

# Diet and Prognosis in Women with Breast Cancer

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## ABSTRACT

Women who have obesity or who have metabolic abnormalities, including diabetes, prediabetes, or hyperglycemia/insulinemia, have poorer survival compared with other women with breast cancer. Data are lacking on specific lifestyle modifications to prevent or treat these conditions to improve women's chances of survival from breast cancer. The Nurses' Health Study cohorts provide new evidence that diets with the potential to elevate circulating insulin or glucose are associated with breast cancer prognosis. The researchers found statistically significant evidence that women in the highest quintile of glycemic load had a 31% higher risk of breast cancer-specific mortality and a 26% higher risk of all-cause mortality. While a randomized controlled clinical trial testing

if a reduced glycemic load diet reduces recurrence or death would be optimal, evidence from this observational study suggests that diet matters in survival from breast cancer. The dietary guidelines provided by the World Cancer Research Fund/American Institute for Cancer Research, the American Cancer Society, and the American Society for Clinical Oncology, which collectively emphasize increased intake of vegetables, fruits, whole grains, and legumes, and reduced intake of sugar, calorie-dense foods, and sugary drinks, are reasonable for most breast cancer survivors to follow for optimal health.

See related article by Farvid et al., p. 335

Worldwide, over two million women are diagnosed with breast cancer each year (1). While survival from this disease depends largely on tumor characteristics, stage of diagnosis, and treatments received, increasing evidence indicates that host factors are critical to breast cancer prognosis (2, 3). Women who have obesity, are insufficiently physically active, or who have metabolic abnormalities including diabetes, prediabetes, or hyperglycemia/insulinemia have poorer survival compared with other women with breast cancer (2, 4, 5). Clinical trials are underway to test medical treatments of these conditions on breast cancer survival, such as metformin (6), but data are lacking on what women can do themselves to improve their chances of survival. One intriguing avenue is diet and nutrition. Women and their clinicians want to know what women with breast cancer should eat, or not eat, to improve their prognosis. The World Cancer Research Fund/American Institute for Cancer Research, the American Cancer Society, and the American Society for Clinical Oncology provide guidelines for nutrition advice for breast cancer survivors, namely to follow a diet high in vegetables, fruits, whole grains and legumes, low in saturated fats, and with limited alcohol intake (7, 8). They do not, however, provide specific guidance on other dietary components or patterns.

Decades of clinical and basic research studies show that carbohydrate intake influences circulating insulin and glucose (9). Moreover, the quality and amount of carbohydrate affect production of glucose and insulin, and indices of dietary intake have shown associations with risk for breast cancer incidence (10), as well as for diabetes, cardiovascular disease, stroke, and mortality (9, 11). Several indices of carbohydrate intake have been developed that depend on individually

reported diets, including glycemic load, glycemic index, insulin load, and insulin index (12, 13). Whether such indices of dietary intake can predict breast cancer prognosis is unknown.

In the article that accompanies this commentary, Farvid and colleagues present data from the Nurses' Health Study on the association between several indices of carbohydrate intake as measured through food frequency questionnaires completed after women had developed breast cancer (13).

Using data from the Nurses' Health Study cohorts, the authors identified 8936 women with incident invasive breast cancer (stages I–III) and followed them for a mean 11.5 years for breast cancer-specific and all-cause mortality. They determined cumulative dietary factors from food frequency questionnaires that were administered every 4 years after diagnosis. A total of 2,523 women died during the follow-up period, of whom 1,701 died from breast cancer. The researchers found that women in the highest quintile of glycemic load had a 31% higher risk of breast cancer-specific mortality and a 26% higher risk of all-cause mortality. Both estimates were statistically significant. Similar statistically significant elevations in risk of all-cause mortality were seen for women in the highest quintiles of glycemic index, insulin index, and insulin load. The findings did not vary to a large degree by hormone receptor status of the women's breast cancers, nor by presence or absence of obesity. There was some variability in effect of glycemic index or load by menopausal status, with greater association of glycemic index in breast cancer specific mortality in postmenopausal women and greater associations of glycemic load in breast cancer specific mortality in premenopausal women.

This study was well-designed and executed, and provides new evidence that specific dietary macronutrients are associated with breast cancer prognosis. This analysis of the Nurses' Health Study included large numbers of cases of breast cancer and deaths, giving the study strong power to detect statistically significant associations in the range typically seen in dietary studies and cancer. The cohorts had relatively long follow-up, which is critical given the long-term survival seen in most survivors, as well as the risk of recurrence and breast cancer death that can occur decades after initial diagnosis. Importantly, the study estimated dietary indices from a number of food frequency questionnaires, which can reduce measurement error. The study also adjusted for multiple possible confounding factors, including categories of treatments received, tumor characteristics, stage of disease, and various diet and physical activity variables.

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Several issues were not addressed in the study. Almost all of the women were non-Hispanic White, and therefore the results cannot be assumed to pertain across races and ethnicities. Residual confounding from disease progression and specifics of received treatment could be present, and could account for some of the observed associations. Definitive data on the effects of a high or low glycemic or insulin index/load diet would need to be confirmed in a well-powered randomized clinical trial. However, because most trials focused on specific dietary patterns are unlikely to be large enough or of long-enough duration to determine survival effects, the best available data may be from a combination of observational data such as this study and results of small clinical trials testing diet effects on biomarkers such as insulin and glucose. Controlled feeding studies have demonstrated that reduced glycemic load diets decrease postprandial insulin and glucose, and trials show that weight-loss reduced-calorie diets reduce insulin resistance (14, 15).

This is not the first foray of the Nurses' Health Study cohorts into looking at dietary indices and risk of breast cancer mortality. In 2013, an analysis examined the association between the Dietary Approaches to Stop Hypertension (DASH) score, and the Alternative Healthy Eating Index (AHEI)-2010, and the risk of breast cancer mortality and total mortality (16). The authors found that adherence to DASH-style and AHEI-2010 diets were statistically significantly associated with reduced risk of non-breast cancer mortality, but not with breast cancer-specific mortality. A 2005 analysis found that higher consumption of a "prudent" diet and lower consumption of a "Western" diet were associated with improved survival in women with breast cancer (17). These earlier studies had smaller numbers of cases, shorter follow-up periods, and used diet data from only one or two food frequency questionnaires.

Completed and ongoing randomized controlled clinical trials have tested the effects of other dietary patterns on breast cancer prognosis, namely low-fat dietary patterns, a Mediterranean diet, and reduced-calorie weight loss interventions (18). In the Women's Intervention Nutrition Study (WINS) low-fat diet trial in 2,437 women with early-stage breast cancer, recurrence-free survival was higher in women randomized to a low-fat diet versus control (19). In another similar trial, a low-fat diet had no such effect (20). In a trial stopped early, a reduced-calorie, low-fat diet plus exercise weight loss program improved disease-free survival by 29% compared with no diet/exercise change in 338 women with early-stage breast cancer treated with letrozole, but the results were not statistically significant (21).

Several dietary intervention trials in breast cancer survivors are ongoing. The DIANA-5 study is testing the effect of a 5-year Mediterranean-macrobiotic diet that includes moderate calorie restriction, reduced energy density and glycemic index, reduced non-fish animal protein and increased physical activity versus control on breast cancer recurrence in 1,208 women with stage I–III breast cancer and high risk of recurrence (22). The SUCCESS-C trial will test

the effects of a diet intervention on 2,292 women with node positive or high-risk node negative breast cancer on disease-free survival (23). The intervention includes a 2-year reduced calorie, low-fat, increased fruit and vegetable diet, and increased physical activity. Interim results found no difference between intervention and control on disease-free survival, although subgroup analyses of adherent women showed significant improvements in disease-free survival (24). The B-AHEAD3 trial is testing the effect of a 1-year reduced calorie/increased physical activity intervention versus control in 134 women with advanced breast cancer (25). The PREDICOP trial will test the effect of a reduced calorie/increased physical activity intervention versus control on breast cancer recurrence and survival in 2,108 women with stage I–IIIa breast cancer with 5-year follow-up (18). Results are expected in 2022. The BWEL trial is randomizing 3136 women with stage II–III breast cancer to a 2-year reduced calorie/increased physical activity intervention or control (26). The primary endpoint is invasive disease-free survival over a planned 10-year follow-up. Estimated study completion is 2030. One trial in Italy is testing the effect of a low-glycemic Mediterranean diet plus exercise plus vitamin D versus control in 506 breast cancer patients on breast cancer recurrence (27).

A conundrum in dietary studies is that change in one macronutrient usually results in changes in others. Thus, persons following a lower glycemic load diet may have a higher intake of protein, for example, than persons with a high glycemic load diet. While the Farvid and colleagues study adjusted for other dietary variables, it may not be possible to fully adjust if there is a high correlation among dietary variables.

Still the evidence from this observational study as well as human intervention trials suggest that diet matters in survival from breast cancer. For women and clinicians searching for answers, the dietary guidelines provided by the World Cancer Research Fund/American Institute for Cancer Research, the American Cancer Society, and the American Society for Clinical Oncology, which collectively emphasize increased intake of vegetables, fruits, whole grains, and legumes, and reduced intake of sugar, calorie-dense foods, and sugary drinks are reasonable for most breast cancer survivors to follow for optimal health (7, 8).

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