Dietary Intervention Trial Reports No Effect on Survival After Breast Cancer

By Nancy Nelson

Most of the 2.4 million breast cancer survivors are highly motivated to make healthy changes to their diets to improve their chances of survival, studies have shown. This willingness makes them an eager audience for the results of the Woman’s Healthy Eating and Living (WHEL) trial, a phase III dietary intervention trial involving breast cancer survivors.

The WHEL investigators examined whether eating less fat and more vegetables, fruits, and fiber could improve survival among women diagnosed with early-stage breast cancer. The answer, published in the *Journal of the American Medical Association* last July, was a resounding no.

On the surface, these results contradict those of several hundred dietary prevention studies, although only a few of these involved breast cancer survivors. A closer look, however, reveals a more complex picture, which makes researchers hesitant to discount dietary recommendations altogether. Instead, they are trying to understand the interplay of several factors—including diet, weight, and physical activity—that may affect breast cancer recurrence.

“It doesn’t mean that a healthy diet doesn’t matter,” said the study’s lead author, John Pierce, Ph.D., of the cancer prevention and control program at the University of California in San Diego. “It means that a healthy diet in moderation probably matters, but there’s no evidence that going above a certain threshold is beneficial.”

Of the 3,088 women recruited for the study, the half in the control group were asked to follow the government-recommended daily 5-A-Day diet, which entails eating five servings of vegetables and fruit, more than 20 g of fiber, and less than 30% of calories from fat. In contrast, researchers encouraged the women in the intervention group to consume five vegetable servings and 16 ounces of vegetable juice, three servings of fruit, and 30 g of fiber, as well as to reduce their fat intake to 15%–20%. The women were enrolled between 1995 and 2000 and followed up through June 1, 2007.

At the end of 4 years, the intervention group was eating 65% more vegetables, 25% more fruit, 30% more fiber, and 13% less fat than women in the control group. Although good eating habits began to decline by the end of the trial, the differences in consumption between the two groups remained statistically significant throughout. Despite these differences, breast cancer recurrence and death rates during the follow-up period were practically identical in the two groups: 16.7% in the intervention group and 16.9% in the comparison group developed breast cancer, and 10.1% in the intervention group and 10.3% in the comparison group died.

Most experts seem to agree on their interpretation of the results. Wendy Demark-Wahnefried, Ph.D., professor of behavioral science at the University of Texas M. D. Anderson Cancer Center in Houston, pointed out that the women were already on a healthful diet when they enrolled in the trial, eating on average 7.3 servings of fruits and vegetables and getting 29% of their calories from fat. This situation contrasts sharply with that of most American women, who eat fewer than five servings of fruits and vegetables per day and about 33% of their calories are from fat, according to the Centers for Disease Control and Prevention. “So, going on a superdiet when you are already eating more fruits and vegetables than the average American to begin with may not do too much good. That’s one of the major messages,” she said.

Cheryl Rock, Ph.D., another WHEL investigator and Pierce’s colleague at UCSD, believes that diet may matter a lot for some women. “It may be that dietary changes would benefit women eating below the current level of recommendations. But our study couldn’t measure that because..."
most women entering the trial were already eating well.”

**Previous Studies**

WHEL is the second randomized dietary intervention trial to look at breast cancer recurrence or survival. The first was the Women’s Intervention Nutrition Study (WINS), in which investigators found—in contrast to WHEL—that reducing dietary fat intake prolonged survival of women with early-stage breast cancer (J Natl Cancer Inst 2006;98:1767–76). After 5 years of follow-up, 9.8% of women in the dietary group, compared with 12.4% in the control group, suffered a relapse. Surprisingly, the benefits appeared to occur in women with estrogen receptor–negative tumors but not in those with estrogen receptor–positive tumors.

Various theories have been proposed to explain the difference in the two trials. According to Susan M. Gapstur, Ph.D., of the department of preventive medicine at Northwestern University in Chicago, either lower dietary fat or lower weight could account for the survival benefits in WINS. Women in the WINS intervention group reduced their intake of calories from fat more than the WHEL group. Consequently, there was a 6-pound difference in weight between the intervention and control groups in the WINS trial at 5 years, whereas no statistically significant weight difference between the groups appeared at any point in the WHEL trial.

Rowan Chlebowski, M.D., Ph.D., the lead author in the WINS study, pointed out that there were also differences between the trials’ participants that make comparisons difficult. For example, the WINS trial included only postmenopausal women, whereas the WHEL trial included both pre- and postmenopausal women. Participants in the WHEL trial were also enrolled up to 4 years after their cancer diagnosis, compared with only 1 year for WINS participants.

Previous observational studies investigating the effects of diet on breast cancer survival or recurrence have been limited to 18 prospective reports, Rock said. In the 10 studies that examined vegetables, fruit, or nutrients such as beta-carotene or vitamin C, seven found that fruits and, in particular, vegetables are associated with a lower risk of breast cancer recurrence, Rock said. Reports on the effect of dietary fat on breast cancer recurrence, however, have been inconsistent. Nearly as many studies have found no relationship between fat intake and survival or recurrence in women diagnosed with breast cancer as those that did find an association. No statistically significant associations between fiber and survival after breast cancer have been found, she said.

**Next Steps**

Suggestions for follow-up studies are varied. Pierce wants to study the role of both exercise and diet in certain high-risk women. By analyzing the lifestyle habits of the 1,490 survivors in the WHEL control group, he found that women who followed both diet and exercise recommendations—five or more servings of fruits and vegetables and 30 minutes of moderate-paced walking 6 days per week—had lower recurrence and better survival rates. Also, his team and others have identified a subgroup of women who do not experience hot flashes when treated with either tamoxifen or aromatase inhibitors and have a 50% greater risk of cancer recurrence and death than those who experience hot flashes.

“Does exercise or diet have impact on the risk of breast cancer recurrence?” Rock asked.

“The question is, what can we do for these women,” he said. “Can exercise and diet improve prognosis? We think there may be a significant role for both behaviors in this high-risk group of women.”

Rock is content to analyze the data they already have. “We don’t necessarily need to do another study, but more analysis of the results of the WHEL study would be useful,” she said. Rock has identified another subgroup of women at high risk of recurrence—those with lower levels of blood carotenoids, indicators of vegetable and fruit consumption. “It will be important to find out if their risk can be lowered by diet or other lifestyle factors,” she said.

She and her colleagues also plan to use tumor tissue from WHEL participants to identify particular genetic alterations that put women at greater risk of recurrence. The genetic differences may dictate which interventions are most effective. “We’re pretty crude in our approach to diet intervention so far. We offer everyone the same diet. It is possible that different subgroups may respond differently to particular components of the diet or exercise or weight gain,” Rock said.

Another approach for the future is to focus on energy balance, the interplay between physical activity and calories consumed. Demark-Wahnefried sees this as an important field. “This is an area where a host of research questions need to be answered, both to prevent a primary tumor as well as recurrence,” she said. “We need to know if weight loss, exercise, or a combination can benefit women with breast cancer in terms of recurrence, other diseases, ability to function, and overall survival. Observational data suggest that the magnitude of these lifestyle effects may be comparable to the effect of chemotherapy, but we truly need data from well-controlled trials to determine if this is the case.”