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CANCER (MF LEITZMANN, SECTION EDITOR)

The Impact of Diet on Breast Cancer Outcomes

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Abstract

Purpose of Review Breast cancer is the most common cancer in women, yet conclusive evidence of the effects of dietary modification in breast cancer survivors is lacking. Here, we summarize the literature and highlight important data regarding the association between dietary interventions and breast cancer outcomes.

Recent Findings Long-term follow-up and secondary analysis of the Women's Health Initiative study demonstrated a significant improvement in overall survival for women who were randomized to the low-fat diet pattern compared with those in the usual-diet group. Dietary quality as measured by Healthy Eating Index score was also associated with both a decrease in cancer-specific mortality and overall mortality.

Summary Despite current evidence on the role of diet and nutrition in breast cancer outcomes, conclusive data to translate current findings to clinical practice is lacking and requires multidisciplinary prospective research to advance the field.

Keywords Breast cancer · Breast cancer survivors · Diet intervention · Diet quality · Low-fat diet · High-quality diet · Mortality

Introduction

Breast cancer (BC) is the most common cancer among women worldwide and is a major global health priority. In the USA, an estimated 268,670 new cases (women and men) of BC were diagnosed in 2018 [1]. As of January 1, 2016, more than 3.5 million women with a history of BC were alive in the USA and this number is expected to rise to approximately 4.5 million in 2026, accounting for approximately 45% of all women cancer survivors [2]. There is a significant interest in lifestyle modification, including dietary interventions, weight loss, and physical activity in improving BC outcomes. There is ample data supporting the benefits of physical activity in mitigating and recovering from treatment-related side effects and consistent observational data in its ability to improve cancer outcomes [3]. However, the role of dietary modification in BC outcomes is less clear and requires further study.

Studies of dietary modification in BC have shown conflicting results, with some but not all showing an association between dietary modification and improved prognosis. The prospective, randomized controlled trial is the gold standard study design to provide direct evidence whether an intervention, such as dietary modification, can affect oncologic outcomes. However, this is methodologically difficult for several reasons. First, adopting and adhering to a lifestyle change such as dietary modification is challenging, as is monitoring adherence in the context of a clinical trial. Second, early prognostic biomarkers which might be used as short-term endpoints are lacking, making larger most costly studies with longer follow-up and traditional outcomes such as disease-free survival necessary. Finally, it is difficult to isolate the effect of diet from factors such as weight loss and physical activity, which often accompany dietary modification.

In this review, we will summarize data from observational studies and prospective randomized controlled trials that provide direct and indirect evidence of dietary modification in BC outcomes. We will review the current dietary guidelines for cancer survivors. We will also discuss the ongoing clinical trials and translational research in the field, and highlight potential areas for future research.

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Diet and Breast Cancer Incidence

Descendants of those who migrate from countries with a low incidence of BC to countries with a high incidence will have a higher rate of BC [4,5] emphasizing the impact of environmental factors on BC development. There are significant geographical differences in dietary patterns and components which suggest that diet may be a factor in BC risk and has led to the investigation of dietary interventions and BC incidence and outcomes. The evidence for diet and BC risk is complicated, but it has provided some rationales and foundation to understand and study dietary modification after a diagnosis of BC.

One difference between Western and Eastern diets is the high fat component in the Western diet. Several mechanisms of how a high-fat diet may affect BC incidence have been proposed [6]. High fat intake leads to the accumulation of adipose tissue, where the conversion of androstenedione to estrone occurs, increasing the concentrations of estrogens which subsequently activate BC growth. Polyunsaturated fatty acid (PUFA) is metabolized to arachidonic acid, which activates P450 aromatase, further promoting the conversion of androstenedione to estrone [7]. Furthermore, PUFA can reduce the binding of estrogens to serum binding proteins, increasing the proportion of circulating free estrogens that are biologically more potent [6].

Additionally, more than a decade ago, researchers noted the similarity between the risk factors for cancers with higher incidence in Western countries and risk factors for insulin resistance. This has led to the insulin-cancer hypothesis [8], which has been supported by both animal and human data [9]. Chronic hyperinsulinemia downregulates insulin-like growth factor binding proteins (IGFBP), leading to an increase of free IGF-1. Free IGF-1 is the bioavailable form and may promote mutagenic change in tissues including breast tissue [9]. Insulin can also activate intracellular signaling pathways implicated in BC, including the PI3K/mTOR pathways, promoting cancer cell growth [10].

One meta-regression analysis, including a total of 21 eligible studies, 3609 cases and 7137 controls, demonstrated that high concentrations of IGF-1 and its binding protein, IGFBP-3, is associated with increased risk of BC in premenopausal women [11]. In an analysis of 21,103 women in the Women's Health Initiative (WHI) with 14.7 years of follow-up and 1185 BC cases, [12] fasting baseline insulin level was positively associated with BC risk (multivariable-adjusted HR for highest vs. lowest quartile 1.41, 95% CI 1.16–1.72, $p < 0.0003$) [12]. This study provided support for an association between hyperinsulinemia and BC risk.

In animal models, high-fat diets were shown to increase the occurrence of mammary tumors in rodents [13]. However, individual human case-control and cohort studies have shown mixed results. A meta-analysis of 45 published studies (including 31 case-control and 14 cohort studies with a total of 25,015 cases of BC and over 580,000 control subjects) examined the role of dietary fat in relation to BC risk and found that higher fat intake is associated with an increased risk of BC [14]. Subjects consuming the highest vs. lowest levels of total fat had a 13% increase in BC risk (RR 1.13, 95% CI 1.03–1.25) [15]. This increase in BC risk was most pronounced for saturated fat (RR 1.19, 95% CI 1.06–1.35) [15]. The WHI Dietary Modification (WHI-DM) trial is a randomized controlled study evaluating a low-fat diet intervention for prevention of breast and colorectal cancer. It demonstrated a numerical but non-significant reduction in BC incidence after a mean of 8.3 years intervention (during intervention HR 0.92, 95% CI 0.84–1.01; post-intervention HR 0.97, 95% CI 0.89–1.05) [16].

Epidemiological studies have linked the Mediterranean diet to a reduced risk of BC. Adherence to the Mediterranean diet can be measured by a Mediterranean Diet Score (MDS), ranging from 0 (lowest adherence) to 9 (highest adherence). As demonstrated in a case-control study performed in Italy and Switzerland, the odds ratio for BC was 0.82 (95% CI, 0.71–0.95) in women with a MDS of 6–9 compared with those with a MDS of 0–3 [17]. In the PREDIMED (Prevención con Dieta Mediterránea) study conducted in Spain, participants were randomized to a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control diet (advised to reduce dietary fat). Breast cancer incidence was lower in the two Mediterranean diet groups combined than in the control group (HR, 0.43, 95% CI, 0.21–0.88) [18], suggesting a beneficial effect of a Mediterranean diet in the primary prevention of BC.

Our knowledge on diet and BC risk has provided the rationale and foundation to investigate and apply dietary modification in women with a diagnosis of BC. The data has suggested potential mechanisms by which diet may impact BC survival, including various signaling pathways essential in the pathogenesis of primary BC which may be important in the development of BC recurrence or a second primary cancer.

Associations Between Dietary Patterns and Quality and Breast Cancer Outcomes

Dietary Pattern

The two largest prospective randomized studies in the USA to investigate the association between dietary pattern and BC outcomes are the WHEL (Women's Healthy Eating and Living) and WINS (Women's Intervention Nutrition Study) studies (Table 1).

The WINS trial enrolled 2437 postmenopausal women between 48 and 79 years of age who were treated for early stage BC. They were randomized into a dietary intervention

Table 1 Observational studies and clinical trials assessing the association between diet and mortality and/or survival

Study Author Year	Patients	Follow-up (years)	Study design	Breast cancer specific mortality	All-cause mortality	Non-breast cancer mortality	Survival	Comments
Nurses' Health Study (NHS) Kroenke 2005	2619	9	Observational, Western diet vs. Prudent diet[a]	Prudent pattern $p = 0.57$ Western pattern $p = 0.87$	Prudent pattern $p = 0.25$ Western pattern $p = 0.13$	Prudent pattern $p = 0.03$ Western pattern $p = 0.03$	N/A	A higher intake of the prudent diet pattern and a lower intake of the Western pattern diet were associated with decreased mortality from non-breast cancer causes.
Life After Cancer Epidemiology (LACE) Study Kwan 2009	1901	5.93	Observational, Western diet vs. Prudent diet	Prudent pattern $p = 0.57$ Western pattern $p = 0.60$	Prudent pattern $p = 0.02$ Western pattern $p = 0.05$	Prudent pattern $p = 0.003$ Western pattern $p = 0.02$	N/A	A higher intake of the prudent diet pattern and a lower intake of the Western pattern diet were associated with decreased overall mortality and mortality from non-breast cancer causes.
Health, Eating, Activity, and Lifestyle (HEAL) Study George 2011	670	6	Observational, High-quality vs. poor-quality diet	HR 0.12 (95% CI 0.02–0.99)	HR 0.40 (95% CI 0.17–0.94)	N/A	N/A	A high-quality diet assessed by HEI score was associated with decreased risk of overall mortality and breast cancer–specific mortality when compared with a poor-quality diet.
The Third National Health and Nutrition Examination Survey (NHANES III) Deshmukh 2018	1191	17.2	Observational, High-quality vs. poor-quality diet	HR 0.35 (95%CI 0.19–0.63)	HR 0.59 (95%CI 0.45–0.77)	N/A	N/A	A high-quality diet assessed by HEI score was associated with decreased risk of overall mortality and breast cancer-specific mortality when compared with a poor-quality diet.
Women's Healthy Eating and Living (WHEL) Study Pierce 2007	3088	7.3	Prospective, randomized controlled trial, plant-based diet vs. usual diet	N/A	10.1% vs. 10.3% (intervention group vs. control group)	N/A	Disease-free survival: 16.7% vs. 16.9% with events, HR 0.96 (95% CI 0.80–1.14)	High vegetable/fruit and low-fat diet intervention did not lead to significant improvement in disease-free survival or overall mortality.
Women's Intervention Nutrition Study (WINS) Chlebowski 2006	2437	5	Prospective, randomized controlled trial, plant-based diet vs. usual diet	N/A	N/A	N/A	Relapse-free survival: 9.8% vs. 12.4% with events, HR 0.78 (95% CI 0.60–0.98, p = 0.03)	Low-fat diet intervention was associated with improved breast cancer relapse-free survival during the 5-year intervention period.
Women's Intervention Nutrition Study (WINS) Chlebowski 2008	2437	8.1	Prospective, Randomized controlled trial, Low-fat diet vs. usual diet	N/A	All: 9.1% vs. 11.1% (RR 0.83, $p = 0.146$); ER-/PR-subgroup: 7.5% vs. 18.1% (RR 0.41, $p = 0.003$)	N/A	N/A	Low-fat diet intervention was not shown to significantly decrease mortality in all participants during the 8-year follow-up, but may benefit women with ER-/PR- disease.
Cancer Prevention Study-II (CPS-II) McCullough	4452	9.9	Observational, diet score based on ACS recommendations	Post-diagnosis diet score of 6–9 compared with a score of 0–2: RR	N/A	Post-diagnosis diet score, per 2-point increase in score:	N/A	There was no association found between post-diagnosis diet score based on ACS recommendations and breast cancer–specific

Table 1 (continued)

Study Author Year	Patients	Follow-up (years)	Study design	Breast cancer specific mortality	All-cause mortality	Non-breast cancer mortality	Survival	Comments
2016				1.44 (95% CI 0.90–2.30)		RR 0.88 (95%CI 0.79 to 0.99)		mortality, but there was an inverse relationship with mortality from other causes.
Women's Health Initiative (WHI) Study Chlebowski 2017, 2018	48,835	16.1	Prospective, Randomized controlled trial, dietary intervention initiated before breast cancer diagnosis	HR 0.91 (95% CI 0.72–1.15)	HR 0.82 (95%CI 0.70–0.96)	N/A	10-year overall survival: 82% vs. 78%, HR 0.78 (95% CI 0.65–0.94)	Dietary intervention was associated with few deaths after breast cancer diagnosis and improved overall survival, probably mediated by non-breast cancer causes.

[a] Prudent dietary pattern was characterized by a diet high in fruits, vegetables, whole grains, legumes, poultry, and fish, and the Western pattern was characterized by high intake of refined grains, processed and red meats, desserts, high-fat dairy products, and French fries

(targeting fat intake reduction) or a usual-diet control group. Women in the intervention group were given a fat gram goal by centrally trained, registered dieticians and received eight biweekly individual counseling sessions and subsequent contacts every 3 months, while the control group received general dietary guidelines and dietician contacts every 3 months. After a median follow-up of 60 months, fat intake was significantly reduced in the intervention group (29.2–20.3% of calories, $p < 0.0001$), but not in the control group [19•]. Importantly, participants in the intervention group achieved a 2.7 kg lower mean body weight than the control group ($p = 0.005$) [19•]. Relapse-free survival, the primary endpoint, was significantly lower in the intervention group compared with the control group (9.8% vs. 12.4% with events, HR 0.78, 95% CI 0.60–0.98, $p = 0.03$) [19•]. Exploratory subgroup analysis by receptor status revealed a particularly favorable impact in women with hormone receptor-negative BC (HR 0.44, 95% CI 0.25–0.77), but not in women with hormone receptor-positive cancer. Although there were fewer deaths observed in the intervention group, the difference between the two groups was not statistically significant (9.1% vs. 11.1% cumulative mortality, RR 0.83, $p = 0.146$) [20].

The WHEL study used a slightly more comprehensive approach by targeting a diet high in vegetables, fruits, and fiber in addition to being low in fat. Three thousand eighty-eight women (2448 were postmenopausal at participation) were randomly assigned to the intervention or comparison group. Participants in the intervention group received telephone counseling from trained counselors, 12 cooking classes in the first year, and monthly newsletters throughout the study. Women in the comparison group were provided general guidelines on dietary intake, 4 optional cooking class in the first year (average attendance: 1 out of 4), and 24 newsletters during the first 4 years. After a mean of 7.3-year follow-up, there was no significant difference in invasive BC events (intervention vs. control 16.7% vs. 16.9%, HR 0.96, 95% CI 0.80–1.14, $p = 0.63$) or all-cause mortality (intervention vs. control 10.1% vs. 10.3%, HR 0.91, 95% CI 0.72–1.15, $p = 0.43$) [21•]. It is noteworthy, however, that women in the intervention arm of this study did not lose weight compared with the control arm, which is in contrast to the WINS study. A subsequent analysis focusing on women without baseline hot flashes (more likely to have higher circulating estradiol concentrations) was conducted and demonstrated a decrease in BC recurrence, predominantly distant recurrence (intervention vs. control 83.9% vs. 76.4% BC free, $p = 0.002$), regardless of hormone receptor status ($p = 0.63$) [22].

Although the conflicting results of these studies have made it difficult to translate dietary modification into practice, there are some fundamental differences between these two studies which may in part explain the contradictory results. [23] The WINS focused on a low-fat diet whereas the WHEL study adopted a plant-based diet including high vegetable, fruits,

and fiber in addition to the low-fat component. Decrease in dietary fat intake was less pronounced in the WHEL study than in WINS. There were also differences in study populations. WINS included only postmenopausal women 48–79 years old, while the WHEL study included both pre- and postmenopausal women 18–70 years old. WINS participants had more favorable prognosis compared with those in WHEL with more than 50% of patients having stage I disease while only one-third of patients in the WHEL had stage I disease. Furthermore, the WINS enrolled all participants within 1 year of diagnosis and the WHEL study enrolled patients up to 4 years post diagnosis. Finally, women in WINS study intervention arm lost weight (2.7 kg between-group difference at year 5), while there was no between-group difference in the WHEL study, suggesting weight loss may be necessary to improve prognosis.

Importantly, both studies relied on self-reported dietary assessment. The survey completion rate in the WINS declined with time (~ 70% at year 3 and ~ 40% at year 5), while the completion rate in the WHEL study only experienced a small decline, about 85% at year 6. The authors of both studies reported a completers-only analysis in terms of dietary data, BC free survival, and mortality. This assumed that diets of the non-responders were similar to the diets of the responders, which may lead to selection bias; however, in WINS, there was an improvement in relapse-free survival in this analysis (9.8% vs. 12.4% with events, HR 0.78, 95% CI 0.60–0.98, $p = 0.03$) [19•].

Most recently, a secondary post-hoc analysis of WHI-DM was published, which focused on overall survival and mortality in postmenopausal women who developed BC during the low-fat dietary intervention. After an average of 11.5 years' follow-up, overall survival was improved in women in the intervention group than in the usual-diet comparison group (10-year survival of 82% and 78%, respectively; HR 0.78, 95%CI 0.65–0.94; $p = 0.01$) [24••] (Table 1). Although there were fewer deaths from BC, other cancers, cardiovascular disease, and other causes in the dietary intervention group than the control group, only deaths from cardiovascular disease were statistically different between the two groups (HR 0.62, 95% CI 0.39–0.99). This study highlighted that a low-fat diet may reduce cardiovascular deaths in women diagnosed with BC, which is a major source of mortality for this population [25, 26].

Additional dietary patterns have been investigated. For example, the prudent diet (as characterized by a diet high in fruits, vegetables, whole grains, legumes, poultry, and fish) and the Western pattern (as characterized by high intake of refined grains, processed and red meats, desserts, high-fat dairy products, and French fries) were analyzed in the NHS (Nurses' Health Study) and LACE (Life After Cancer Epidemiology) trials [27, 28] (Table 1). The NHS demonstrated an inverse relation between the prudent diet and non-BC mortality (relative risks of non-BC death were 0.85 [95% CI, 0.53 to 1.35], 0.74 [95% CI, 0.45 to 1.21], 0.70 [95% CI, 0.42 to 1.17], and 0.54 [95% CI, 0.31 to 0.95]; $p = 0.03$, from lowest to highest quintile of intake of prudent diet). Likewise, LACE confirmed an inverse association between the prudent diet and non-BC mortality. In addition, adhering to a prudent dietary pattern was shown to correlate with all-cause mortality (p trend 0.02; HR for highest quartile 0.57; 95% CI, 0.36 to 0.90).

Diet Quality and Inflammation

Recent studies and guidelines have emphasized the quality of "total diet," most often assessed by the Healthy Eating Index (HEI). The HEI score is calculated based on a variety of food components according to recommendations of the Dietary Guidelines for Americas, with higher HEI scores correlating with better-quality diet. The Health, Eating, Activity, and Lifestyle (HEAL) Study demonstrated that women who consumed better-quality diets (as defined by the highest-quartile HEI-2005 score) had a 60% reduction in all-cause mortality compared with those who consumed mixed-quality diet (middle quartiles HEI-2005 score) or poor-quality diet (lowest quartile HEI-2005 score) (HR 0.40, 95% CI 0.17–0.94), and an 88% reduction in BC related mortality (HR 0.12, 95% CI 0.02–0.99) [29]. The NHANES (National Health and Nutrition Examination Survey) III study showed similar results with a 41% reduction in overall mortality (HR 0.59, 95% CI 0.45–0.77) and a 65% reduction in all cancer-related mortality (HR 0.35, 95% CI 0.19–0.63) in women with high-quality diets (highest-quartile HEI score) [30••] (Table 1). Another diet score was developed based on the ACS (American Cancer Society) recommendations, which was used in the Cancer Prevention Study-II (CPS-II) Nutrition Cohort [31]. The score was derived from summing three key food-based recommendations (fruits/vegetables, whole grains, and limited consumption of red and processed meats). The score ranges from 0 to 9, with a score of 9 reflecting the optimal adherence to the ACS guidelines. There was no association between post-diagnosis diet score with either BC-specific mortality (scores 6–9 vs. 0–2 RR 1.44, 95% CI 0.90–2.30) or cardiovascular disease mortality (scores 6–9 vs. 0–2 RR 0.81, 95% CI 0.47–1.39), but a higher score was associated with a borderline lower risk of other causes of death (scores 6–9 vs. 0–2 RR 0.78, 95% CI 0.56–1.07; continuous diet score RR 0.88, 95% CI 0.79–0.99, p trend = 0.03) [31] (Table 1). These studies demonstrate the need for further research on the "total diet" approach.

Interestingly, dietary quality is inversely associated with inflammatory potential of diet and high-quality diets have lower dietary inflammatory index (DII) scores [32]. The association between baseline dietary inflammatory potential and BC mortality was evaluated in the WHI. A total of

122,788 postmenopausal women with a mean of 16-year follow-up completed a baseline food frequency questionnaire, among which, 7495 developed BC and 667 died of BC[33]. DII was calculated based on a comprehensive literature review on the association between dietary factors and six inflammatory markers (IL-1β, IL-4, IL-6, IL-10, TNFα, and C-reactive protein [CRP]). Higher DII scores signify a more inflammatory diet and lower scores indicate a less inflammatory diet. Although there was no significant association between baseline DII scores with BC incidence, a higher risk of death from BC was noted in those with the highest vs. lowest DII scores (HR 1.33 95% CI 1.01–1.76 $p = 0.03$) [33]. A second analysis of the WHI evaluated the association between post-cancer diagnosis DII and mortality. A total of 2150 postmenopausal women were included in the study. Energy-adjusted DII (E-DII) scores were inversely associated with cardiovascular mortality (HR Q1VSQ4 0.44; 95% CI 0.24–0.82; p trend 0.005), but no association was found between E-CII scores and BC-specific mortality (HR Q1VSQ4 0.96; 95% CI 0.62–1.49; p trend 0.96) or all-cause mortality (HR Q1VSQ4 0.82; 95% CI 0.63–1.05; p trend 0.17) [34].

Post-diagnosis CRP, one of the six inflammation markers used in DII, was examined separately in an analysis of the WHEL study [35]. CRP was measured by high-sensitivity electrochemiluminescence assay and had a positive association with death due to any cause, death due to BC, and additional BC events. CRP, an acute phase protein in response to inflammation, thus may have potential as a prognostic biomarker for BC survival, modifiable by improving diet quality and adopting other healthy lifestyle modifications.

Prolonged Nightly Fasting

Another novel dietary intervention approach is to prolong the nightly fasting interval. Although patients enrolled in the WHEL study were randomized, the two cohorts were combined for the analysis of the effects of prolonged nightly fasting. A total of 2413 women reported a mean fasting duration of 12.5 h per night. Nightly fasting interval less than 13 h per night was associated with a 36% increase in BC recurrence compared with those reported nightly fasting interval more than 13 h. During a mean of 11.4 years of follow-up, there was no significant difference in BC mortality or all-cause mortality based on fasting interval [36].

Dietary Modification and Weight Loss

Two-thirds of BC survivors are overweight or obese at the time of diagnosis [37]. There is increasing evidence indicating that being overweight/obese increases the risk of BC recurrence and decreases survival [38–42]. Although it is currently unknown whether intentional weight loss will improve prognosis, there are some data supporting this hypothesis and a clinical trial to answer this question is ongoing [43]. Frequently, dietary intervention will result in weight loss, making it difficult to separate the effects of dietary change from those from weight loss. In the WHI-DM trial, body weight was 2.2 kg lower in the dietary group compared with the usual-diet control group ($p < 0.001$) [24••]. Similarly, participants in the WINS lost an average of 2.7 kg more weight in the intervention vs. control group [19•]. The LEAN (Lifestyle, Exercise and Nutrition) study randomized BC survivors to either a usual care or lifestyle intervention (by either in-person or telephone-based counseling on healthy diet, physical activity, targeting weight loss) [44]. The intervention led to a successful decrease in total fat/saturated fat intake and an increase in fiber and fruit intake. Participants in the intervention group who lost ≥ 5% body weight demonstrated a significant improvement in their HEI score compared with those who did not lose ≥ 5% body weight [44]. This, like the conflicting results of the WINS and WHEL studies, raises the question of whether the impact of dietary modification may be partially or entirely mediated by weight loss and whether outcomes can be affected by dietary modification without significant weight loss.

Ultimately, there is no conclusive evidence to support any one specific dietary pattern in BC survivors. The WINS study demonstrated an improved relapse-free survival in women on low-fat diet intervention, but this has not been confirmed by other large studies. Novel dietary interventions further evaluating fasting intervals, dietary inflammation, and overall quality are needed.

Clinical Trials and Future Research

Further investigation of the effects of dietary patterns and components on BC prognosis is needed to refine dietary recommendations for cancer survivors. There are dozens of active trials (clinicaltrials.gov) on dietary intervention either alone or combined with other behavioral therapies. These studies evaluate different dietary patterns (such as Mediterranean diet), compositions (such as low-carbohydrate diet), energy restrictions (such as low-calorie diet), supplements (such as fish oil), and include biomarker identification and analysis. Among these, the SUCCESS C trial uses a telephone-based lifestyle intervention to have patients adopt a hypocaloric diet with less fat, more whole grain products, and fruit and vegetables with a goal to lose weight, as well as a gradual increase in physical activity. Interim analysis reported at the 2018 San Antonio Breast Cancer Symposium demonstrated promising results for those who lost weight. At the end of the 2-year follow-up period, patients in the intervention group lost an average of 1.0 kg and those in the control

arm gained an average of 0.95 kg. Interestingly, those who completed the lifestyle intervention program had improved disease-free survival compared with those who completed a general program in the control arm (events 5.1% vs. 8.8% , HR 0.51, 95% CI 0.33–0.78, $p = 0.002$) [45].

One challenge we face is the lack of biomarkers to evaluate patients' adherence to dietary interventions and to predict long-term outcomes. Nutritional biomarkers may provide complementary information beyond self-reported food intake data. In the field of metabolic syndrome, dietary biomarkers (DB) including pentadecanoic acid /α-linolenic acid (markers for total fatty acid), EPA/DHA (markers for fatty fish), β-carotene, and alkylresorcinol (markers for vegetables and whole grains) were combined to create a DB score to assess dietary compliance [46]. This same study found that median DB score was 57% higher in the healthy Nordic diet group than the control diet group, suggesting this and/or other dietary biomarkers may be a useful tool to assess compliance in diet intervention studies.

Of equal importance is the need for prognostic biomarkers. Prognostic biomarkers would allow for shorter and more diverse studies (thus allowing for evaluation of a larger number of dietary interventions) to be conducted with biomarker endpoints. Such studies could then inform the design of larger clinical trials with traditional BC outcomes such as risk of recurrence and death. Post-diagnosis high-sensitivity CRP, as mentioned above, may serve as one such potential biomarker, but this requires validation. Obesity-related markers have also been investigated. In a nested case-control study using Cancer Prevention Study-II (CPS-II) Nutrition Cohort, low level of adiponectin and high levels of IGF-1, CRP, and C-peptide have been linked with postmenopausal BC risk, but only the association between C-peptide and BC risk was statistically significant (OR 1.63, 95% CI 0.08–2.45, p linear trend 0.001) [47]. In the HEAL study, fasting C-peptide in patients without type II diabetes was associated with increased all-cause mortality and BC-specific mortality. In patients with type II diabetes, the association between C-peptide levels and BC-specific mortality was stronger [48]. Another prospective cohort study including 512 women with early stage BC observed positive associations between fasting insulin levels and BC outcomes (distant recurrence HR for highest vs. lowest quartile 2.0, 95% CI, 1.2–3.3; all-cause mortality HR for highest vs. lowest quartile 3.1, 95% CI 1.7–5.7) [49]. Additional research is necessary to validate these inflammatory and obesity-related markers and to identify novel prognostic lifestyle linked biomarkers.

Current Guidelines

The American Institute for Cancer Research (AICR) publishes comprehensive guidelines for the prevention of cancer, yet guidelines for cancer survivors remain relatively vague. The AICR acknowledges the WINS and WHEL studies, but finds it difficult to translate these results into recommendations for BC survivors given the discrepancies in results and potential confounding factor of weight loss. With respect to micronutrient supplements, the AICR guidelines do not support their use as a means of improving outcome in cancer survivors, based on data from 39 randomized controlled trials [50].

The ACS also publishes guidelines on nutrition and physical activity in cancer survivors, with an emphasis on achieving and maintaining a healthy diet and weight [51]. The ACS guidelines stress the importance of eating a diet high in vegetables, fruits, and whole grains. Similar to the AICR guidelines, ACS states that dietary supplements are unlikely to improve prognosis or overall survival in cancer

Table 2 Resources for dietary intake and weight management in breast cancer survivors

Organization	Tool	Website
AICR	portion control	http://www.aicr.org/new-american-plate/reduce_diet_new_american_plate_portion.html
ACS	healthy recipes	https://www.cancer.org/healthy/eat-healthy-get-active/eat-healthy/find-healthy-recipes/main-dishes.html
USDA	food plate volumes	https://www.choosemyplate.gov/
CDC	BMI calculator	https://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/english_bmi_calculator/bmi_calculator.html
ASCO	toolkit on obesity and cancer	https://www.asco.org/practice-guidelines/cancer-care-initiatives/prevention-survivorship/obesity-cancer
LIVESTRONG	My Plate Calorie Tracker	https://www.livestrong.com/myplate/

AICR, American Institute for Cancer Research; *ACS*, American Cancer Society; *USDA*, United States Department of Agriculture; *CDC*, Centers for Disease Control and Prevention; *ASCO*, American Society of Clinical Oncology

survivors and importantly, some supplements may cause harm. With regard to diet composition, the ACS adopts both the Institute of Medicine and current Federal Guidelines, and the American Heart Association (AHA) guidelines that the spectrum of dietary composition for an adult cancer survivor should include fat 20 to 35% of energy (AHA 25–35%), carbohydrate 45 to 65% of energy (AHA 50–60%), and protein 10 to 35% of energy (at least 0.8 g/kg). Choices of food sources are also important. For example, healthy carbohydrate sources are foods like vegetables, fruits, whole grains, and legumes. A list of resources on nutrition and weight management is summarized in Table 2.

The National Comprehensive Cancer Network (NCCN) Survivorship guidelines (version 2.2018) address nutrition and weight management as well. The guidelines emphasize dietary patterns as well as eating habits including portion size, night grazing, snacking habits, and use of added fats and/or sugars to foods and beverages. Supplement use is again not recommended by NCCN, except in women with documented deficiencies, inadequate diet, or comorbid conditions, such as osteoporosis.

Conclusions

It is currently unknown whether weight loss is required to improve prognosis, as suggested by the conflicting results of WINS and WHEL, and the WHI-DM and LEAN studies, or whether specific diets alone may have an impact. Healthy diet and weight management should be encouraged for all BC survivors as it may decrease mortality from other causes, especially cardiovascular disease, a significant concern for BC survivors. In addition to dietary patterns and weight loss, dietary quality has been an emerging research topic. The HEAL and NHANES III studies substantiated the need for further research on "total diet" approach, perhaps a more feasible approach than specific diet patterns, in BC survivors. Identification of novel lifestyle linked prognostic biomarkers would allow us to design more versatile yet efficient studies to better define the role of dietary intervention in BC survivors and ultimately provide more personalized dietary recommendations for cancer survivors.

Compliance with Ethical Standards

Conflict of Interest Lai Xu declares that she has no conflict of interest.

Lindsay L. Peterson has received compensation from the American Cancer Society for participation as a member of its external review board.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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