

# Dietary Modification and Risk of Breast Cancer

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**B**REAST CANCER IS THE SECOND MOST COMMON CANCER in the world and the most common cancer among women in the United States and in other Western countries.<sup>1</sup> The incidence rate is about 5 times higher in Western countries than in developing countries.<sup>2</sup> Measurable success in multifaceted approaches for prevention and treatment has reduced breast cancer mortality in the United States and in a number of Western countries.<sup>3</sup> These approaches include mammography screening, identification of very high-risk families with deleterious mutations within the *BRCA1* and *BRCA2* genes, and optimal use of adjuvant therapies with endocrine agents, chemotherapeutic agents, and biologically targeted therapy in patients with *ERBB2*-positive (*HER2*) disease.<sup>4-7</sup> A woman's risk of developing breast cancer in the next few years and/or her lifetime risk can be estimated using risk assessment tools.<sup>8</sup> In women at risk of developing breast cancer, pharmacological interventions with antiestrogens (tamoxifen and raloxifene) can reduce this risk.<sup>9</sup> However, these pharmacological interventions are associated with significant adverse effects and have not been adopted on a large scale.<sup>10</sup> Aromatase inhibitors also are under evaluation for the at-risk population.

Diet is another area that is receiving attention as a way to reduce the risk of breast cancer.<sup>11,12</sup> Data regarding geographic variations and dietary patterns have been intriguing. For example, changing from a traditional Oriental diet to a Western diet has been shown to increase the risk of breast cancer.<sup>13</sup> International comparisons and case-control studies have suggested a positive association between dietary fat intake and breast cancer risk.<sup>14</sup> Some of this variation may be due to reproductive risk factors modified by diet, such as age of menarche, which is partly determined by dietary factors (for example, restricted dietary intake during childhood and adolescence delays menarche). Population-based and case-control studies have provided evidence that diet-related factors may account for approximately 30% of cancers in Western countries.<sup>11</sup>

The high-fat content of a Western diet may play a role in the causation of breast cancer.<sup>15</sup> Much research and controversy has surrounded the relationship between high-fat

intake and the risk of breast cancer. Obesity increases the risk of breast cancer in postmenopausal women by approximately 50%, probably in part by increasing serum concentrations of estradiol.<sup>16</sup> Available data have not consistently supported the idea that a change in dietary fat can alter the level of this hormone. However, estradiol and other hormones play a key role in the etiology of this disease<sup>17,18</sup> and some of the dietary effect on breast cancer risk may be mediated by other hormonal pathways. For example, plasma estradiol levels in participants in the Nurses' Health Study were significantly inversely associated with fat intake.<sup>19</sup> This finding was consistent with that of a cohort study in which the risk of breast cancer was associated with fat intake.<sup>20</sup> Similar findings have been reported for postmenopausal Japanese women<sup>21</sup>; those with a high-fat intake had higher serum levels of estrone and dehydroepiandrosterone sulfate than women with a low-fat intake. Dietary modifications also have been reported to alter insulin-like growth factor or carotenoid levels. In one study, patients with a history of breast cancer and a high plasma level of carotenoids had a lower risk of cancer recurrence than patients with this history and a low plasma carotenoid level.<sup>22</sup>

In this issue of *JAMA*, Prentice et al<sup>23</sup> report findings from the Women's Health Initiative (WHI) Dietary Modification Trial, a large clinical trial (N=48 835) that evaluated dietary modification and the subsequent risk of breast cancer in postmenopausal women in their middle to later decades of life. The women were randomly assigned to a dietary modification group or a comparison group. The aim of the dietary modification intervention was to reduce the intake of total fat to 20% of total energy and increase the daily consumption of vegetables and fruit and grains. The comparison group was not asked to make dietary changes. The primary end point of the study was the incidence of invasive breast cancer.

At approximately 8 years of follow-up, the incidence was 9% lower in the dietary modification group than in the comparison group (95% confidence interval, 0.83-1.01;  $P=.09$ ). Thus, the low-fat dietary pattern did not achieve a statistically significant reduction in the risk of invasive breast cancer in these women, although the nonsignificant trends ob-

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served and the results of secondary analyses provide suggestive evidence that the risk of breast cancer may be modified by changing an individual's diet. For instance, Prentice et al showed that dietary modification significantly reduced the risk of breast cancer for disease that was positive for the estrogen receptor and negative for the progesterone receptor (hazard ratio, 0.64; 95% confidence interval, 0.49-0.84;  $P = .001$ ). A modest reduction in levels of estradiol,  $\gamma$ -tocopherol, and low-density lipoprotein cholesterol and an increase in levels of  $\alpha$ -carotene,  $\beta$ -carotene,  $\beta$ -cryptoxanthin, and sex hormone-binding globulin were observed in the dietary modification intervention group. The dietary intervention was not reported to be associated with any adverse effects or any major weight loss.

The specific component of dietary change responsible for the trends toward reduction in the risk of breast cancer remains undefined. The findings of the WHI Dietary Modification Trial are complemented by the initial findings from another prospective dietary study, the Women's Intervention Nutrition Study, in which women with successfully treated early stage breast cancer received dietary modification.<sup>24</sup> Initial data from that study demonstrated that a lifestyle intervention resulting in dietary fat intake reduction can improve the relapse-free survival of postmenopausal breast cancer patients. Another prospective randomized trial of a dietary intervention in patients with early stage invasive breast cancer, the ongoing Women's Healthy Eating and Living study,<sup>25</sup> is evaluating the impact of a low-fat diet with increased consumption of vegetables on disease-free and overall survival in this study population. The initial findings of these 2 trials should encourage additional research in this area.

After a diagnosis of cancer, patients seek advice from their physicians and other health care professionals regarding dietary modifications that could reduce the risk of disease recurrence and also could decrease their family members' risk of cancer. In addition, many patients follow various popular diets or use complementary and alternative medicine therapies, such as various dietary supplements, which have not been evaluated in a rigorous scientific manner. In contrast, the well-designed rigorous Women's Health Initiative dietary modification study by Prentice et al provides important data that may prove useful for counseling patients. Intriguingly, in a large, prospective study,<sup>26</sup> a diet rich in fruit and vegetables was not associated with breast cancer risk reduction suggesting that increased intake of fruit and vegetables may be more useful in secondary rather than in primary prevention of breast cancer.

Breast cancer comprises a biologically distinct group of malignancies. Oncologists are beginning to understand which approaches may be effective for particular subsets of patients with this disease. Additional research is needed to determine the specific dietary elements that may help prevent breast cancer, the optimal time to initiate dietary interventions, and the duration these diets should be followed to achieve the maximum benefit. In the future it may

also be possible to counsel women about the optimal combined dietary and pharmacological interventions for reducing or eliminating the risk of breast cancer.

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