

Editorial

The Long and Winding Road of Diet and Breast Cancer Prevention

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The question of whether lifestyle factors, such as diet, physical activity, and energy balance, can prevent or delay breast cancer recurrence or progression in women with a previous breast cancer diagnosis is an important one. A breast cancer diagnosis is often a strong motivator for women to make lifestyle modifications such as beginning an exercise program or adding more fruits and vegetables to their diet (1, 2). In 2003, the American Cancer Society convened an expert panel and published a comprehensive guide to nutrition and physical activity after cancer treatment for health care providers and cancer patients. The report offers specific dietary advice to cancer patients, which is quite similar to the U.S. Dietary Guidelines, including recommendations to eat five servings of fruit and vegetables per day, choose whole grains, limit alcohol, and engage in 30 minutes of daily physical activity (3). In addition to the standard dietary recommendations suggested by the Panel, many breast cancer patients follow "alternative" diets or use high-dose dietary supplements without clear evidence of their safety or efficacy. However, other than the growing evidence that obesity and weight gain may lead to poor prognosis in breast cancer patients (4-6), the report graded most of the published evidence on dietary factors and prevention of breast cancer recurrence or breast cancer-related mortality as "insufficient" (3). Clearly, there is still much to be learned about the role of dietary factors and disease-free survival following a breast cancer diagnosis.

In this issue of *Cancer Epidemiology, Biomarkers & Prevention*, Pierce et al. (7) report findings from the Women's Healthy Eating and Living (WHEL) Study, an investigation that may help provide responses to some of the unanswered questions on the efficacy of dietary modification for prevention of breast cancer recurrence. The overall goal of this randomized trial is to test whether a low-fat, plant-based diet will reduce the risk of subsequent breast cancer events and breast cancer-related mortality among women with a previous diagnosis of stage I to IIIA breast cancer. Women in the WHEL intervention group are counseled to consume nine servings of vegetables per day, three fruit servings, 30 g of fiber, and <20% energy from fat. The comparison group is offered the standard U.S. Dietary Guidelines to consume five servings of fruits and vegetables per day but receives no explicit advice on fat or fiber intake. Here, the authors report baseline to 12-month changes in serum carotenoid concentrations among women in both arms of the study. After 12 months, women in the intervention group had a notable 51% statistically significant increase in total serum carotenoid concentrations and an upward shift in the distributions of individual carotenoids. There were no such observable changes for women in the comparison group.

One of the conclusions drawn by Pierce et al. from these results is that an intervention which "minimizes the proportion of women below the cut point for the lowest baseline quartile of

carotenoid concentrations and maximizes those above the cut point for the highest quartile could reduce additional breast cancer events." The authors base this conclusion on a nested case-control study showing that the relative differences between the cases and controls with regard to serum carotenoid concentrations ranged from 11% to 21% (8), and that the larger relative increases in the WHEL study (51%) should be able to detect similar or stronger effects. However, it is important to note that the Toniolo study examined breast cancer incidence and not recurrence. It is unknown whether the same apparent protective mechanisms may be applied to prevention of recurrence or mortality and whether elevated carotenoids mean the same in observational and intervention studies.

The WHEL investigators have already published results on plasma carotenoids and recurrence-free survival in the comparison group (9). Among women in the comparison arm, there were 205 cases of a breast cancer recurrence or a second primary breast cancer. After a median follow-up time of 7 years, women in the top quartile of baseline total plasma carotenoids had a 43% reduced risk of an additional breast cancer event (hazard ratio, 0.57; 95% confidence interval, 0.37-0.88) compared with women in the lowest quartile of baseline plasma carotenoids. Of particular interest is that the mean value for the top quartile in these comparison group results was 4.19 $\mu\text{mol/L}$, which is about 22% higher than the mean concentration in the intervention group results presented here. We do not know how the top quartile in the intervention group compares with this previously published value from the comparison group; we are informed only of the upward shift for all carotenoids except β -cryptoxanthin (7) and are not provided with cut point values. Without further information, it is hard to fully evaluate the effect of the intervention, but we would hope that the mean of the top quartile of the intervention group is substantially larger than 4.19 $\mu\text{mol/L}$ in the comparison group (9). Nonetheless, the results presented in this report suggest that if the large intervention-versus-comparison group differences in mean circulating carotenoid concentrations is maintained over the course of the WHEL study, the investigators should be well poised to test the primary study aims. This assumes, of course, that the follow-up time in the WHEL study is sufficient to gather additional breast cancer outcomes, that drop-in and drop-out rates remain as they were 12 months post-baseline, and that the low-fat, plant-based diet is biologically effective.

The WHEL study is scheduled to conclude in 2007. In the meantime, we can wrestle with the fact that diet and disease-free survival in breast cancer patients is a complex issue. Although Pierce et al. may have sufficient power to test whether carotenoids may be effective preventive compounds in early-stage breast cancer patients, it is unclear whether any subgroup analyses will be possible. The initial design of the study was based on disease stage but not on tumor characteristics. There may be differential responses to a dietary intervention based on hormone receptor status (10). Indeed, the recent results from the Women's Health Initiative Dietary Modification Trial reported differential effects of the low-fat eating pattern by tumor hormone receptor status: the hazard

ratio for progesterone receptor–negative breast cancers was 0.76 (95% confidence interval, 0.63–0.92; $P < 0.004$; ref. 10). Although the Women’s Health Initiative tested breast cancer incidence and not recurrence, preliminary results from another dietary intervention trial in breast cancer survivors also reported differential effects of the intervention by hormone receptor status (11). These are important considerations in evaluating any intervention for breast cancer recurrence or progression. Despite the fact that pharmacologic therapies, such as tamoxifen and raloxifene, are very effective at reducing the risk of subsequent breast cancer outcomes for women with estrogen receptor–positive (ER+) tumors (12), the effectiveness of these drugs for women with estrogen receptor– (ER–) or progesterone receptor–negative (ER–) tumors is less clear. Women with hormone receptor–negative tumors continue to remain at high risk of a poor outcome. Whether a low-fat, plant-based diet can reduce the risk of breast cancer recurrence or progression in women with estrogen receptor– (ER–) or progesterone receptor–negative (PR–) tumors or the extent to which such an intervention may have an additive or no effect for women with estrogen receptor–positive (ER+) tumors using either tamoxifen or raloxifene are important questions that deserve further scrutiny in existing breast cancer survivor cohorts (13–15). Such approaches will help tailor individual therapies for optimal breast cancer outcomes.

The popular press and the Internet abound with dietary and other lifestyle advice for women to improve their chances for disease-free survival after a breast cancer diagnosis. Because much of the advice is untested, the WHEL study and other studies in progress (7, 13–15) provide extremely important opportunities to support, or lay to rest, the role of lifestyle interventions in maximizing disease-free survival among breast cancer patients. We look forward to these results with the hope that the long and winding road of diet and breast cancer prevention may lead to the door of improved health for all breast cancer patients.

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