#### **CPE MONTHLY**





# NUTRITION AND BREAST CANCER

Studies Show a Nutrient-Dense Diet Plus Daily Exercise Can Lower Risk of Recurrence

By Suzanne Dixon, MPH, MS, RD

During a routine breast self-exam, Diane felt a lump in her left breast she hadn't noticed before. Her mammogram showed a small abnormal mass that concerned her doctor. After undergoing a breast ultrasound and a core needle biopsy, Diane was diagnosed with stage 1 invasive ductal carcinoma. Frightened that she might die, Diane was reassured by her doctor that the cancer was confined to her breast and that treatment would consist of the surgical removal of the tumor followed by several rounds of radiation therapy.

A breast cancer diagnosis is among the most frightening medical experiences a woman can have. Those who receive treatment and become breast cancer survivors often live in fear of its possible return. But research shows a nutrient-dense diet and regular physical activity can help prevent recurrence. This is good news that RDs can share with patients to help them continue leading healthful, cancer-free lives.

This continuing education activity will review the epidemiology of breast cancer, the common types and comorbid conditions that impact survivorship, and how nutrition can play a role in preventing cancer recurrence.

#### Background and Epidemiology

Cancer is a disease of uncontrolled cell growth and can occur in nearly any tissue in the body, including breast tissue. Solid tumor cancers form a collection of cells, called a tumor. Breast tumors are defined based on the area of the breast in which they originate. Cancer arising in the lobules, which are the milk-producing glands of the breast, is referred to as lobular carcinoma. Cancer of the ducts that connect the lobules to the nipple, which is how Diane's disease was defined, is called ductal carcinomas. The majority of breast cancers are ductal carcinomas.

Excluding nonmelanoma skin cancer, breast cancer is the most commonly diagnosed tumor among women in the United States. An estimated 229, 315 women will be diagnosed with the disease in 2012, accounting for 29% of cancer diagnoses this year. Breast cancer is the second leading cause of cancer death among US women, and approximately 38,552 deaths in 2012—14% of all cancer deaths in women—will be attributable to the disease.<sup>3</sup> The median age at breast cancer diagnosis is 61, and about one-quarter of cases are diagnosed in women between the ages of 55 and 64, making this decade of life the one during which the most women will be diagnosed with the disease.<sup>4</sup>

Breast cancer incidence rates are highest among white women (127 per 100,000), followed by black women (121 per 100,000), Asians and Pacific Islanders (95 per 100,000), and Hispanic women (93 per 100,000). Incidence is lowest among women of American Indian and Alaskan Native ancestry (81 per 100,000). Breast cancer death rates are highest among black women (32 per 100,000) and lowest among Asians and Pacific Islanders (12 per 100,000).

One potential cause of the disparity in breast cancer death rates is a later stage at diagnosis among black women. Social factors, including lack of access to cancer screening and care facilities and financial constraints, may play a role as well.<sup>5</sup> Biological factors, including obesity and tumor characteristics, offer additional clues regarding why breast cancer incidence and death rates are higher among certain ethnic groups.<sup>6,7</sup> It's possible that the stress associated with a low socioeconomic status, through effects on physiology, contributes to more malignant tumor phenotypes.<sup>7</sup>

Based on data collected from 2007 to 2009, approximately one in eight women will develop breast cancer in her lifetime.<sup>4</sup>

#### LEARNING OBJECTIVES

After completing this continuing education activity, nutrition professionals should be better able to:

- Evaluate relevant facts and trends in the epidemiology of breast cancer and its risk factors.
- Distinguish the difference between estrogen receptorpositive (ER+) and estrogen receptor-negative (ER-) breast cancer.
- **3.** Assess the research supporting dietary interventions to reduce the recurrence risk of ER+ and ER- breast cancer.
- **4.** Formulate appropriate dietary recommendations for breast cancer survivors based on knowledge of current research.

This number raises alarm among most women; however, it's reassuring to consider that this figure also means that 87.7% the majority of women—won't develop breast cancer.

Another bright spot is that 60% of breast cancers are diagnosed as stage 1, when still confined to the breast, and the fiveyear survival rate for stage 1 breast cancer is 98.4%.4 And after a steady average annual increase in breast cancer rates of 0.4% between 1975 and 1990, breast cancer rates have declined by 2.2% annually between 1990 and 2007.3

However, it's important to note that the five-year survival rate for all stages of breast cancer combined is 90% for white women and 78% for black women. 4 This highlights the need for a better understanding of the etiology of racial/ethnic disparities in breast cancer survival and a concerted effort on the part of public health agencies, scientists, and clinicians to eradicate these differences by improving survival in affected groups.

The National Cancer Institute (NCI) defines a cancer survivor as any individual with cancer from the time of diagnosis forward, regardless of whether that person is considered "cured." As of January 2009, approximately 2.7 million women living in the United States were breast cancer survivors.4 This high prevalence of breast cancer survivorship calls attention to the need for RDs to gain a basic understanding of the condition and how diet and nutrition can affect breast cancer recurrence.

#### **Breast Cancer Risk Factors**

Some risk factors for breast cancer are beyond our control, while others are not. Common non-modifiable risk factors include gender, age, menstrual history, family history, and genetics. Women are nearly 100 times more likely to develop breast cancer than men and, as with many tumor types, risk increases with age. First menses before the age of 12 and late menopause (after the age of 55) both increase breast cancer risk.<sup>2</sup>

Women with a strong family history of breast and/or ovarian cancer should be evaluated for the presence of breast cancer genes, which are mutations in the BRCA1 and BRCA2 genes. All women have copies of the BRCA1 and BRCA2 genes, which normally function as tumor-suppressor genes, regulating cell growth and replication. It's when these genes are defective that the risk of breast and/or ovarian cancer is increased. Women with BRCA1 or BRCA2 mutations have up to an 80% lifetime risk of developing breast cancer.2

Having dense breasts, referred to as mammographic density, also is linked with increased breast cancer risk.9 Researchers are continuing to investigate how and why denser breasts are more prone to cancer development.

Lifestyle practices, which are under an individual's control, also can contribute to breast cancer risk, positively and negatively. Alcohol use is a recognized breast cancer risk factor. A recent meta-analysis found moderate use—one drink per day is associated with a 4% increase in the relative risk of developing breast cancer.<sup>10</sup> Other data have suggested that women have up to a 15% increased relative breast cancer risk with just three to six drinks per week, 11 which is well below the suggested intake of one drink per day for women, and two drinks per day for men, to improve cardiovascular health.12

While 15% may seem like a small number, breast cancer is the most common tumor type in women, so even a small relative risk increase translates into large numbers of affected women. Heavy drinking, defined as three or more drinks per day, raises the relative risk of breast cancer 40% to 50%. Taken together, it's estimated that 5% of breast cancer cases in North America and Europe are attributable to alcohol consumption.<sup>10</sup>

Overweight, obesity, and lack of physical activity all play a role in breast cancer risk in developed countries. A rigorous review of more than 7,000 studies on physical activity, excess weight, and cancer risk concluded that there's convincing evidence of an association between excess weight and increased risk of postmenopausal female breast cancer.<sup>13</sup> Equally alarming is that overweight and obesity are adverse prognostic factors. Dozens of studies support the finding that women who are overweight or obese at breast cancer diagnosis, or who gain weight after diagnosis, are more likely to experience a breast cancer recurrence and decreased survival. 14,15

Having children early—defined as before the age of 25 in some research literature and before the age of 30 in other studies and breast-feeding are protective against later breast cancer development.<sup>16,17</sup> Other hormonal factors have a role in determining susceptibility to breast cancer, including the following:

- Certain forms of postmenopausal hormone replacement therapy (HRT): Estrogen therapy alone (without progesterone) appears not to increase breast cancer risk, and some data suggest estrogen therapy may even decrease risk.<sup>18</sup> Combined estrogen and progesterone (HRT) is implicated in increasing breast cancer risk.<sup>19</sup> Newer forms of hormone delivery, including transdermal routes, may mitigate these risks.20
- Oral contraceptive use: Prolonged use of oral birth control is associated with an increased breast cancer risk, with estimates of increased relative risk ranging from 10% to 50%. However, data suggest that mortality rates from breast cancer diagnosed in oral contraceptive users are lower or equivalent

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to nonusers, and that increased breast cancer risk associated with oral contraceptive use disappears within five years of stopping the medication.21

• In utero exposure to diethylstilbestrol (DES): DES was given to pregnant women in the 1940s through 1960s because it was thought to lower the risk of miscarriage. In utero exposure to this drug increases breast cancer risk in female fetuses, though the magnitude of the risk hasn't yet been clearly defined, because many exposed women haven't lived long enough to quantify the lifetime risk.22

#### Estrogen and Progesterone Receptor Status

Oncologists use several tumor markers to guide treatment decisions for each woman diagnosed with breast cancer. Of primary importance is the classification of breast cancer by estrogen receptor (ER) status.23 Tumors that are ER+ are responsive to estrogen, meaning estrogen will fuel their growth. ER- tumors don't respond to the presence of estrogen. Physicians can use this information in their treatment

### **CANCER-FIGHTING FOODS, BEVERAGES, AND SPICES\***

- Apples
- Berries, especially deep purple and red (eg, blackberries, blueberries, strawberries, raspberries)
- Cruciferous vegetables (eg, arugula, bok choy, broccoli, Brussels sprouts, cabbage, cauliflower, chard, collard greens, daikon, kale, kohlrabi, mustard greens, rutabega, turnips, watercress)
- Carrots, sweet potatoes, and other yellow-orange vegetables
- Citrus fruit
- Cold-water fish (eq. anchovies, cod, herring, mackerel, salmon, sardines)
- Flaxseed
- Garlic
- Green tea
- Legumes
- Mushrooms (edible and medicinal)
- Nuts
- Olive oil
- Seaweed and sea vegetables
- Sov
- Turmeric
- Whole grains

\*This list, compiled with information from Eat to Defeat Cancer (www.eattodefeat.org/food) isn't intended to be exhaustive or all-inclusive.

and disease management decisions. For example, women with ER+ breast cancer can receive medications to block estrogen's actions or production in the body, which helps stop tumor growth and can minimize recurrence risk in breast cancer survivors.

It's important to note that tumors have varying levels of estrogen receptor positivity. Tumors are scored based on how strongly they express estrogen receptors: a score of 0 indicates no estrogen receptors are present; 1+ shows a small number of receptors; 2+ indicates a medium number; and 3+ demonstrates a large number of estrogen receptors in the tumor sample.24 ER status scores may be given as a percentage of cells in the samples that have receptors as well. For women with borderline ER+ status, more sensitive testing can reveal exactly how much the tumor is expected to respond to the presence of estrogen, although even women with tumors with a low number of receptors may benefit from medications that block estrogen's actions or production.<sup>25</sup>

Approximately 70% of breast cancers are classified as ER+, which has a more favorable prognosis than ER- breast cancer. ER- status occurs more frequently in younger, premenopausal women and women of nonwhite race/ethnicity.26,27

Progesterone receptor (PR) status also is a prognostic indicator. When both estrogen and progesterone receptors are positive, there's a higher likelihood a patient will respond well to endocrine therapies, which include selective estrogen receptor modulators and aromatase inhibitors. PR status also may be an important indicator of tumor aggressiveness and, when negative, may indicate that the patient will benefit from using more than one endocrine therapy approach simultaneously.<sup>28</sup>

The least favorable prognosis is associated with tumors that are ER and PR negative and negative for another growth factor called human epidermal growth factor receptor 2. These are referred to as triple-negative breast cancers and are more likely to be diagnosed in non-Hispanic black and Hispanic women for reasons that aren't completely understood.<sup>27</sup> This triple-negative status contributes to higher mortality rates after breast cancer diagnosis among some nonwhite ethnic groups, but doesn't completely account for the disparity in survival rates.29

#### **ER Status and Dietary Recommendations**

Just as the ER status of breast cancer tumors guides treatment decisions, it also should be considered when making dietary recommendations. The first piece of solid evidence showing that ER status may be an important factor in identifying the optimal diet for breast cancer survivors came from results of the Women's Intervention Nutrition Study (WINS), presented at the 2005 American Society for Clinical Oncology annual meeting.30

WINS, a randomized trial of nearly 2,500 breast cancer survivors, revealed that a very low-fat diet significantly reduced breast cancer recurrence risk but only among

women with ER- breast cancer. After five years of followup, women with ER- breast cancer who were randomized to the very low-fat diet group had a 42% reduced risk of recurrence compared with women with ER- cancer in the control group. The very low-fat group consumed an average of 33 g of fat per day (about 20% of total calories from fat) vs. the control group's average fat intake of 51 g per day (about 32% of total calories from fat).31 Women in the very low-fat diet group with ER+ breast cancer had a statistically nonsignificant 15% reduction in recurrence risk.30

The Women's Healthy Eating and Living (WHEL) study is another important, large-scale, randomized, controlled diet intervention among breast cancer survivors. 32 In this study, approximately 3,000 breast cancer survivors were randomly assigned to a high fruit and vegetable, high-fiber, low-fat diet or a control diet. The goals for the intervention group were to consume five vegetable servings, 16 oz of vegetable juice, three fruit servings, 30 g of fiber, and 15% to 20% of energy from fat daily. Women in the control group were instructed to follow dietary guidelines established by the NCI and the USDA, including eating five servings of fruit and vegetables per day and getting no more than 30% of calories from fat.

Results from the WHEL study have contributed significantly to our understanding of how diet and physical activity may affect breast cancer recurrence risk. Among the earliest findings from this trial are that women with the highest blood carotenoid concentrations were 43% less likely to have a breast cancer recurrence compared with women with the lowest blood levels.33 Blood carotenoid levels are a marker of fruit and vegetable intake, which suggests that a more healthful diet at, around, or just after diagnosis may be protective against breast cancer recurrence.

A follow-up analysis of the WHEL cohort in 2007 didn't find a significant difference in recurrence rates between the intervention and control groups.<sup>34</sup> It's possible that the lack of benefit was due to inaccurate accounting of true dietary intake by study participants; the control group eating a more healthful diet than intended, which would diminish differences in nutritional intake between the groups; or that dietary changes postdiagnosis are less important for long-term survival and health than the baseline diet before diagnosis.

Regardless, this study suggests that increasing vegetable and fruit intake above and beyond the standard five-a-day recommendation for the general public may not reduce breast cancer recurrence. However, there may be subsets of women

who benefit from this dietary intervention. A 2009 analysis of data from this cohort found that women without hot flashes who were assigned to the intervention group had 31% fewer breast cancer recurrence events than hot flash-negative women assigned to the control group. The intervention didn't affect the prognosis of women who had hot flashes at the time of the study's enrollment.35

An additional analysis found that women who ate a minimum of five servings of vegetables and fruit per day combined with regular physical activity roughly equivalent to 30 minutes of brisk walking daily, reduced their risk of recurrence by approximately 50%.36 Interestingly, this protective effect was observed in lean and obese women alike, an important finding given that obesity itself is an adverse prognostic factor after a breast cancer diagnosis.<sup>37</sup> Also of note is that neither healthful eating nor exercise alone resulted in a survival benefit, suggesting that combining these two positive health behaviors after a breast cancer diagnosis offers the greatest opportunity for improved health and disease-free survival.

#### Comorbid Conditions and Breast Cancer Survival

One of the most important aspects of breast cancer survival is achieving a healthful body weight. Obesity is commonly comorbid with breast cancer, and data support that obesity decreases survival. 37,38 Obesity at diagnosis, as well as weight gain after diagnosis, increases the likelihood of recurrence and death among breast cancer patients.37,39

A cohort of 1,436 women diagnosed with breast cancer, who were followed for approximately five years postdiagnosis, suggests that women who gain 10% or more than their baseline body weight after diagnosis are nearly three times more likely to have a breast cancer recurrence compared with women who remain within 5% of their baseline body weight. This effect was particularly pronounced within the first two years, when weight gain was associated with a nearly sixfold increase in recurrence risk.39

To date, definitive data don't exist to demonstrate whether weight loss at or after diagnosis or regular physical activity alone among obese breast cancer survivors will improve survival or other health markers. Some future trials will assess biomarkers associated with increased or decreased cancer recurrence risk, such as elevated levels of insulin, insulin-like growth factor, C-reactive protein, and leptin. Some of these studies will assess long-term survival rates among obese breast cancer survivors who do or don't lose weight as well as the impact of weight





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loss on other factors, including quality of life and development of long-term complications such as lymphedema. Examples include the Fit for the Fight and WISER clinical trials. 40,41

Data support that type 2 diabetes, another nutrition-related comorbid condition, is associated with an increased risk of breast cancer and a higher risk of recurrence in women who have been diagnosed with the disease. 42,43 Researchers are investigating whether a pathophysiologic pathway underlying both diabetes and cancer predisposes women with diabetes to breast cancer, or whether the association occurs primarily due to risk factors common to both type 2 diabetes and breast cancer, such as obesity and lack of physical activity. 44

Recent findings on how the diabetes drug metformin may improve treatment outcomes in various tumor types suggest that proper management of diabetes may mitigate the risk of cancer recurrence that's linked to the presence of type 2 diabetes. 45 A retrospective analysis of 112,408 people seen in more than 350 primary care clinics in the United Kingdom noted that 8,392 people, approximately 7.5% of the study population, had type 2 diabetes. 46 The risk of breast cancer was 32% higher in women with diabetes compared to those without the disease.

Among people with diabetes, those taking only sulfonylureas to manage the condition were 13% more likely to die after a breast cancer diagnosis than those without diabetes; people taking insulin therapy alone were 13% more likely to die after diagnosis than those without the disease. However, compared with individuals without diabetes, people with diabetes who were taking metformin were 15% less likely to die after a breast cancer diagnosis. 46 In summary, metformin was associated with a survival benefit when compared with other treatments for diabetes and even compared with cancer survivors who didn't have diabetes.

These findings are observational and can't prove cause and effect, but along with other studies on metformin use and improved cancer outcomes, 47 they've led to the launch of numerous clinical trials to investigate metformin as an adjunct to conventional cancer treatment options. These trials address the use of metformin for treating women with early- to latestage breast cancer and metastatic disease. 48,49

#### Cancer-Fighting Foods

Unlike the number of metformin studies under way, controlled clinical trials on specific foods to reduce the risk of breast cancer recurrence are few and far between. Despite this, copious observational data show that certain foods may be worth adding to the diet for the breast cancer survivor. This is particularly true of foods that may have other health benefits and have no known risks. The sidebar on page 50 presents a list of foods that may offer anticancer benefits, and that deserve a place in any healthful diet—for cancer survivors and the general public alike.

However, there is confusion about which foods may offer benefits to breast cancer survivors and whether some foods are unsafe and should be avoided. The confusion persists for people affected by cancer and their healthcare providers, and no food exemplifies this issue better than soy.

The term "phytoestrogens" is used to describe a class of nutrients in soy called isoflavones, and unfortunately suggests that estrogenic activity of soy nutrients is the only, or the most important, aspect of these foods. Many of the anticancer properties attributed to soy are unrelated to so-called estrogenic effects. These include inhibition of angiogenesis through actions on the vascular endothelial growth factor and epidermal growth factor pathways, induction of G2/M cell cycle phase arrest through increased expression of p21, inhibition of tyrosine kinases, binding and activation of peroxisome proliferator regulators, upregulation of natural killer cell function, inhibition of endogenous steroid biosynthesis, and antioxidant actions. 50-52

Three large-scale, well-designed epidemiologic studies report no adverse effects of soy food consumption on breast cancer prognosis. 53-55 The study populations include different ethnic/cultural groups—two from the United States and one from China—and examine various types of soyfood consumption. These three studies concur that not only are soyfoods safe for breast cancer survivors, they also may be protective against breast cancer recurrence. The magnitude of the protective effect in these studies ranged from a 33% to 60% reduced risk of recurrence among women consuming the most soy compared with women consuming the least.

Human feeding studies provide additional reassurance that these foods likely are safe for female breast cancer survivors. Among 96 women in a randomized, crossover design, two servings of soyfoods daily, which provided 50 mg total isoflavones per day, didn't affect nipple aspirate fluid (NAF) estrogen levels.<sup>56</sup> In a similarly designed crossover trial, the volume of NAF—higher volume is a possible indicator of breast cancer risk—didn't significantly increase over a period of six months in women fed a high soy diet (two servings per day).57

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Regardless of the group (high vs. low soy) to which they were initially assigned, all women produced similar NAF volumes at the start of the study. Both groups of women produced less NAF, on average, during the first three months on a high soy diet; although both groups' NAF volumes returned to baseline by month six on a high soy diet.

A recently published meta-analysis evaluated four studies on breast cancer recurrence and 14 studies on breast cancer incidence. 58 Higher soy intake was associated with a modest reduction in breast cancer risk overall (24%), though this protective effect was observed only in Asian populations. Among Western populations, soy didn't significantly decrease breast cancer risk. Among all populations combined, women with the highest reported soy intake were 16% less likely to experience a breast cancer recurrence compared with women with the lowest intake.

Evidence for soy-based dietary supplements is lacking, and women should be counseled to avoid soy supplements because of their potential for unnaturally high isoflavone concentrations. However, current human data support that whole soy foods as part of a balanced diet are safe, and possibly beneficial, for women with a history of breast cancer.

#### Meeting the Client Where She Is

It's important for RDs to understand the basics of a patient's breast cancer diagnosis to develop the best nutrition care plan. As mentioned, knowing the ER status of a woman's tumor will help determine whether a very low-fat diet is worth recommending. Given the challenges of reducing dietary fat intake to 20% or less of total calories, it makes sense to apply this approach only to women who may benefit from it. This includes women with a history of ER- breast cancer.

In the WINS study, the goal for women in the intervention group was to reduce dietary fat to 15% of total calories, but most of them didn't reach this goal. Despite this, however, the women with ER- breast cancer had profound reductions in their risk of recurrence. This reveals insights that can improve nutrition counseling. Dietitians can advise women with a history of ER- breast cancer to follow a diet that provides 15% of total calories or fewer from fat. RDs also should counsel patients that it's OK if they don't meet this target. By aiming for 15% of calories from fat, more women will eventually reach 20% of calories from fat, which WINS indicates will provide a survival benefit.

For all breast cancer survivors, the evidence makes clear that achieving a healthy body weight should be a long-term wellness

goal. However, tackling weight loss can be fraught with anxiety, guilt, and a host of other negative emotions. For these reasons, RDs should meet the patient where she is, regardless of whether she's ready to deal with weight-loss issues.

The WHEL study findings support that even if a woman doesn't lose weight, simply eating more plant foods and engaging in 30 minutes of daily exercise can provide a survival benefit. Therefore, it makes sense to work with overweight breast cancer survivors to help them meet their goal of eating more vegetables and fruits—at least five to seven servings per day—and engaging in daily physical activity. These behavioral changes should take precedence over any weight loss focus unless a client is clear that weight loss is a goal at that time.

Finally, dietitians should counsel women in a way that helps remove the fear surrounding nutrition and cancer. The soy food question presents an excellent example of why this is a valuable approach. Soy food consumption appears safe and possibly beneficial for breast cancer survivors; however, superimposing soy foods onto a typical American diet that's high in fat, low in fiber, and heavy on processed foods is unlikely to be helpful. Total diet quality matters, and an undue focus on any one food can be counterproductive to dietary improvement.

Along these lines, consider a client who may be experiencing significant stress about reading labels to ensure no soy-based ingredients creep into her diet. Rather than convincing her that soy is safe and she shouldn't worry about it, counsel her about a healthful diet overall that will lower cancer risk. The solution isn't to teach her how to read labels: it's to help her focus on unprocessed, whole foods that don't contain unhealthful ingredients. Clients can learn they don't need a label to know that plain oatmeal, broccoli, berries, apples, carrots, and kale are healthful food choices.

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