The Ecology of Breast Cancer

The promise of prevention and the hope for healing

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Diet, nutrition, and breast cancer

Chapter Summary

For many years, the relationship between diet and breast cancer has been of great interest. Scientists have studied this connection particularly intensively over the past 30 years. Initial case-control studies were followed by the addition of large prospective cohort observational studies and occasional intervention trials. Inconsistency in findings is a recurrent theme. Perhaps this is inevitable for at least two reasons. Breast cancer is not a single disease. It is comprised of different subtypes—classified according to menopausal status, hormone receptor status, or other markers—with differing and complex biology. Many studies attempting to shed light on their origins make no distinction. Beyond that, studies with a singular focus on diet, by their design, often prevent understanding the ways diet can interact with other risk factors such as exercise or exposure to environmental chemicals. The research agenda has largely featured a reductionist approach—but that is slowly beginning to change.

At the outset, studies largely examined the influence of single dietary variables or macronutrients on breast cancer risk and prognosis. Initial enthusiasm surrounding the role of dietary fat waned as results from prospective cohort and intervention studies did not confirm findings from case-control studies showing an association between higher dietary fat and breast cancer risk. Subsequent studies examined the role of fruits, vegetables, soy, carbohydrates, dairy, and fiber. Occasional more recent studies examine dietary patterns.

Most analyses have assumed that if a nutrient group is related to breast cancer, the relationship will be in the same direction—that is, if some particular food is beneficial, more will be more beneficial; or if some is harmful, more will be more harmful. But that assumption may be incorrect. There may be optimal amounts of nutrient groups or micronutrients, above and below, which breast cancer risk increases or prognosis is poorer. This gives a J-shaped dose response curve that most existing epidemiologic studies do not consider in data analyses.[1]

With a few exceptions, almost all early epidemiologic studies examined the influence of adult diet on breast cancer risk. Most concentrate on current or fairly recent diet. But if most breast cancer has a latency of 15-20 years or even longer, as experts generally agree, recent dietary information tells us more about associations with cancer progression than initiation. Laboratory animal and more recent human epidemiologic studies now show that diet in childhood and adolescence has a stronger link to breast cancer risk—perhaps more than diet in adulthood. This has striking implications for breast cancer prevention, as well as posing challenges for the design of future research.

Recent studies also show that exercise, which is often ignored in dietary studies, is a significant confounder and may modify the effect of dietary variables on breast cancer risk. Exercise influences what and how much individuals eat and is also independently associated with breast cancer risk. Exercise influences some of the same biologic pathways through which dietary variables may act. The few studies that consider diet and exercise together show the magnified value of eating well and exercising. These reinforce the idea that breast cancer is a disease arising out of system conditions—the result of interacting multi-level variables that begin early and extend throughout life. More complex analyses hold the most promise for better understanding and designing interventions that help to prevent the disease and improve outcomes.

Overweight and obesity are associated with an increased risk of post-menopausal breast cancer and less favorable prognosis after diagnosis and initial treatment. Excess body weight typically has multiple contributing causes, but dietary interventions, along with exercise, can help maintain a healthy body weight and reduce risk. For premenopausal breast cancer, however, overweight and obesity are associated with a slightly decreased risk.[2]

Dietary fat

Independent of weight gain, most analysts conclude that total dietary fat, within the range common in the Western diet, has a weak, if any, association with breast cancer risk in general.[3] Evidence linking higher total dietary fat to breast cancer is stronger in post-menopausal women. Some evidence shows that reducing total dietary fat to 20 percent or less of total calories, an uncommonly low level in the United States, is likely to lower breast cancer risk.[4] Higher amounts of saturated fat and trans-fats modestly increase breast cancer risk. Trans-fats are, to a large extent, the result of partial hydrogenation

of vegetable oils used in processed foods although some are present in trace amounts in meat and dairy. In addition, trans-fats are clearly linked to cardiovascular disease risk and should be avoided.

Diets high in omega 6 fatty acids (FAs) (e.g., from corn, safflower, and soy oils; processed foods) that do not also contain adequate amounts of omega 3 FAs (e.g., from wild fish, fish oil, flax, walnuts) are likely to increase breast cancer risk. Laboratory animal studies clearly show this to be true, but epidemiologic studies are somewhat inconsistent. Ideally, some omega 6s should be replaced with omega 3s and mono-unsaturated FAs, like oleic acid in olive oil, which is prominent in the Mediterranean diet.* Excessive dietary levels of omega 6 FAs may be particularly problematic in individuals who disproportionately metabolize them into higher levels of pro-inflammatory substances, based on genetic variability.

Meat

Results of studies of dietary meat in adulthood and breast cancer risk have been inconsistent and largely negative. However, the Nurses' Health Study (NHS) II found a strong association of higher meat consumption during adolescence with increased premenopausal breast cancer risk. This is consistent with additional findings described in this and other chapters suggesting that early-life experiences help shape susceptibility to breast cancer. They provide strong support for beginning efforts to prevent breast cancer early in life and continuing through adolescence and adulthood.

Fruits and vegetables

Despite inconsistent evidence in early studies, more recent analyses show that higher dietary levels of fruits and vegetables significantly reduce the risk of developing breast cancer. Inconsistencies in the evidence may be due to different ways of estimating consumption. Studies using serum measures of carotenoids as a marker for fruit and vegetable consumption, rather than food-frequency questionnaires, find a significant protective association with higher levels. The Women's Healthy Eating and Living (WHEL) intervention study and others also showed improved prognosis after breast cancer diagnosis in individuals with the highest baseline levels of carotenoids.

Dietary pattern studies fairly consistently show modest risk reduction with a diet featuring plant-based foods. And, a WHEL analysis of postmenopausal women with breast cancer found that a diet with more than five servings of fruits and vegetables daily, combined with a level of exercise equivalent to brisk walking 30 minutes daily, six days/week, reduced mortality risk by half over a 10 year period.[5]

* It should be emphasized that omega 6s and 3s are both essential fatty acids (FAs). But based on a large number of animal studies and less consistent human data, high omega 6 FA intake in the setting of low omega 3 FA intake is likely to increase the risk of breast cancer.

It is increasingly clear that higher soy consumption decreases the risk of breast cancer, although the level at which risk reduction becomes significant is uncertain, and the kind of soy-derived food is an important consideration (Although not reviewed here, an expert panel concluded that higher soy consumption also reduces the risk of uterine cancer.[6]). Higher soy consumption more persuasively lowers breast cancer risk in Asians than in Westerners, perhaps because Asians traditionally eat whole soy foods and consume 10-100 times more soy-derived isoflavones than Westerners. In many studies these larger amounts appear to confer more significant protection. The traditional Asian diet includes tofu and fermented soy products, such as miso and tempeh made from the whole bean. Soy oil and soy protein isolates are more common in the United States, particularly in processed foods. Health benefits from this heavily processed soy should not be inferred from the results of studies of more traditional soy-based food.

Available studies consistently show that higher soy consumption during childhood and adolescence is associated with lower breast cancer risk than higher dietary levels in adulthood. The findings are striking. Multiple mechanisms are likely to be involved. Here again, it looks as if early life experience may influence breast cancer risk years later. This has profound implications for breast cancer research and public policy.

Despite evidence in laboratory studies that genestein can cause breast cancer cells to proliferate,[7] three well designed, prospective studies with follow up periods of up to six years conclude that higher soy consumption post-diagnosis and treatment is associated with improved survival and lower risk of recurrence. The association is strongest in Asians, who may have been consuming traditional soy products throughout life. These findings cannot, however, be generalized to include soy supplements or purified isoflavones that may be added to processed, non-traditional soy food products. There is no evidence that soy consumption at current levels in Westerners or Asians post-diagnosis interferes with tamoxifen therapy and efficacy.

Other foods

Consistent, but limited, evidence from laboratory animal and epidemiologic studies points to a beneficial role of dietary seaweed in breast cancer prevention—even more in combination with soy, fish, fruits, and vegetables. Data also show a protective effect of mushrooms, which are commonly included in traditional Asian diets in countries where breast cancer is less common.

The role of carbohydrates, glycemic index, and glycemic load in the origins or prognosis after treatment of breast cancer is unclear. To the extent that refined carbohydrates, independently or along with other dietary features, promote elevated blood sugar, insulin resistance, metabolic syndrome, or overt diabetes, breast cancer risk will increase and prognosis after diagnosis will be less favorable. Comprehensive efforts to improve normalize blood sugar, improve insulin sensitivity, and reduce insulin levels are likely to be protective and beneficial.

Dietary patterns

Some epidemiologic studies have addressed the association of breast cancer with dietary patterns rather than single nutrient groups. In general, diets featuring higher amounts of fruits and vegetables, particularly those that are darkly colored, traditional soy products, whole grains and less refined carbohydrates, low-fat dairy, with poultry and fish and less red meat are associated with lower breast cancer risk. In some studies, where tumor subtypes are considered, this relationship is stronger for estrogen-receptor negative (ER-) breast cancer.

A number of observational and two large intervention studies provide varying levels of evidence that lower levels of dietary saturated fat and higher amounts of fruits and vegetables may reduce or delay cancer recurrence and improve survival. Higher amounts of dietary soy pre- and post-diagnosis are associated with decreased mortality and may be associated with decreased likelihood of recurrence.

When combined with weight loss in people who are overweight and regular exercise, benefits of this dietary pattern increase (See Appendix A).

Conclusions

Efforts to prevent breast cancer should begin in utero and continue throughout infancy, childhood, adolescence, and adulthood. Significant opportunities to reduce breast cancer risk through dietary interventions begin early in life and may be even more effective than steps taken later. That said, dietary interventions in adulthood can also reduce risk and importantly, improve prognosis after the diagnosis of breast cancer. Strong evidence shows that obesity is a significant risk factor for developing post-menopausal breast cancer and for progression of pre- and post-menopausal breast cancer. Dietary changes can be combined with other efforts aimed at weight control.

Breast cancer is less common in countries where people consume less meat and fat. But many aspects of lifestyle are also markedly different in these countries than in affluent Western countries, including physical activity, body composition, diet other than meat and fat consumption, and exposures to other environmental agents. Thus, cross-country comparisons are useful for generating hypotheses, but they are subject to considerable confounding and more detailed studies are needed.

Studying the impact of diet on breast cancer risk is complicated. Data are difficult to gather and their quality varies significantly. Unlike laboratory animal studies, where careful dietary control allows close monitoring of impacts, human studies are less precise. They often rely on food frequency questionnaires to reconstruct dietary histories, even from the distant past. Prospective studies can use food diaries since current eating patterns can be recorded more accurately than past practices can be recalled, but these too are often inaccurate. Moreover, in a population where the differences in dietary fat or food groups may not vary dramatically between the highest and lowest consumers, influences on cancer risk may be difficult to identify, even when they exist.

In recent years it has become increasingly apparent that nutrition, along with other environmental exposures, during fetal development, infancy, childhood, and adolescence influences subsequent breast cancer risk—perhaps even more than adult diet. This conclusion is based on diverse threads of evidence. Animal studies show that maternal diet during pregnancy significantly alters mammary cancer risk in female offspring—including susceptibility to mammary carcinogens before or after a first pregnancy.[8,9]

A prospective cohort study of 3,834 people who took part in a family diet and health survey between 1937 and 1939 reported increased cancer mortality, including breast-cancer related deaths, associated with higher levels of total childhood energy intake.[10] An ecologic study found that during World War II in Norway, peri-pubertal women whose diets were calorie-restricted but otherwise adequate had decreased risk of subsequent breast cancer compared with women exposed to both severe calorie restriction and poor food quality.[11]

A retrospective analysis from Nurses' Health Study (NHS) II found decreased risk of breast cancer with higher intakes of vegetable fats (RR=0.58) and vitamin E (RR=0.61) in adolescence and increased risk with a high glycemic diet (RR=1.47).[12] Another analysis from NHS II found that a higher level of meat consumption in adolescence increases the risk of breast cancer (RR=1.34). Several studies show that increased soy consumption in childhood decreases risk (see below).

These findings are among the increasingly persuasive evidence pointing to the developmental origins of adult diseases. They are consistent with studies of survivors of the atomic bombing of Japan in WWII showing that radiation exposure during childhood and adolescence most strongly increased breast cancer risk while exposure after age 40 had a much smaller effect.[13]

Migration studies show that breast cancer risk remains low in first generation immigrants who have spent their early life in a country with low risk of breast cancer, but increases among second generation immigrants who spend their childhood in a country with higher risk.[14] And, in a study that was able to determine the age of participants at the time of ex-

posure to the insecticide DDT, higher exposures before age 14 were associated with much higher breast cancer risk but not in women who were older when exposed (see chapter 5).[15] These findings are biologically plausible inasmuch as puberty and adolescence are times of unique susceptibility to environmental exposures because of rapid cellular proliferation and development of tissue architecture in the breast prior to pregnancy. Unique events during fetal development are also likely to contribute. But as important as it may be, accurate information about maternal, childhood, and adolescent nutrition can be extremely challenging to acquire decades later.

In general, nutritional studies tend to control for other variables that influence breast cancer risk, such as age at menarche and menopause, history of pregnancies, and alcohol and tobacco use, but some do that more rigorously than others. To add to the complexity, diet probably has different influences on pre- and post-menopausal cancer risk, but many studies do not report data by menopausal status, making interpretation difficult.

Case-control epidemiologic studies dominated early investigations. These compare diets of people with breast cancer to a control group without cancer. They depend on dietary recall. Prospective cohort studies, which assemble a group of participants without cancer, gather dietary and other relevant information, and periodically check on health status, soon followed. In general, case-control studies are subject to more dietary recall bias than cohort studies, which may explain at least some of the differences in their findings. Population-based, nested case-control studies are also fairly common in breast cancer research. Even though they are of case-control design, they have the advantage of being drawn from a fairly large, previously defined population being followed prospectively. They minimize some of the difficulties associated with matching cases with controls and controlling for recall bias.

The following sections summarize the results of many studies, most of which examined the independent influence of dietary fat, meat, soy, or fruits and vegetables on breast cancer risk or outcomes. Dietary pattern analysis shows up in more recent studies. This approach may add value since people eat complex diets with important interactions among nutrients that are likely to be missed when concentrating on single nutrient groups. Information from studies looking at dietary influences on breast cancer outcomes following diagnosis is also included.

The emphasis here is on prospective observational cohort studies and intervention trials, although occasional case-control studies are included, along with some laboratory animal data. Inconsistencies in findings are common, some of which are undoubtedly due to differences in study design. Moreover, virtually none of these studies considered exercise or activity levels as a potential confounder or modifier of the effect of diet on breast cancer risk. This is a regrettable shortcoming since the intertwined biologic effects of diet, exercise, and

body weight can strongly influence breast cancer risk. Analyzing dietary data independently, without accounting for interactions with exercise or other relevant variables, can obscure its relevance.

Dietary fat and breast cancer

Initial enthusiasm for the idea that higher amounts of dietary fat would explain most of the elevated incidence of breast cancer in some countries has waned to a large degree, based on inconsistent results from a number of prospective studies. Until recently, however, these studies almost always evaluated diets in adults rather than childhood or adolescence. Despite inconsistent results, some conclusions can be drawn:

- Reduced dietary saturated fat and total fat may modestly reduce breast cancer risk, particularly in post-menopausal women. In the Women's Health Initiative intervention study of post-menopausal women, reduced fat consumption was associated with most risk reduction in women who had higher baseline levels of dietary fat. Increasing trans fat consumption is associated with increased risk.[16]

- The NHS II found a significantly increased risk of premenopausal breast cancer with higher dietary levels of animal fat. Premenopausal breast cancer risk was also higher in women who had higher dietary levels of fat or red meat consumption during adolescence. This will be important to keep in mind, along with other adolescent dietary patterns discussed below, because childhood and adolescent diets may have a greater influence on breast cancer risk than diets later in life.

- Studies examining the effect of total polyunsaturated FAs (PUFAs) on breast cancer risk are inconsistent, but some studies with PUFA subtype analyses show that high intake of omega 6 FAs combined with low levels of dietary omega 3s increase risk. Relatively new evidence of individual differences in metabolism of omega 6 FAs suggests the possibility that high dietary levels of omega 6 FAs may increase risk more in people who, because of genetic variability, metabolize them more completely into pro-inflammatory compounds associated with a number of chronic diseases, including cancer. In order to address this, reducing dietary omega 6 FAs and adding long chain omega 3 FAs from fish or monounsaturated fats from, for example, olive oil are likely to be most helpful, not only to reduce breast cancer risk but also other chronic diseases in which inflammation plays a role.

Study descriptions: Dietary fat and breast cancer

Many studies have examined the relationship between dietary fat and breast cancer risk because the two are highly correlated at the national level, particularly for animal fat consumption.[17] Considerable laboratory animal data show that dietary fat can significantly enhance mammary tumor growth, apart from total calories consumed. In fact, a relationship between dietary fat and breast cancer risk may begin as early as fetal development, and changes in hormone levels may play a role.

In rodents, high levels of maternal dietary omega 6 FAs during pregnancy and lactation alters breast development in offspring, increasing susceptibility to cancer later in life.[18,19] High levels of maternal dietary omega 6 FAs are also associated with higher estrogen levels in pregnancy. A meta-analysis of animal studies concluded that omega 6 FAs had the strongest mammary gland tumor promoting properties, while the effect of saturated fat was somewhat less, and omega 3 FAs seemed slightly protective.[20]

One study of 189 women who gave birth to single female babies showed that higher intake of omega 6 FAs was associated with significantly higher umbilical cord blood levels of estriol and testosterone.[21] Higher dietary omega 3 FAs were linked to lower levels. A meta-analysis of ten intervention studies found that a low-fat, high-fiber diet had an estrogen-lowering effect in premenopausal women.[22] This occurred both in studies in which women lost weight and when they did not. A recent study in Japan found higher dietary saturated fat intake associated with higher estrogen levels in premenopausal adult women.[23]

Initial epidemiologic studies supported a link between dietary fat and breast cancer risk. A large 2003 meta-analysis of 45 case-control and cohort studies concluded that higher amounts of dietary fat during adulthood increased the risk of breast cancer by about 13 percent, largely attributable to saturated fat.[24] But findings from several large, prospective cohort studies have not been entirely consistent, and differences in study design make interpretation more uncertain.

Prospective cohort studies

Nurse's Health Studies: The NHS, established in 1976, is a prospective cohort study consisting of 121,701 U.S. registered nurses aged 30–55 years at baseline. At enrollment, women completed a mailed questionnaire regarding their medical histories and lifestyles. Follow-up questionnaires are mailed every two years in order to update information on health and lifestyle. In 1980, a food frequency questionnaire was added. A second Nurse's Health Study (NHS II) consisting of 116,671 female nurses 25-42 years old was begun in 1989. The NHS II racial/ethnic distribution is about 96 percent white with the remainder being roughly similar numbers of African-Americans, Asians, and Hispanics.

- ***NHS: dietary fat and breast cancer:*** NHS: 89,494 women 34-59 yrs old; eight year follow up; 1,439 cases of breast cancer, including 774 post-menopausal; adjusted for age, established risk factors; no positive association between total fat intake and breast cancer incidence in the entire group or among just post-menopausal women; no evidence of protective effect of dietary fiber.[25]

- ***NHS: Dietary fat and post-menopausal breast cancer:*** NHS; Over 80,000 participants; average 20 years follow-up; no relationship between mid- to later life dietary fat and postmenopausal breast cancer risk. This was also true for specific kinds of fat with the exception of trans fat intake where the risk of breast cancer increased by 8 percent for every 1 percent increase of trans fats as a percentage of total calories.[26]

- ***NHS II: Dietary fat and premenopausal breast cancer:*** NHS II; 90,655 premenopausal women ages 26-46 years; >90 percent Caucasian; fat intake was assessed with food-frequency questionnaires; eight years of follow-up; 714 cases of pre-menopausal breast cancer; 25 percent increased risk of breast cancer with total dietary fat although this was not statistically significant (RR 1.25; 95 percent CI 0.98-1.59); 33 percent increased risk associated with higher intake of animal fat. Higher intake of red meat and high-fat dairy each associated with increased risk of breast cancer, but this was largely attributable to higher amounts of animal fat in general.[27] The association between dietary animal fat and breast cancer was stronger in women who were using or who had ever used oral contraceptives and in women whose tumors were ER+ or PR+.

- ***NHS II: Adolescent diet and premenopausal breast cancer:*** NHS II; 39,268 premenopausal women completed a 124-food item questionnaire about their diets during high school; 7.5 yrs follow up; 455 cases of breast cancer occurred; 35 percent increased risk of breast cancer in the group with the highest total fat consumption in adolescence compared to the lowest.[28] The risk was higher for hormone-receptor negative tumors than hormone-receptor positive tumors. Risk also increased (34 percent) with highest red meat consumption during adolescence.[29] In this case, the increased risk associated with higher amounts of meat consumption was not explained by higher amounts of animal fat alone—red meat independently was associated with higher risk. Adolescent dietary milk, dairy, total carbohydrate, glycemic index, dietary fiber were not associated with breast cancer risk.

Canadian National Breast Screening Study: 56,837 women;[30] 40-59 yrs. old at enrollment; dietary information obtained by questionnaire at the time of enrollment; over five years of follow-up, 519 cases of breast cancer diagnosed; menopausal status of cases was not specified, but most were post-menopausal at diagnosis. When dietary fat was treated as a continuous variable in the statistical model, there was a 35 percent increased risk of

breast cancer per 77 gm of dietary fat, (which represented the differences in dietary fat between the highest and lowest quartiles; 47 percent vs. 31 percent of total calories from fat), independent of total calories consumed; no evidence of an association with protein or carbohydrate intake.

Swedish Women's Lifestyle and Health Cohort:[31] 49,261 women enrolled; 30-49 yrs. old; 9 percent post-menopausal at enrollment; dietary history over the past six months obtained by questionnaire; average follow up 13 years; 974 cases of breast cancer; 432 occurred before the age of 50. Total fat was not associated with breast cancer risk before or after age 50; compared to the lowest intakes, highest intake of monounsaturated fat was associated with a significant 55 percent decreased risk of breast cancer after age 50; higher polyunsaturated fat also associated with decreased risk while higher amounts of saturated fat associated with increased risk after age 50; the decreased risk with PUFAs most marked in ER + and PR+ tumors.

Swedish Mammography Screening Cohort study:[32] 61,471 women enrolled; 40-76 yrs old; 4.2 years average follow up; 674 cases of breast cancer diagnosed; dietary history over past six months obtained by questionnaire. There was no association of breast cancer risk with total dietary fat, adjusted for total calories. However, when treated as continuous variables, increasing amounts of monounsaturated fat was associated with decreased risk of breast cancer whereas increasing amounts of PUFAs was associated with increased risk. Results based on quartiles were in the same direction but not significant.

The European Prospective Investigation into Cancer and Nutrition (EPIC): EPIC is a large prospective study in ten countries in the EU; 319,826 participants; average 8.8 years follow up; diet assessment through food frequency questionnaires and 24 hr. food recall interviews in a subset. The study found a 13 percent increase in breast cancer risk for the highest consumers of saturated fat.[33] This association did not vary with BMI or menopausal status although in post-menopausal women, it was stronger among those who never used hormone replacement therapy. No association with total fat, monounsaturated, or polyunsaturated fat was found. Higher BMI[34] and lower amounts of exercise[35] were associated with increased risk. No consistent findings with meat, dairy, egg consumption.[36] In subgroup analyses, higher processed meat consumption associated with 13 percent increased risk of BC in post-menopausal women; no association with red meat consumption over all, but in countries where red meat is typically cooked at higher temperatures, consumption associated with higher risk of breast cancer. This suggests that carcinogens, such as heterocyclic amines and polyaromatic hydrocarbons, produced by high temperature cooking, may play a role. In this study higher butter consumption was also associated with increased risk of breast cancer in premenopausal women. EPIC did not identify or analyze data by hormone receptor status of breast tumors.

National Institutes of Health-AARP Diet and Health Study: dietary fat and postmenopausal breast cancer: A U.S. study of 188,736 postmenopausal women who completed a 124-item food-frequency questionnaire in 1995-1996; approximately 88 percent white, 6 percent African-American, 2 percent Hispanic; average follow up 4.4 years; 11 percent higher incidence of BC in women in highest quintile of total fat compared to lowest; this association was also observed for all fat subtypes.[37] There was no association of meat intake or meat cooking methods with breast cancer after 8 years follow up.[38]

Women's Health Initiative Dietary Modification Trial (an intervention study): The Women's Health Initiative (WHI) trial is a prospective, randomized, intervention study of 48,835 postmenopausal women, aged 50-79 years;[39] 81 percent white, 11 percent African-American, 4 percent Hispanic; 4 percent Asian/Pacific, American Indian. Intervention group: reduction of dietary fat to 20 percent of total energy, increased consumption of fruits, vegetables, whole grains. Control group: given health related printed materials but not advised to make any dietary changes; average follow up 8.1 years. Results: 9 percent lower risk of breast cancer in intervention group although this was not statistically significant; however, in subgroup analyses, women who had higher baseline percentages of total energy from dietary fat experienced 22 percent reduction of risk of breast cancer from the intervention; risk reduction from intervention much greater in ER+/PR- tumors. Only 14 percent of women met the dietary target of 20 percent of energy from fat. Fat mass reduction was greater in women in the intervention group than in controls.[40]

In the WHI prospective intervention study, breast cancer incidence was more dramatically reduced by a low-fat diet in women who had experienced hot flashes compared to women who had not (73 percent vs. 58 percent reduction).[41] This finding was specific for ER+/PR+ tumors and suggests that some post-menopausal women may particularly benefit from low-fat dietary intervention.

Pooled analyses of prospective studies of dietary fat and breast cancer

A pooled analysis of 8 prospective cohort studies including 7,329 cases of breast cancer among over 350,000 women concluded that the risk of breast cancer increased modestly with increased saturated fat consumption (9 percent for every 5 percent increase in saturated fat as a percentage of total caloric intake).[42] Menopausal status did not alter this association.

A recent pooled analysis of data from 52 cohort and case control studies examining the relationship between dietary fat and breast cancer, published over the past 20 years concluded:[43]

- In studies that did not distinguish by menopausal status, there is a small but significant increased risk of breast cancer with increased amounts of dietary PUFA and total fat;

- Among post-menopausal studies only, breast cancer risk increases with higher dietary PUFA and total fat;
- Among pre-menopausal studies only, no increased risk of breast cancer with total dietary fat or any subtypes.

Polyunsaturated fatty acids and breast cancer risk

A 2006 review of omega 3 FAs and cancer risk included analysis of 8 prospective studies of breast cancer.[44] Two of four using fish consumption as a marker for omega 3s found no association with breast cancer risk, one found an increased risk, and one a decreased risk. Studies that included omega 3s from all sources found no association.

A 2013 meta-analysis of 21 prospective cohort studies including 20,905 cases of breast cancer among 883,585 participants found the highest level of dietary marine omega 3 FA was associated with a 14 percent reduction in breast cancer risk, whether measured as dietary intake or as tissue biomarkers.[45] This association was stronger in studies that did not adjust for BMI. No significant association was observed for dietary fish or exposure to alpha linolenic acid (a somewhat shorter-chain omega 3 FAs compared to marine omega 3 FAs).

Occasional studies examine breast cancer risk associated with varying combinations of omega 3 and omega 6 FAs. The large prospective Singapore Chinese Health Study of over 35,000 women 45-74 yrs of age found that higher intakes of omega 3 FA, primarily from fish/shellfish was associated with a 24 percent lower risk of developing breast cancer. Moreover, among women whose omega 3 FA intake was low, high levels of dietary omega 6 FAs was associated with a near doubling of breast cancer risk.[46] This was also reported in another large prospective study in France.[47]

Several things could explain inconsistent outcomes of studies of the impacts of omega 6 and omega 3 FAs. In Asian populations with low breast cancer incidence, marine fish are a major source of long chain omega 3 FAs. In laboratory and some epidemiologic studies these have the most protective effect with respect to breast cancer risk. In the typical Western diet, alpha-linolenic acid, a shorter chain omega 3 FA, is dominant. Humans do not biochemically convert this FA to the longer chain omega 3 very efficiently. As a result, the omega 3 FAs in diets that do not contain marine fish may not be as protective. Traditional Asian diets also often contain soy products and seaweed, which seem to confer additional protection, as discussed below.

In addition to being incorporated into cell membranes throughout the body, omega 6 and omega 3 FAs are enzymatically converted into a family of chemicals called eicosanoids, which are signaling molecules that influence a number of biologic processes, including inflammation and immune system function. Omega 6 FAs are converted largely, although

not entirely, into eicosanoids that promote inflammation. Omega 3 FAs, however, are converted almost exclusively into anti-inflammatory compounds. Thus, a diet featuring higher amounts of omega 6s and low amounts of omega 3s would generally be pro-inflammatory. It is increasingly clear that chronic inflammation plays an important contextual role in carcinogenesis and cancer progression, as well as a number of other chronic diseases, including cardiovascular disease, diabetes, metabolic syndrome, arthritis, asthma, Alzheimer's disease, and other neurodegenerative disorders.[48,49,50]

The dominant dietary omega 6 FA, linoleic acid, obtained from some vegetable oils, margarine, and processed foods, is partially converted enzymatically into arachadonic acid, an essential but inflammation-promoting eicosanoid. Early studies generally concluded that only a small portion of dietary linoleic acid was converted into arachadonic acid, but now it appears that enzyme levels influencing this conversion (FA desaturase) vary with genetic inheritance. A recent study showed that the genetic variations responsible for higher enzyme levels leading to higher levels of arachadonic acid production are much more common in people of African than of European ancestry.[51] The implications could be profound, since African and African-American women are at higher risk of more aggressive and hormone-receptor-negative tumors than white American women.[52]

5-lipoxygenase is an additional enzyme that converts arachadonic acid to various inflammatory mediators called leukotrienes. The 5-lipoxygenase pathway has been implicated in carcinogenesis and tumor progression in several different tissues.[53] A case-control study of White, Latina, and African-American women with breast cancer in the San Francisco area found that women with a particular polymorphism of genes responsible for levels of this enzyme and its activating protein were at an 80 percent increased risk of breast cancer only if their diet contained high levels of linoleic acid, the most prominent omega 6 polyunsaturated FA.[54] In this study, the polymorphism associated with increased risk was rare in African-American women and much more common in White and Latina participants.

Thus, health risks associated with high dietary levels of omega 6 FAs may be most marked in people who more readily metabolize them into arachadonic acid and other pro-inflammatory compounds. Since linoleic-to-arachadonic acid conversion appears to be more pronounced, on average, in African-Americans, this could help to explain black-white health disparities for a number of diseases, including various kinds of cancer, where those differences cannot otherwise be fully accounted for. Gene-related differences in FA metabolism may also help explain some of the inconsistency in the studies examining the relationship between omega 6 FAs and breast cancer risk.

Dietary meat and breast cancer

Among many case-control and cohort studies, evidence linking meat consumption to breast cancer risk is inconsistent. Prospective studies generally find little or no relationship between meat consumption in mid- or later-life and breast cancer risk. But these studies usually determine meat consumption at baseline and perhaps one time thereafter in relatively short periods of follow up and cannot shed light on the extent to which earlier life meat consumption influences breast cancer risk. .

The NHS II found a significantly increased risk of pre-menopausal breast cancer with increased meat consumption during adolescence. Moreover, several studies find that higher amounts of dietary meat in childhood are associated with earlier age at menarche—a well-recognized risk factor for breast cancer (See Box 3.1).

Increased breast density is strongly associated with increased breast cancer risk. Data linking meat consumption with increased breast density are mixed (See Box 3.2). Inconsistent findings may be due to differences in study design, including the potential for "over controlling" for age of menarche when analyzing data.

Thus, higher levels of meat consumption in childhood and adolescence may increase the risk of premenopausal breast cancer significantly while meat consumption in mid-life and later is probably not independently associated with breast cancer risk much, if at all. That said, other reasons for keeping red meat consumption low, even in adulthood, include a reduced risk of diabetes and cardiovascular disease[55,56] as well as environmental benefits.[57]

It should also be noted that the nutritional profile of beef varies with production methods. The omega 3 FA content is higher in grass-fed animals than in those fed corn.[58,59] To my knowledge, no study has examined the influence of variable kinds of animal feed or the use of hormones during meat production on breast cancer risk.

Dietary meat and breast cancer study descriptions

The NHS II (see above) found an increased risk of premenopausal breast cancer with higher levels of red meat consumption during adolescence.

A 2002 pooled analysis of data from eight prospective studies found no significant relationship between mid- or later life dietary meat and risk of pre- or post-menopausal breast cancer.[60] None of these eight studies attempted to estimate meat consumption earlier in life.

Box 3.1: Should studies of diet and breast cancer always control for age at menarche?

Most investigations into impacts of environmental factors on breast cancer risk use statistical methods to control for known risk factors, such as age at menarche, age at first pregnancy, number of pregnancies, use of oral contraceptives, and so on. This is intended to isolate the influence of the variable of interest, by mathematically holding the other risk factors "constant." In some circumstances, however, this might be an example of inappropriate "over-controlling." Here's why.

Although in NHS II, information was gathered about diet during high school, when presumably most participants had already undergone menarche, a study examining childhood dietary influences on breast cancer risk that controlled for age at menarche would tend to miss the impacts of diet on both age of menarche and breast cancer risk. For example, if higher childhood meat consumption advances the age of menarche and thereby, the subsequent risk of breast cancer, controlling for age of menarche in statistical data analyses will tend to obscure the influence of childhood dietary meat on cancer risk.

This is not just a theoretical concern. A prospective study of more than 3,000 girls in the United Kingdom, followed since birth, found that earlier menarche was strongly associated with higher consumption of red meat, total protein, animal protein and total energy measured at ages three and seven.[61] There was no impact of total dietary fat or fruit and vegetable consumption on age at menarche in this group.

A similarly designed study of 67 white girls born in Boston in the 1930s and 1940s found that age at menarche was earlier with higher amounts of dietary animal protein at ages three-five and five-eight years and delayed with higher vegetable protein intakes at three-five years.[62] There was no association with total energy or fat intake.

A cross-sectional study in the UK found no difference in age at menarche among women who were life-long vegetarians vs. those who became vegetarian as adults. However, age at menarche was later in those who became vegetarian at age 10-14 years.[63]

Studies that measure protein intake around the time of menarche rather than earlier in childhood generally do not find an association with the onset of menses.[64,65]

A second example arises from concerns that low levels of vitamin D may increase breast cancer risk (see chapter 6). Considerable evidence supports this relationship although epidemiologic studies are somewhat inconsistent. However, a recent prospective study of 242 girls in Bogata, Columbia found that lower serum levels of vitamin D were associated with significantly earlier menarche.[66] This association remained after controlling for BMI. If follow-up studies confirm this relationship, controlling for age of menarche when examining the link between vitamin D and breast cancer would be inappropriate.

As more studies begin to look at the influence of early life diet or other environmental factors on breast cancer risk, it will be important to avoid "over-controlling" for risk factors, like early onset of menses, which may actually be driven by the exposures of interest.

A more recent meta-analysis of 10 studies found a significant 24 percent increased risk of premenopausal breast cancer with increased meat consumption.[67] This finding was largely driven by case-control rather than cohort studies, which generally find no association when meat consumption at study baseline is used as an estimate. One population-based case-control study that found an increased risk concluded that the association was particularly strong with a high intake of well-done meat.[68] This is consistent with the EPIC study, discussed above.

The large, prospective NIH-AARP study of 120,755 post-menopausal women identified 3,818 cases of breast cancer in eight years of follow-up.[69] Information on diet at baseline was obtained by questionnaire, with follow-up at six months, including questions about meat preparation and degree of "doneness." Age-adjusted or fully-adjusted data analysis showed no significant associations between meat consumption or methods of meat preparation and breast cancer risk. Fully adjusted models controlled for age, BMI, height, age at first men-

Box 3.2: Diet and breast density

Increased breast density is strongly associated with increased risk of breast cancer[70] and investigators have wondered if childhood diets can influence breast cancer density in adulthood. Study results are inconsistent.

A study of 250 women of Chinese ancestry who had migrated to the U.S. in adulthood found that increased breast density after age 40, as determined by mammography, was strongly associated with higher meat intake during adolescence.[71] Interestingly, age at menarche was not associated with breast density and was not adjusted for in the models examining the relationship between dietary meat and breast density.

The Minnesota Breast Cancer Family study found no association between diet at age 12 and later breast density.[72] This study did adjust for age at menarche in the final analysis. Was that appropriate or is it an example of over-controlling in data analysis? Neither of these studies had information about diet in earlier childhood.

A prospective study of 1,161 women in the UK collected data on dietary habits at age 4 and again at several times during adulthood.[73] The authors found no association between diet at age 4 and breast density on mammography in adulthood. However, dietary patterns at age 4 were classified as breads and fats, fried potatoes and fish, and milk, fruit, biscuits, with no attempt to examine the impact of meat independently. Moreover, data analyses were adjusted for age at menarche, potentially obscuring the effect of childhood meat consumption on age at menarche. In this study, higher total energy in mid-adulthood was associated with higher breast density 15 years later.

strual period, age at first live birth, age at menopause, number of breast biopsies, family history of breast cancer, menopausal hormone therapy, education, race, total energy intake, saturated fat, alcohol, physical activity, and smoking.

In the prospective study of over 60,000 women in the Swedish Mammography Cohort over an average of 17 years of follow up, no association was found between risk of breast cancer and red meat consumption.[74] However, higher consumption of pan-fried meat was association with a 45 percent increased risk of breast cancer for ER+/PR- tumors.

Dairy product consumption and breast cancer risk

A relationship between breast cancer risk and milk and dairy consumption has been proposed for many years and is biologically plausible. In addition to its nutritional composition, milk contains various hormones and growth factors that are potentially associated with increased breast cancer risk, including estrogens, progesterone, and insulin-like growth factors (IGFs). Earlier age of menarche, a risk factor for breast cancer, is weakly associated with higher total dairy consumption.[75] In adolescent girls, milk consumption results in higher IGF-1 levels.[76] IGF-1 promotes cellular proliferation and impedes apoptosis and higher levels may be associated with increased risk of breast cancer, although study results are inconsistent. In a prospective study of pre-menarchal girls, higher levels of dairy consumption were associated with more rapid height growth,[77] which in turn is related to increased breast cancer risk.

But, epidemiologic studies have yielded inconsistent results regarding dairy consumption and breast cancer, ranging from increased risk to reduced risk.[78,79,80] Childhood or adolescent milk consumption is associated with decreased risk in several studies.[81,82,83]

In laboratory studies, dietary milk in adulthood inhibits the regression of chemically induced mammary gland tumors in rodents.[84] On the other hand, dietary milk administered to rodents before puberty reduced susceptibility to tumor development after administration of a carcinogen (DMBA) in adulthood.[85] Similarly, diethylstilbestrol, a synthetic estrogen, administered in the neonatal period reduces susceptibility to a mammary gland carcinogen (DMBA) administered in adulthood,[86] whereas prenatal exposure increases mammary gland cancer risk. This suggests that the impact of dietary cow's milk on breast cancer risk, as with other hormonally-active substances, may depend on life-stage and the relative timing of other exposures. Dietary dairy products containing hormones and other growth factors could promote tumors that have already been initiated, for example. The nature and timing of co-exposures may underlie the inconsistencies of epidemiologic studies looking at dairy products and breast cancer risk.

Fruits and vegetables and breast cancer risk

Higher amounts of fruit and vegetable consumption appear to reduce breast cancer risk, along with many other well-established benefits. Carotenoids are pigmented compounds in many fruits and vegetables—particularly yellow and orange fruits and vegetables and green, leafy vegetables. They are antioxidants; some inhibit cellular proliferation, induce apoptosis (programmed cell death), and have other beneficial effects on physiology and metabolism.[87] Beta-carotene, one of the major carotenoids, may be particularly important because it is converted to vitamin A. Vitamin A is in turn converted to retinoic acid, which tends to reduce cellular proliferation and encourage cellular differentiation. Thus, dietary carotenoids may not only reduce breast cancer risk but also be beneficial after breast cancer diagnosis.* Carotenoid absorption from the intestine and the extent to which it is converted to vitamin A is highly variable and can be affected by the food matrix, food-processing, and amounts of dietary fat and fiber, as well as genetic differences in carotenoid metabolism.[88]

Enterolactone and enterodiol are two dietary lignans formed in the intestine from precursors in whole grains, vegetables, fruits, and berries. Some data show that higher serum levels of enterolactone are associated with reduced risk of post-menopausal breast cancer[89] and improved survival after diagnosis.[90]

Studies show that women eating a vegetarian diet excrete higher levels of estrogen in their feces than do omnivores, reducing circulating levels.[91] Lower levels of estrogen are likely to contribute to lower breast cancer risk.

A meta-analysis of 26 studies looked at the role of dietary vegetables, fruit, carotene, or vitamin C.[92] It included more case-control than cohort studies of both pre- and post-menopausal breast cancer. Study designs varied considerably, including dietary assessment ranging from current diet to one, two, and five years prior to interview. All studies used a food-frequency questionnaire to obtain information on diet, although there were large differences in the number of food items listed. Data were analyzed in a number of ways and subject to sensitivity analysis. The results showed a moderately protective role, particularly for higher intake of vegetables, which showed a 25 percent reduction in breast cancer risk.

An analysis of eight prospective cohort studies from North American and Europe observed only a weak, non-significant protective effect of fruits and vegetables in the adult diet, with follow up ranging from five-10 years.[93] Similarly, a large prospective study in the EU in which most participants were 35-70 yrs old when entered, found no protective effect of

* The effects of dietary carotenoids may be quite different from effects of supplements, which may not be beneficial.

higher dietary fruits and vegetables after a relatively short average follow up period of 5.4 years.[94]

A number of studies have investigated associations of dietary carotenoids with breast cancer risk. Two meta-analyses have been reported. The first pooled the results of seven case-control and four cohort studies and found that higher dietary levels of beta-carotene were associated with a 20 percent reduced risk of breast cancer.[95] The second meta-analysis considered data from 33 studies—a mixture of case-control, nested case-control, and cohort designs—and found a six percent reduced risk with the highest amounts of dietary beta-carotene and nine percent reduced risk with highest amounts of alpha-carotene. These studies generally obtained dietary information in adulthood from food-frequency questionnaires.
In some cases, scientists have measured blood levels of carotenoids at the beginning of a study and then followed participants over a period of time to see if there is an association with subsequent development of breast cancer. A recent study analyzed data from eight prospective studies using that approach.[96] The time between blood collection and breast cancer diagnosis ranged from 0.8 to 13.7 years, with an average of 4.3 years. The analysis included 3055 cases of breast cancer and 3,956 controls. Mean age at blood collection for cases was 51.3-66.0 in the eight studies, and 67 percent of all participants were postmenopausal. The authors reported statistically significant decreased risk of breast cancer in women with higher baseline levels of alpha-carotene (RR=0.87), beta-carotene (RR=0.83), lutein + zeaxanthin (RR=0.84), lycopene (RR=0.78), and total carotenoids (RR=0.81).

Among the limitations of these studies is the lack of information about diet during childhood and adolescence. Studying adult dietary habits will not help to clarify potential benefits (or risks) associated with fruit and vegetable consumption during vulnerable periods of breast development earlier in life.

Dietary soy and breast cancer risk

The effect of dietary soy on breast cancer risk has long been of interest primarily because Asian women, living in their ancestral countries, whose diets traditionally include a variety of soy products, are much less likely to develop breast cancer than women consuming a more Western diet. The studies summarized below show that dietary soy appears to have a protective effect against breast cancer and higher amounts in childhood and adolescence seem to be particularly beneficial. That conclusion does not extend to soy formula in infancy and subsequent breast cancer risk, which has not been investigated. It also does not extend to highly processed soy components, common in processed food in the U.S., or to soy supplements.[97]

The biologic effects of soy isoflavones

Although the mechanisms by which dietary soy may be protective are not completely understood, animal studies show that pre-pubertal exposures to soy isoflavones, a family of compounds in soy products, promote cellular differentiation so that the resulting tissue structure is more mature and less likely to develop cancer. Pre-pubertal exposures also alter the expression of a number of different genes, thereby influencing hormone receptor levels and various other chemical signaling molecules and pathways in ways that would be expected to inhibit tumor development and progression (also reviewed in Warri, 2008).[98]

Soy isoflavones are sometimes called phytoestrogens because they have structural similarities to the hormone estrogen and have some estrogenic activity, although it differs in important ways from endogenous hormones. The impact of isoflavones on breast cancer risk deserves a close look because of concerns that estrogenic stimulation may actually promote cancer growth. But studies show that soy isoflavones have a diverse array of biologic activities, including blocking cell signaling mechanisms important in cancer development, reducing cellular proliferation, inducing apoptosis, altering hormone metabolism, and anti-oxidant effects, among others.[99,100]

Estrogen-like compounds influence gene expression through multiple mechanisms. Estrogen receptor (ER)-alpha and ER-beta activation are among several receptor-mediated pathways—others include cell membrane bound receptors and estrogen-related receptors. Each of these has different biologic activity when activated. (Chapter 5 discusses the influence of bisphenol A, an environmental chemical, on these receptors and how it might influence breast cancer risk by mechanisms independent of its activation of the classic estrogen receptor).

Genestein and daidzein are two isoflavones at relatively high concentrations in soybeans and soy products, particularly miso and tempeh. Several others, including glycitein, are present in lower amounts. Intestinal bacteria can metabolize daidzein into another isoflavone called equol. Equol has a particular affinity for the ER-beta receptor. This may be important because, in many studies, ER-beta activation inhibits breast cancer cell proliferation in tissue cultures, while ER-alpha activation promotes proliferation.[101] Equol also has anti-androgenic activity.

Studies show that only 20-30 percent of Western adults harbor intestinal bacteria that metabolize daidzein to equol, compared to 50-60 percent of Asian adults.[102] Among Western adults, vegetarians are more common equol-producers. This suggests that regular consumption of larger amounts of soy products can modify intestinal bacterial composition, which may help to explain discrepancies in the relationship between diet and health outcomes in populations with different amounts of soy in their daily diets.

Study summaries: Dietary soy and breast cancer risk

Individual and grouped epidemiologic studies, including some looking at differences in Asian and Western populations, have produced different results. A 2006 meta-analysis of 18 studies (12 case- control, 6 cohort or nested case-control) found a 14 percent reduction of breast cancer risk associated with higher dietary soy intake.[103] The magnitude of the risk reduction was similar in Asian and Western populations and was slightly stronger for pre-menopausal breast cancer. In this study, the Western category included Asian Americans.

A 2008 meta-analysis looked at 8 studies conducted in Asia and in Asian Americans (1 cohort; 7 case-control) and separately, at 11 studies (4 cohort, 7 case-control) in Western populations. Studies of Asians, including women living in Asia and Asian Americans, showed a significant 29 percent reduction in both pre- and post-menopausal breast cancer risk in women with highest soy consumption compared to those with the lowest.[104] The meta-analysis of studies of Western populations, which did not include Asian Americans, found no significant relationship between dietary soy and breast cancer risk.[105]

A 2011 meta-analysis of 14 prospective studies (cohort or nested case-control; average follow-up 2-13 years) of dietary soy and breast cancer found higher isoflavone intake associated with a 24 percent risk reduction in Asian but not Western populations.[106] Risk reduction was greater among post-menopausal women.

These apparently inconsistent results may be reconcilable. Soy consumption was dramatically different in the two different populations in the 2008 meta-analysis. In the Asian studies, 20 mg. or more daily isoflavones in the highest vs. 5 mg. or less in the lowest subgroup compared to 0.8 mg. or more vs. 0.15 mg. or less in the Western population studies—a 25-fold difference. Moreover, participants in the Western studies were more likely to obtain their dietary isoflavones from soy fillers in baked goods and canned products, whereas Asians were more likely to be consuming tofu and other traditional Asian products. The amount and ratios of isoflavones in soy-containing food can vary considerably depending on whether or not the whole bean or just the protein isolate is used.[107]

These findings are consistent with a protective effect in Asian and Asian American women who consume soy on a daily basis and who may well have been regularly consuming soy products throughout their lives. It is entirely plausible that a protective effect is also realized by Western women under similar circumstances.

Dietary soy in childhood and adolescence and subsequent breast cancer risk

A number of laboratory animal studies show that early life exposure to soy isoflavones can influence mammary gland development and in some instances protect the mammary glands, reducing the risk of cancer after later exposure to known mammary carcinogens.[108] In rodent studies, however, the effects of genestein on growth and development depend on the dose, timing, and route of exposure. This is particularly important because many infants in the U.S. consume soy formula soon after birth.

In mice treated with genestein soon after birth, a high dose caused a decrease in the number of terminal end buds (TEBs) and decreased branching in the mammary gland at puberty, while a low dose caused increased branching and ductal elongation.[109] The high-dose changes persisted into adulthood.

In rats, pre-pubertal genestein exposure decreased the number of TEBs in the mammary glands of adults and increased the number of more mature lobules.[110] Animals treated with genestein pre-pubertally also had reduced numbers of mammary gland tumors after treatment with DMBA, a mammary carcinogen. Another rodent study showed that higher exposures to an isoflavone-rich or genestein-rich diet *in utero* and up to young adulthood reduced mammary gland responsiveness to estrogen.[111]

These findings are all consistent with the hypothesis that dietary soy during childhood may contribute to earlier breast tissue differentiation and reduced susceptibility to cancer. They are also consistent with results of several epidemiologic studies published within the past 10 years.

A population-based case-control study of women of Chinese, Japanese, or Filipino descent living in California or Hawaii examined the impact of dietary soy during childhood and adolescence on subsequent breast cancer risk.[112] The study included 597 cases and 966 controls all of whom were 22-55 yrs old. Seventy-three percent of cases were premenopausal at diagnosis. Dietary histories were obtained from participants and when possible, from their mothers. Comparing highest soy intake with the lowest in childhood, adolescence, and adulthood, breast cancer risk was reduced by 60 percent, 20 percent, and 24 percent respectively. The risk reduction associated with higher soy intake in childhood was highly significant, seen in women from all three countries, in all study sites, and women born in Asia and the U.S.

Two studies of Asian or Asian American women in the 2008 meta-analysis mentioned above had asked and found that higher soy consumption during adolescence had a more protective association than high consumption in adulthood.[113,114]

The Shanghai Women's Health Study was included in the 2011 meta-analysis.[115] This is a prospective study of more than 70,000 women, 40-70 years old, with an average follow-up of 7.4 years. Higher intake of soy protein and isoflavones was associated with a lower risk of breast cancer, and this association was particularly strong for pre-menopausal women. Information about the adolescent diet of participants had also been collected. Higher soy intake during adolescence was highly significantly associated with lower breast cancer risk in adulthood, independent of adult soy intake. Women with the highest adolescent and adult soy intake showed the most dramatic reduction in breast cancer risk—60 percent lower than women in the lower intake categories.

Similarly, in a population-based case control study of non-Asians in Canada, higher intake of isoflavones, lignans, and total phytoestrogens in adolescence were each associated with lower risk of breast cancer.[116] Lignans are the principal phytoestrogen in typical Western diets—present in grains, nuts, fruits, vegetables, tea, and coffee.

Thus, each study that examines the relationship between dietary soy in childhood and subsequent breast cancer risk finds a protective association—higher intake is associated with lower risk. Evidence consistently shows that higher soy intake in childhood and adolescence is associated with even greater reduction of risk than higher amounts in adulthood. Most laboratory animal studies also show a preventive effect of early-life soy isoflavone exposure on mammary tumor development.[117]

Whether or not soy formula in infancy has an influence on breast cancer risk is an important question that is largely unexplored. In addition, it is important to note that the findings in these epidemiologic studies do not mean that soy supplements will be beneficial and protect against breast cancer. Dietary soy is consumed as part of a complex meal pattern. In one study of soy supplements for six months in women at risk for breast cancer, aspirates of breast epithelial cells showed a small increase in cellular proliferation in premenopausal women using the supplements, suggesting an estrogenic effect.[118] Whether or not this will increase breast cancer risk is unknown.

Seaweed, mushrooms

Soy content is not the only difference between traditional Asian and Western diets. In Japan, where breast cancer incidence has historically been quite low, although increasing in recent years, diets regularly contain fish, seaweed, mushrooms, rice, and fruit as well as soy products.[119] Sushi wrappings, seasonings, condiments, and other dishes contain seaweed, and it can be a significant part of the daily diet.

Brown, green, and red seaweeds are rich in unique polysaccharides (fucans), iodine, minerals, vitamins, and dietary fiber.[120,121] Thirty years ago, cancer researcher Jane Teas wondered if seaweed in the Japanese diet might help explain the low incidence of breast cancer in that country compared to others.[122] She proposed that alteration of cholesterol and hormone metabolism, alteration of intestinal flora, increased consumption of iodine and other trace minerals, and anti-oxidant properties might explain a protective effect. Anti-oxidant and anti-tumor effects of seaweeds have been reported in studies *in vitro* and *in vivo* since then.[123,124] For example, extracts from two different kinds of seaweed, wakame and mekabu, administered in drinking water dramatically reduced carcinogen-induced mammary tumors in rodents.[125]

A case-control study in Korea found that increasing amounts of dietary seaweed (gim) were associated with decreased breast cancer risk in both premenopausal and postmenopausal women.[126] This association was less robust when dietary soy, mushrooms, and vitamins were taken into account—suggesting that dietary patterns are important.

Studies of Japanese postmenopausal breast cancer survivors report serum estrogen levels far lower than in postmenopausal breast cancer survivors in the U.S.[127,128] A double blind cross-over study of 15 healthy non-Asian post-menopausal U.S. women showed that seaweed-soy supplements caused significantly lower serum estrogen levels with a sharp increase in estrogen excretion.[129] The amounts of seaweed associated with this effect are about four to seven gm. daily, depending on body weight—well within the typical range of seaweed consumption in Japan. Since higher estrogen levels drive cellular proliferation in ER+ breast cancer, diets regularly containing soy and seaweed that reduce estrogen levels may therefore be beneficial not only for breast cancer prevention but also after diagnosis.

Mushrooms are also more common in the Asian than American diet. A case-control study in Korea found that post-menopausal women who ate mushrooms at least three times a week had a sharply reduced breast cancer risk compared to women who ate few or no mushrooms.[130] A subsequent study found reduced risk in both pre-menopausal and post-menopausal Korean women.[131] Risk reduction was highest for ER+/PR+ tumors in pre-menopausal women. A protective effect of dietary mushrooms is plausible since studies show that mushroom extracts reduce oxidative stress, inhibit cell proliferation, and reduce aromatase activity, an enzyme essential for estrogen production. Aromatase inhibitors are now used to treat some kinds of breast cancer.[132]

Carbohydrates and breast cancer

Studies investigating dietary carbohydrates and breast cancer risk have inconsistent results but generally find no significant relationship.[133,134] Occasional studies find an increased risk

associated with higher consumption of sucrose-containing foods, including desserts. For example, the Long Island Breast Cancer study found a 27 percent increased risk with higher consumption of desserts, sweetened beverages, and added sugars.[135] The risk was about 50 percent higher when just desserts were considered and was higher for pre-menopausal than post-menopausal breast cancer. Other case-control studies have also found a modestly increased risk of premenopausal breast cancer with higher intake of sweet foods and beverages.[136,137,138] However, some studies find no relationship.[139,140]

Dietary patterns

In recent years studies have begun to evaluate dietary patterns rather than concentrating almost exclusively on individual nutrients.[141] Intuitively, this makes sense. People eat food and meals—not individual nutrients. Complex combinations of nutrients and food groups have biologic effects that are independent of the contribution of individual nutrients in isolation and cannot be predicted easily. One nutrient may influence the intestinal absorption of another. Or, one may increase cancer risk while others are protective, and their impacts in the aggregate will matter most. Dietary patterns also influence the composition of the microbial inhabitants of the intestine (the intestinal microbiome), which in turn influences systemic hormone levels.[142]

From a research perspective, the high degree of correlation of some nutrients also makes it difficult to study their effects independently. The effect of a single nutrient may be too small to detect, but combinations of nutrients may have a larger effect easier to see. These are among the reasons that dietary pattern analysis has entered into breast cancer research.

But, dietary pattern analysis also presents new research challenges. How is a pattern defined? Researchers often group dietary components together in various ways and name them—for example, the "prudent healthy diet," the "Mediterranean diet," the "recommended food score," among others—with the hope that useful groupings will become apparent and move our understanding forward.

With few exceptions, dietary pattern analyses show reductions in breast cancer risk in women whose diets feature more plant based foods and seafood and less meat. The reduced risk in some studies is small but in others quite dramatic. Overall the findings are quite consistent. No research has yet addressed patterns of childhood and adolescent diets and breast cancer risk.

Study summaries: Dietary pattern analysis and breast cancer risk

In 2010, a meta-analysis of 39 case-control and cohort studies reported on dietary patterns and breast cancer risk, using the prudent healthy, Western/unhealthy, and drinker dietary patterns for analysis.[143] The prudent/healthy pattern tended to have higher amounts of fruit, vegetables, poultry, fish, low-fat dairy, and whole grains. Western/unhealthy dietary patterns had higher amounts of red and/or processed meat, refined grains, potatoes, sweets, and high-fat dairy. Drinker dietary patterns had higher amounts of wine, beer, and spirits. In general the dietary information obtained in these studies was restricted to current or fairly recent dietary habits. The analysis found a significant 10 percent decreased risk of breast cancer among women in the highest compared with the lowest categories of intake of the prudent/healthy diet. Higher intake of an unhealthy/Western diet was associated with a slight increase in risk that was not statistically significant. The four studies identifying a drinker dietary pattern collectively showed a 20 percent increased risk.

The analysis included a long-term follow up of participants in the NHS. It found a reduced risk of ER-postmenopausal breast cancer with stronger adherence to the alternative Mediterranean Diet,* Alternative Healthy Eating Index,† and Recommended Food Score.‡[144]

The reduced risk was mostly explained by the vegetable component and higher polyunsaturated:saturated fat ratio of the Alternative Healthy Eating Index. The higher monounsaturated:saturated fat ratio in the Alternative Mediterranean Diet Score explained most of its reduced risk. No association was observed with the nuts and soy component, cereal fiber, white: red meat ratio, trans-fats, multivitamin use, or the alcohol component of that dietary pattern. The vegetable component explained most of the reduced risk associated with the Recommended Food Score.

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* The Mediterranean diet scale is based on the intake of vegetables, legumes, fruits and nuts, dairy, cereals, meat and meat products, fish, alcohol, and the monounsaturated:saturated fat ratio. Lower intake of meat and dairy scores higher. The alternative Med diet excludes potato products from the vegetable group, separates fruits and nuts into 2 groups, eliminates the dairy group, includes whole-grain products only, includes only red and processed meats for the meat group, and assigns 1 point for alcohol intake between 5 and 15 g/day

† The Healthy Eating Index contains 10 components consisting of grains, vegetables, fruit, milk, meat, total fat, saturated fat, cholesterol, sodium, and diet variety. It reflect recommendations based on the USDA Food Guide Pyramid and the 1995 Dietary Guidelines for Americans. The AHEI differs by removing potatoes from vegetables, and including fruit, nuts and soy, white/red
meat ratio, trans fat and the polyunsaturated:saturated fat ratio, cereal fiber, and adding long-term multivitamin use, and alcohol intake.

‡ The RFS features fruits, vegetables, whole grains, lean meats or meat alternates, and low-fat dairy products

A more recent analysis of dietary data from 86,620 participants in the NHS examined whether a low carbohydrate or the DASH (Dietary Approaches to Stop Hypertension) diet was associated with postmenopausal breast cancer risk.[145] The DASH diet features plant proteins, fruits and vegetables, moderate amounts of low-fat dairy, and limited sugary foods and salt. In up to 26 years of follow up, neither low-carbohydrate diets nor the DASH diet were associated with overall incidence of breast cancer or ER+ breast cancer. But both the vegetable/low-carbohydrate diet and the DASH diet were associated with decreased ER- breast cancer risk.

A recent large prospective study of women 35-79 years of age in the UK found that stronger adherence to a Mediterranean Diet was associated with a 35 percent reduced risk of developing breast cancer in pre-menopausal women over an average follow up period of nine years, although the result did not quite reach statistical significance.[146] The Mediterranean Diet includes higher intakes of vegetables, fruits, legumes, whole grains, fish, and moderate amounts of red wine during meals.

A prospective study of 20,967 women in the Melbourne (Australia) Collaborative Cohort Study[147]; 27-76 years old at baseline; average follow-up 14.1 years; dietary habits ascertained through food frequency questionnaire and 121 food items analyzed using principal factor analysis, a technique for identifying groups of variables that explain most of the variability in the diets of participants. For example, some groups of variables correlate well with high vegetable intake, while others correlate with high intakes of fruits, cereals, or meat. These were called the vegetable, fruit and salad, traditional Australian, and meat diets. Results: The fruit and salad pattern correlated with reduced risk of breast cancer. The correlation was much stronger for hormone receptor negative tumors.

Two recent studies are available from China, where breast cancer incidence is about 5-fold lower than in the U.S. but recently increasing. In the Singapore Chinese Health Study; (a prospective study of 34,028 women without cancer at baseline, 72 percent post-menopausal; average 10.7 yrs follow-up); meat-dim sum vs. fruit-vegetable-soy dietary patterns; 30 percent decreased risk of post-menopausal breast cancer in women who highest adherence to fruit-vegetable-soy dietary pattern compared to lowest adherence to that pattern.[148]

The second is a case-control study of 438 Chinese women with breast cancer and 438 controls.[149] Dietary history over the previous year was obtained with food frequency questionnaires. After adjustment for confounders, women in the highest quartile of vegetable-fruit-soy-milk-poultry-fish dietary pattern had a 74 percent decreased risk of breast cancer compared to the lowest quartile. The refined grain-meat-pickle pattern was associated with 2.6-fold increased risk.

Similarly, a case-control study in Korea showed an 86 percent decreased risk of breast cancer in women with the highest intake of the vegetable-seafood pattern compared to the lowest.[150] This association was not affected by menopausal status. No significant differences in risk were seen across the quartiles of the meat-starch pattern.

Diet and breast cancer outcomes following diagnosis

Interpreting available data addressing the relationship between diet and breast cancer prognosis and survival is complex for a number of reasons. Pre-diagnosis as well as post-diagnosis diets can influence breast cancer outcomes, and each introduces its own measurement challenges. Moreover, after the diagnosis of breast cancer, stress levels increase and individuals often change their daily routines in various ways, including physical activity levels, diet, and use of nutritional supplements.[151] Individually and collectively these may influence outcomes. Thus, isolating and evaluating the impacts of dietary variables is difficult.

Despite these challenges, a number of observational and two large intervention studies provide varying levels of evidence that lower levels of dietary saturated fat and higher amounts of fruits and vegetables, combined with regular exercise and weight loss in people who are overweight, reduces mortality following breast cancer diagnosis and treatment and may also reduce or delay recurrence. Higher amounts of dietary soy pre- and post-diagnosis are associated with decreased mortality and may be associated with decreased likelihood of recurrence.

Study summaries: Dietary associations with breast cancer outcomes after diagnosis and treatment

Conclusions from observational studies of the association between dietary fat and breast cancer outcomes are mixed. In general, they find that higher levels of fat weakly increase the risk of recurrence or death or that dietary fat has no discernible effect on outcomes.[152,153,154,155,156,158,159] Obesity, however, is associated with increased risk of all-cause and breast cancer specific mortality after diagnosis in both pre- and post-menopausal cases.[160] Diet, of course, is not the only determinant of body weight, but it plays a substantial role, and dietary changes can contribute significantly to weight loss in overweight or obese individuals diagnosed with breast cancer.

Some evidence suggests an influence of dietary fat prior to diagnosis on breast cancer outcomes. A 1994 Canadian study of 678 women with breast cancer found that lower levels of pre-diagnosis dietary saturated fat and higher levels of beta-carotene and vitamin C were associated with increased survival.[161] The association with saturated fat was most marked in post-menopausal women.

A Swedish study examined the dietary patterns of 240 women recently diagnosed with breast cancer (209 post-menopausal) and found that higher amounts of total and saturated fat around the time of diagnosis were associated with shorter period of disease-free survival over four years of follow-up in those with ER+ tumors.[162]

Initial analyses of data from the NHS showed that higher amounts of dietary fat were associated with a modestly increased risk of death from any cause after the diagnosis of breast cancer.[163] The NHS also found that a prudent diet, high in fruit, vegetables, whole grains, and low-fat dairy products was associated with lower overall mortality but not breast-cancer specific mortality.[164] Conversely, a diet high in refined grains, processed meat, high fat dairy, and desserts was associated with higher mortality from non-breast cancer related causes. Subsequently, however, when data were reanalyzed and included more breast cancer cases, it became clear that the relationship between dietary fat and all-cause mortality was strongly influenced by exercise levels.[165] Higher levels of physical activity attenuated the relationship. As it turned out, women who exercised more tended to have healthier diets with lower amounts of fat, and more exercise, rather than lower dietary fat, largely explained the lower mortality. In a subsequent analysis, greater adherence to the Mediterranean diet was associated with lower overall but not breast-cancer specific mortality in women who were less physically active.[166]

A 1992 study of 103 women in the UK with breast cancer (menopausal status not specified) showed that higher levels of vegetable, fruit, beta-carotene, and fiber consumption was associated with more favorable characteristics in tumors at diagnosis—smaller size, more highly differentiated cells, and less blood vessel invasion.[167] Over six years of follow up, higher intake of beta-carotene in this group, as estimated by questionnaire responses shortly after diagnosis, was associated with improved survival.[168] Beta-carotene is a marker for fruit and vegetable consumption and other nutrients in those foods may also be responsible for these findings.

The Health, Eating, Activity, and Lifestyle (HEAL) study is a multicenter, multiethnic (58 percent white, 28 percent African American, 12 percent Hispanic, two percent Asian or mixed ethnicity) cohort study of 1,183 breast cancer patients designed to examine whether weight, physical activity levels, diet, and hormones influence breast cancer prognosis and survival.[169] A study of 688 members of the HEAL cohort (60 percent post-menopausal at baseline), with an average follow up of 6.7 years, found no relationship between dietary carbohydrates, glycemic load, and risk of death from any cause. However, higher levels of dietary fiber (8.8 gm/day or more) were associated with decreased risk of death and breast cancer recurrence, although this became statistically insignificant when adjusted for total caloric intake. Higher dietary fiber in this study was associated with lower levels of a marker of inflammation (C-reactive protein) in the blood, which may help to explain benefits of fiber.[170]

Another study of 516 post-menopausal women with breast cancer found that higher levels of dietary fiber, fruits, and vegetables, and lower levels of dietary fat in the year prior to diagnosis was associated with significantly lower risk of death from any cause over 7 years of follow up.[171]

The Collaborative Women's Longevity Study[172] examined the relation between post-diagnosis dietary factors and survival in 4,441 women with invasive breast cancer. They were 20-79 years old at diagnosis and followed over a period of 7 years. The study used food-frequency questionnaires and adjusted data for age, state of residence, menopausal status, smoking, breast cancer stage, alcohol, and history of hormone replacement therapy. Women in the highest compared to lowest levels of dietary saturated fat and trans fat had a significantly higher risk of dying from any cause [for saturated fat (HR =1.41, 95 percent CI = 1.06-1.87); for trans fat (HR = 1.78, 95 percent CI = 1.35-2.32]. Associations were similar, though did not achieve statistical significance, for breast cancer-specific death.

Dietary soy prior to diagnosis and breast cancer prognosis

Two fairly large studies have looked at relationships between dietary soy prior to diagnosis and course of the disease after diagnosis. In the population-based case control Long Island Breast Cancer study, 1,508 women with breast cancer completed food frequency questionnaires reporting on their diets for the year prior to diagnosis.[173] Over 6 years of follow up, women with the highest intake of flavones, isoflavones, and anthocyanidins (in darkly pigmented berries, red cabbage, eggplant) had reduced risk of death from any cause (37 percent, 48 percent, and 36 percent reduction respectively) compared to those with the lowest intake. Reductions in mortality were most marked among post-menopausal women. Breast cancer specific mortality data were similar. Isoflavone intakes in this study ranged from very low to 7.5 mg or more daily in the upper quintile. As previously noted, daily isoflavone intakes of 20 mg or more from traditional soy products are common among Asians.

In the Shanghai breast cancer study[174] of 1,459 breast cancer patients, soy food intake was assessed using a validated food frequency questionnaire at baseline. In an average follow-up of 5.2 years, soy intake pre-diagnosis was unrelated to disease-free breast cancer survival and this did not differ according to ER/PR status, tumor stage, age at diagnosis, body mass index (BMI), or menopausal status. No information on tamoxifen use was provided.

These two studies are not comparable in that the Long Island study looked at risk of death from breast cancer or other causes, whereas the Shanghai study used disease-free survival as the outcome of interest.

Dietary soy after breast cancer diagnosis

Because of concerns that phytoestrogens in soy products could stimulate breast cancer cell growth and proliferation, many patients and health care providers have understandably been cautious about consumption after diagnosis. Three prospective epidemiologic studies have now addressed this concern.

The Shanghai Breast Cancer Survival Study:[175] population-based, prospective study; 5033 participants with diagnosis of breast cancer; all had undergone surgical therapy and combinations of radiation, chemotherapy, immunotherapy, hormone therapy; 20-75 years old; dietary and other information collected at 6, 18, 36, and 60 months; average follow up 3.9 years (range 0.5-6.2); women with the highest soy protein or soy isoflavone consumption were 20-30 percent less likely to die or experience recurrence than women with the lowest consumption. The associations of soy protein and isoflavones with mortality and recurrence followed a linear dose-response pattern until soy protein intake reached 11 gm/day or soy isoflavone intake reached 40 mg/day, where it leveled off. The adjusted four-year mortality rates were 10.3 percent and 7.4 percent and 4-year recurrence rates were 11.2 percent and 8.9 percent respectively for women in the lowest and highest quartiles of soy protein intake. These reductions were seen in women with either ER+ or ER- tumors and were independent of menopausal status. Benefits of tamoxifen were seen in the low and moderate soy consumption groups. In women consuming highest amounts of soy, tamoxifen did not confer additional benefits. And, women who had the highest level of soy food intake and who did not take tamoxifen had a lower risk of mortality and a lower recurrence rate than women who had the lowest level of soy food intake and used tamoxifen, suggesting that high soy food intake and tamoxifen use may have a comparable effect on breast cancer outcomes.

Life After Cancer Epidemiology study:[176] 1,954 women from the U.S.; included white, black, Hispanic, and Asians; criteria for enrollment included breast cancer diagnosis within 39 months; no other cancers within 5 yrs. of enrollment. Participants were 18-79 years old, had completed cancer treatment aside from adjuvant hormone therapy, and were free of recurrence. Soy use since diagnosis was determined by detailed questionnaire. Over an average 6.3 yrs follow up, there was a borderline significant decreased risk of recurrent breast cancer with increasing intake of daidzein and glycetin. Women with the highest intake of these isoflavones had a 50 percent lower likelihood of recurrence. In post-menopausal women who had ever used tamoxifen, higher intake of daidzein was associated with a significant 60 percent decreased likelihood of recurrence. When examined by hormone receptor status, the reduced risk of recurrence with isoflavone intake was limited to those with ER+ or PR+ tumors.

A recent analysis of the association of dietary soy with breast cancer prognosis in the previously mentioned WHEL study also showed that higher soy isoflavone intakes were associated

with decreased risk of death, with a 54 percent risk reduction at the highest intake.[177] No association with cancer recurrence or metastasis was found.

Thus, three studies which vary in ethnic composition, find no adverse effects of soy foods on breast cancer prognosis and considerable evidence of a beneficial role.

Dietary intervention studies

Beginning in the late 1980s, two large prospective studies examined the effects of particular dietary interventions on breast cancer outcomes, supplementing results of the observational studies described above. In the Women's Healthy Eating and Living (WHEL) study, over 3,000 women with breast cancer were followed for an average of 7.3 years.[178] About 85 percent of participants were white, 4 percent African American, 11 percent Hispanic, Asian, or other. Eligibility criteria included diagnosis of a primary operable stage I, II, or IIIA breast cancer within the past 4 years; age at diagnosis was between 18 and 70 years; treatment with axillary dissection and total mastectomy or lumpectomy followed by primary breast radiation; no current or planned chemotherapy; no evidence of recurrent disease or new breast cancer since completion of initial local treatment; and no other cancer in the past 10 years.

Women in the intervention group were encouraged to adopt a daily diet including 5 vegetable servings, 16 oz. of vegetable juice, 3 fruit servings, 30 gm. of fiber and 20 percent energy from fat. They received newsletters and were invited to cooking classes during the first year. Women in the comparison group were advised to consume 5 servings of vegetables and fruit daily, more than 20 gm fiber, and less than 30 percent of calories from fat. They were also offered cooking classes and newsletters. At the beginning of the study, women randomly assigned to both groups were already consuming about seven servings of vegetables and fruits daily.

The intervention group increased their vegetable and fruit consumption, and their plasma carotenoid concentrations were 73 percent higher than the comparison group at one year and 43 percent higher at four years. But there were no differences in any breast cancer event (local, regional, or distant recurrence, or new primary tumor) or overall mortality between the intervention and comparison groups. However, higher blood levels of carotenoids were associated with a significant delay in tumor recurrence, regardless of the study group.[179] In subgroup analyses, peri-menopausal and post-menopausal women who had higher levels of estrogen at baseline were at higher risk of recurrence of disease. And women who had not experienced hot flashes, presumably because of higher estrogen levels, were also at higher risk of recurrence of disease.[180] In an analysis of hormone levels at one year of follow up, higher levels of dietary fiber and lower levels of fat had significantly lowered circulating estrogen levels in the intervention group, compared to baseline.[181]

Another large study, the Women's Intervention Nutrition Study (WINS), was launched in 1987.[182, 183] This was a randomized clinical trial involving 2,437 participants examining whether dietary fat reduction would increase relapse-free survival in women between the ages of 48 and 79 years with early-stage breast cancer. Eligibility criteria included completely resected unilateral invasive breast cancer, baseline caloric intake from fat of >20 percent, and additional therapy appropriate to their condition (e.g., women with estrogen-receptor-positive tumors must have daily tamoxifen, other chemotherapy optional; women with estrogen-receptor-negative tumors must have chemotherapy). Eighty-five percent of participants were white, 5 percent Black, and the remainder Hispanic or Asian-Pacific Islanders.

At baseline, both the intervention and comparison groups obtained about 30 percent of their calories from fat. During the trial, the intervention group succeeded in reducing fat intake to an average of about 20 percent of calories. Although weight loss was not the goal, the intervention group did experience significant weight reduction. After an average follow-up of five years, relapse-free survival (lack of breast cancer recurrence at any site) was 24 percent higher in the intervention group. In subgroup analyses, the intervention effect on relapse-free survival was greater in women with hormone-receptor negative disease than in women with receptor-positive disease. This suggests that factors other than modified estrogen levels are involved and may include reduced insulin levels or improved insulin sensitivity.

WHEL/WINS interventions; summary

WHEL focused on a plant-based dietary pattern that also included reduction in fat. WINS focused exclusively on dietary fat reduction. WHEL included women with pre- and post-menopausal breast cancer, while WINS participants were exclusively post-menopausal. WHEL found no effect of that dietary intervention on prognosis although higher levels of carotenoids, a marker for fruit and vegetable consumption, was associated with delayed recurrence, regardless of the study group. WINS found a beneficial effect from dietary fat reduction.

A subsequent analysis of data from the WHEL study found that the combination of higher levels of dietary fruit and vegetables along with high levels of physical activity reduced the risk of death over 10 years of follow up by half [184] (93 percent survival in the high vegetable/fruit; high physical activity group vs. 86-87 percent survival in the other groups). This effect was most marked in women with hormone receptor positive tumors. Once again, this highlights the difficulty interpreting dietary observational or interventional studies that have not accounted for exercise levels among participants. Looked at another way, combinations of dietary modifications and exercise are likely to be more beneficial than either alone.

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