention to reduce breast cancer recurrence risk: Study design and baseline data. Contemporary clinical trials. 2017;57:1-7.
69. Dieli-Conwright CM, Parmentier JH, Sami N, Lee K, Spicer D, Mack WJ, et al. Adipose tissue inflammation in breast cancer survivors: effects of a 16-week combined aerobic and resistance exercise training intervention. Breast cancer research and treatment. 2018;168(1):147-57.
70. Karimi N, Roshan VD. Change in adiponectin and oxidative stress after modifiable lifestyle interventions in breast cancer cases. Asian Pacific journal of cancer prevention : APJCP. 2013;14(5):2845-50.
71. Winters BL, Mitchell DC, Smiciklas-Wright H, Grosvenor MB, Liu W, Blackburn GL. Dietary patterns in women treated for breast cancer who successfully reduce fat intake: the Women's Intervention Nutrition Study (WINS). Journal of the American Dietetic Association. 2004;104(4):551-9.
72. Chlebowski RT, Rose D, Buzzard IM, Blackburn GL, Insull W, Jr., Grosvenor M, et al. Adjuvant dietary fat intake reduction in postmenopausal breast cancer patient management. The Women's Intervention Nutrition Study (WINS). Breast cancer research and treatment. 1992;20(2):73-84.
73. Rock CL, Flatt SW, Natarajan L, Thomson CA, Bardwell WA, Newman VA, et al. Plasma carotenoids and recurrence-free survival in women with a history of breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2005;23(27):6631-8.
74. Adlercreutz H. Western diet and Western diseases: some hormonal and biochemical mechanisms and associations. Scandinavian journal of clinical and laboratory investigation Supplementum. 1990;201:3-23.
75. Messina M, McCaskill-Stevens W, Lampe JW. Addressing the soy and breast cancer relationship: review, commentary, and workshop proceedings. Journal of the National Cancer Institute. 2006;98(18):1275-84.
76. Turk HF, Chapkin RS. Membrane lipid raft organization is uniquely modified by n-3 polyunsaturated fatty acids. Prostaglandins, leukotrienes, and essential fatty acids. 2013;88(1):43-7.
77. Yenipazar H, Şahin-Yeşilçubuk N. Effect of packaging and encapsulation on the oxidative and sensory stability of omega-3 supplements. Food science & nutrition. 2023;11(3):1426-40.
78. Larsson SC, Kumlin M, Ingelman-Sundberg M, Wolk A. Dietary long-chain n-3 fatty acids for the prevention of cancer: a review of potential mechanisms. The American journal of clinical nutrition. 2004;79(6):935-45.
79. Drummond AE, Swain CTV, Brown KA, Dixon-Suen SC, Boing L, van Roekel EH, et al. Linking Physical Activity to Breast Cancer via Sex Steroid Hormones, Part 2: The Effect of Sex Steroid Hormones on Breast Cancer Risk. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2022;31(1):28-37.
80. Hankinson SE, Willett WC, Manson JE, Colditz GA, Hunter DJ, Spiegelman D, et al. Plasma sex steroid hormone levels and risk of breast cancer in postmenopausal women. Journal of the National Cancer Institute. 1998;90(17):1292-9.