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# Dietary Influences on Cardiovascular Disease and Female Cancer Risk

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**ABSTRACT:** *Cardiovascular disease and cancer are the number one and number two causes of death in women in the United States. Heart disease is responsible for 45% of all deaths among women,[1] and an estimated 39% of all females are expected to develop cancer at some point in their lifetimes.[2] Breast cancer, which is second only to lung cancer as the most common cause of cancer-related deaths among women, causes approximately 44,000 deaths each year.[3] While heart disease is much more prevalent in our society, surveys indicate that women are likely to fear breast cancer most of all. According to the American Dietetic Association and Weight Watchers International, nearly 50% of some 1000 women polled by the Gallup Organization saw breast cancer as their most serious health threat. Heart disease was cited by only four percent of those surveyed. A substantial body of evidence suggests that the development of both heart disease and breast cancer are strongly related to dietary habits and nutrient status. Helping women maintain optimal health with diet and healthy lifestyle choices is sure to have a great impact on the prevalence of disease in our society.*

## HEART DISEASE

Although cardiovascular disease (CVD) is the major cause of death in both men and women, the majority of research has focused on the male population's risk to this disease, unfortunately giving the impression that women need not be as concerned. This perception may also exist because the onset of CVD in women lags behind that of men by about 10 years. Furthermore, public health efforts encouraging women to perform monthly self breast-exams, and that stress the importance of mammograms and annual Pap tests, have perhaps overshadowed the importance of maintaining cardiovascular health.

While genetic predisposition plays an important role in CVD, certain risk factors, such as lifestyle choices (e.g., tobacco use and exercise) and dietary habits, can be modified to help reduce an individual's risk. Recent research demonstrating the cardioprotective effects of several dietary ingredients, such as fiber (e.g., oat bran), antioxidants, and folic acid, has received a considerable amount of public attention which may help to foster a greater awareness among women concerning CVD and how they might modify their risks.

- **Dietary Fats**

Elevated plasma lipids and lipoproteins are recognized as a major risk factor for coronary heart disease.[4] More specifically, a high concentration of plasma low-density lipoprotein cholesterol (LDL) and/or a low concentration of high-density lipoprotein cholesterol (HDL) are associated with an increased risk for coronary artery disease.[4] Diets that are high in cholesterol and saturated fats are known to contribute to unhealthy plasma lipid levels. Cholesterol lowering diets have been shown to be helpful in lowering plasma cholesterol levels; however, whether this has any effect on reducing CVD mortality remains to be proven.

Dietary fatty acids are one of the most important factors determining plasma lipid concentration and, consequently, risk for heart disease. Diets high in cholesterol and saturated fatty acids are known to increase total plasma and LDL cholesterol concentrations. Replacing saturated fatty acids in the diet with polyunsaturated fatty acids (PUFAs) from vegetable oils results in reductions of both total and LDL cholesterol concentrations, but may also lower HDL. Monounsaturated fatty acids, as from olive oil, show either no effect on HDL or an increase in HDL, thus, promoting a less atherogenic lipid profile than either polyunsaturated- or saturated-rich diets.[5] These results are consistent with evidence demonstrating an association between the traditional Mediterranean diet, which is high in monounsaturated fats, and a low rate of coronary artery disease and total mortality.[5]

Fish oils, which are rich in the omega-3 polyunsaturated fatty acids, have also been associated with beneficial cardiovascular effects. Omega-3 fatty acids are precursors to eicosanoids (prostaglandins, prostcyclins, leukotrienes, and thromboxanes) which have antithrombotic, vasodilatory, antiinflammatory, and antiarrythmic properties. Similar to the effects of aspirin, fish oils help to block the arachidonic acid production of thromboxane $A_2$, a potent vasoconstrictor and platelet aggregator.[6] Fish oils are also reported to lower blood pressure and lower plasma triglyceride concentrations; however, a moderate rise in LDL concentrations has been observed.[7] Recently, the fish oil-induced rise in LDL was shown to be ameliorated with the concomitant intake of supplemental garlic.[7] In this study, garlic supplementation significantly decreased both total cholesterol and LDL whereas fish oil supplementation significantly decreased triglyceride concentrations and increased LDL concentration in hypercholesterolemic men. The co-administration of garlic and fish oil provided a combined lowering of total cholesterol, LDL, and triglyceride concentrations along with overall decreases in the ratios of total cholesterol to HDL and LDL to HDL.

- **Fiber**

Diets that are low in fiber are associated with a higher risk of cardiovascular disease and hypercholesterolemia.[6] Although both soluble and insoluble fibers are healthful, soluble fiber, such as pectin or oat bran, appears to have the most consistent beneficial effects on plasma cholesterol levels.[6] Soluble fiber is thought to lower plasma cholesterol levels through its binding action on cholesterol and bile in the colon. The enhanced excretion of bile enables the liver to remove more cholesterol from circulation to form more bile, thus lowering blood cholesterol concentrations.[6] Additionally, fiber in general helps to increase the rate at which food is passed through the digestive tract, which might also enhance the daily fecal loss of cholesterol and bile acids. One group of researchers observed that very high intakes of soluble fiber helped to further lower blood cholesterol levels in individuals whose intake of saturated fat and cholesterol were reduced to very low levels.[8]

- **Antioxidants**

An inverse relationship between plasma levels of dietary antioxidants and the risk of cardiovascular disease has been observed in several epidemiological studies.[9,10] Research suggests that the antioxidants vitamin C, vitamin E, beta carotene, and other carotenoids are important dietary nutrients that may help reduce the risk of cancer, heart disease, and other age-related diseases by helping to scavenge exogenous and endogenously produced free radicals.[9] Epidemiological evidence consistently correlates low intake of fruits and vegetables, which are high in antioxidants, with an increased risk for both heart disease and cancer.[11,12]

Antioxidants help to protect the unsaturated fatty acids in cell membranes from lipid peroxidation caused by free radical oxygen intermediates. The oxidative modification of LDL is believed to play an important role in the development of atherosclerosis. Oxidatively modified LDL has been found in atherosclerotic lesions of humans and experimental animals,[13,14] and lipid peroxide concentrations have been found to be higher in individuals with atherosclerosis.[15] Supplementation with vitamin E has been shown to protect LDL from lipid peroxidation.[16] Two recent studies (one on men; the other, women) demonstrated an inverse association between vitamin E intake and coronary heart disease. Those with the highest intake, achieving a level of at least 100 IU per day through supplementation, had a 40% lower risk of coronary heart disease.[17,18]

Another mechanism by which vitamin E may be cardioprotective is via improved blood circulation and eicosanoid modulation; vitamin E may help to reduce the formation of thromboxane $A_2$, which is known to stimulate platelet aggregation.[6]

The data on vitamin C and beta-carotene are less profound with regard to cardiovascular health; however, because of their abundance in fruits and vegetables, a positive association appears to be likely.

- **Folic Acid**

Elevated plasma levels of homocysteine is an important independent risk factor for cardiovascular disease.[19] Homocysteine is a highly reactive amino acid that promotes vascular injury and thrombosis, and can potentiate the autooxidation of LDL.[19] A recent study showed that the risk of myocardial infarction within 5 years for individuals with no prior history of vascular disease was 3.4 fold greater for those with elevated plasma homocysteine concentrations than for those with normal plasma homocysteine levels.[17] Plasma homocysteine levels have been shown to be inversely associated with vitamin $B_6$, $B_{12}$, and folic acid levels, as well as age.[20] Homocysteine levels were greatest among individuals with low folic acid status. Interestingly, in this study, homocysteine concentration did not reach its nadir until folic acid intake approached around 400 mcg per day, a level far above the recommended dietary allowance (200 mcg/d for men and 180 mcg/d for women).[20]

Adequate intake of folic acid may be important not only in reducing the risk of cardiovascular disease through its effect on homocysteine, but also in helping to reduce the risk of a neural tube defect-affected pregnancy, and to prevent colon polyps, colon cancer, and cervical cancer.[21,22]

## BREAST CANCER

Breast cancer is the second most common cause of cancer-related deaths in U.S. women and its incidence has risen dramatically over the last 50 years.[23] Some of the risk factors that have been identified are early menarche, late age at first birth, late menopause, and increased height and weight. These risk factors clearly suggest the importance of hormone factors in the etiology of breast cancer.[24] Additionally, the wide variance in the rates of breast cancer among countries strongly suggests a role for environmental influences, which are potentially modifiable. Two important environmental risk factors include diet and exposure to environmental xenotoxins. An estimated 80% of cancers are thought to be related to environmental factors; diet alone is estimated to play a role in at least 35% of all cancers.[23] Furthermore, it has been estimated that as much as 50% of breast cancer might be prevented by dietary changes.[3]

- **Diet**

Numerous epidemiological studies have associated a high fat/low fiber diet with an increased risk of developing specific forms of cancer, especially cancer of the colon and breast.[6] Over the last 150 years, fat consumption has increased substantially in Western countries, which also coincides with a dramatic increase in cancer incidence. A prospective population-based study recently demonstrated a positive association between dietary fat consumption, as well as total calorie consumption, and the risk for breast cancer in postmenopausal women.[3] Additionally, a review of epidemiological studies strongly suggests an inverse relationship between the consumption of fresh fruits and vegetables and the incidence of cancer.[12] Fruits and vegetables are rich in fiber, antioxidants, and other plant-derived substances, or phytonutrients, that are thought to have cancer-protective properties.

- **Fat Intake**

Fat intake is thought to influence the secretion and metabolism of hormones that may promote or inhibit the growth of tumors, most notably estrogen and prostaglandins.[6] A substantial percentage of breast cancers depend upon estrogen for growth. Because adipose tissue contributes to circulating estrogen levels, women who are obese or consume high-fat diets tend to have higher circulating levels of estrogen and are also at an increased risk for breast cancer.[3,6] Vegetarian women, who typically consume a low-fat, high-fiber diet, are less prone to breast cancer, and tend to have lower plasma concentrations of estrogens and excrete 2-3 times more estrogen in the feces than non-vegetarians. Rose et al. reported significant decreases in circulating estrogens in women with benign breast disease when they reduced dietary fat

intake to 20% of total calories.[25] Fiber is also thought to influence hormone levels by facilitating the fecal excretion of estrogen metabolites, increasing plasma sex hormone-binding globulin (a serum protein that binds to estrogen and reduces its bioavailability), and decreasing the availability of androgens which are converted in the body to estrogen.[23]

Additionally, the consumption of dietary omega-3 fatty acids from fish has been associated with a lower risk of breast cancer.[6,23] Intake of omega-3 fatty acids contributes to the lowering of arachidonic acid-derived eicosanoids, most notably prostaglandin $E_2$, which is produced in excessive quantities by many types of tumors.[2] Omega-3 fatty acids have an overall inhibitory effect on cancer; however some evidence suggests that fish oils may in some instances suppress the immune system by reducing the release of tumor necrosis factor and interleukin-1 (B and alpha).[6]

- **Environmental Xenoestrogens**

Environmental xenoestrogens are synthetic, hormone-mimicking compounds found in certain pesticides, drugs, fuels, and plastics that may play a role in the etiology of breast cancer. It is thought that environmental xenoestrogens contribute to the synthesis of 16-alpha hydroxyestrone, a variety of estrogen that strongly increases the interaction of the receptor with growth-promoting genes, enhances breast-cell proliferation, and that may damage DNA.[26] Recent animal and human studies have linked elevated levels of 16-alpha-hydroxyestrone to breast cancer.[26] Environmental xenoestrogens tend to accumulate in the fatty tissues of the body where they may remain for decades. Often they are mobilized from fat stores and into the breast milk of lactating women.

- **Calcium D-glucarate**

The metabolism of various xenobiotics occurs via glucuronidation, a principle conjugation pathway which leads to the elimination of carcinogens from the body. β-glucuronidase is an enzyme that catalyzes de-glucuronidation. Elevated levels of β-glucuronidase have been observed in many different disease states including cancer.[27] Calcium D-glucarate is a natural, non-toxic compound present in foods that inhibits the activity of β-glucuronidase, thereby enhancing net glucuronidation activity. It is reported to inhibit the initiation, promotion, and progression stages of chemical carcinogenesis in different animal models. Dietary calcium D-glucarate may be of potential use to help lower blood and tissue levels of β-glucuronidase, which may in turn facilitate the removal of carcinogens that are excreted as glucuronide conjugates.[27]

- **Antioxidants and Breast Cancer**

Antioxidants, such as vitamins C and E, and vitamin A as beta-carotene, are important dietary factors that help to protect cells and genetic material from oxidative damage caused by free radicals. As mentioned earlier, free radicals have been implicated in the etiology of heart disease, cancer, and many other age-related diseases.

In their antioxidant capacity, vitamins C and E play a role in the prevention of nitrosamine formation. Nitrosamines are formed by the reaction of nitrite with amines under conditions of low pH, as in the stomach, and they are also present in foods such as charred meats, cooked bacon, and some alcoholic beverages. Cigarette smoke also contains significant quantities of nitrosamines. Nitrosamines have been reported to induce cancer in a number of animal species.[6] Other antioxidants such as glutathione and polyphenols (present in plant foods) may also inhibit the formation of nitrosamines.

Antioxidant intake has also been inversely associated with the mutagen content of human feces. It has been observed that individuals who consume adequate vitamin C and vitamin E tend to have lower fecal mutagen levels than individuals who consume less than adequate amounts of these vitamins. Furthermore, antioxidant supplements have been reported to be capable of reducing fecal mutagen levels in humans.[6]

In its role as a regulator of cell differentiation, pre-formed vitamin A, or retinol, may have additional cancer-protective properties. Recently, vitamin A intake was demonstrated to be inversely related to risk of breast cancer, and among those with the lowest intakes from diet, use of supplements containing vitamin A was associated with a lower risk.[28] These results support earlier studies which demonstrate an inverse relationship between breast cancer and total intake of vitamin A (preformed vitamin A and carotenoids).[28] In addition, high levels of vitamin A have been shown to have an inhibitory effect on the development of mammary tumors in laboratory animals.[29]

In addition to its antioxidant activity, vitamin C is known to facilitate immune function. Vitamin C intake has been inversely associated with breast cancer, while no association has been observed with vitamin E.[30] Vitamin E, however, is reported to help relieve and possibly reverse symptoms of fibrocystic breast disease, a potential risk factor for breast cancer.[31]

- **Diet and Other Female Cancers**

Epidemiological studies suggest an association between nutrient intake and cervical cancer, particularly with regard to folic acid, which is required for normal cell replication.[23] Several studies suggest that folic acid may play a protective role in the etiology of cervical neoplasms.[32-35] One study demonstrated improvement of cervical intraepithelial neoplasia-1 (CIN-I) and CIN-II in women placed on high-dose folic acid for 3 months.[33] These results support previous work that suggested folic acid supplementation could reverse megaloblastic changes in the cervical epithelium in women taking oral contraceptives.[35] Other reports have associated cervical dysplasia and squamous cell carcinoma of the cervix with low serum and red blood cell folate, as well as low intakes of folic acid. Additionally, inadequate status of vitamin C, vitamin A, and beta-carotene has also been associated with cervical dysplasia and squamous cell carcinoma of the cervix.[23]

Fat intake and obesity appear to be the primary dietary risk factors associated with endometrial and ovarian cancer. Other risk factors for endometrial cancer include aging, hypertension, diabetes, nulliparity, and exogenous estrogen use.[23] Non-dietary risk factors for ovarian cancer include nulliparity, breast cancer, and family history of endometrial cancer.[2]

- **The Benefits of Phytonutrients**

Plant foods contain many phytonutrients that are known to have health promoting properties. For example, phytoestrogens, which are found primarily in whole grains and legumes, such as soybeans, may help reduce the risk of hormone related cancers, such as breast cancer, by affecting estrogen uptake and metabolism. Phytoestrogens act as weak estrogens that bind to estrogen receptor sites, displacing the more potent cancer-promoting estrogens.[35]

Epidemiological evidence suggests that women who include soybeans or soy foods in their diets have a decreased risk of breast cancer.[35]

Other dietary ingredients that have potential anticancer properties are the cruciferous vegetables (e.g., broccoli, Brussels sprouts, and cauliflower). Cruciferous vegetables are rich in indoles and isothiocyanates which may help up-regulate certain liver detoxification enzymes and aid in the removal of carcinogens.[36] Cruciferous vegetables have been reported to suppress mammary carcinogenesis in laboratory animals.[36]

## THE PROTECTIVE PROPERTIES OF BOTANICALS FROM INDOCHINA

Along with dietary modifications that limit fat intake and include fiber, fruits, and vegetables, an herbal strategy that focuses on the promotion of cardiovascular and immunological health in women may offer additional health promoting benefits. Herbs offer a diversity of interesting phytochemicals that appear to work synergistically to support health through a number of mechanisms. For example, many herbs have antioxidant properties and many are known to influence eicosanoid synthesis. Several common herbs known throughout history for their cardiovascular or immune supporting effects are turmeric *(Curcuma longa)*, sage *(Salvia miltiorrhiza)*, white peony *(Paeonia lactiflora)*, and ginger *(Zingiber officinale)*.

Turmeric is a popularly used herb that has also been fairly heavily researched. Its purported benefits include antiinflammatory properties, antioxidant properties, and potential chemopreventive properties, including enhanced fibrinolytic activity.[37] Much of turmeric's beneficial properties are attributed to an inhibitory effect on arachidonic acid-derived eicosanoids.[38] Additionally, research has found that the curcuminoids, which are major components of turmeric, appear to up-regulate liver detoxification enzymes and may therefore help to facilitate carcinogen removal from the body.[39]

Sage, or salvia, is traditionally used to support cardiovascular health. It is highly prized in Chinese medicine because it is said to harmonize the spirit, a metaphor which translates to cardiovascular benefits. Animal studies have corroborated the perceived cardiovascular effects of salvia, demonstrating beneficial effects on blood pressure and improved blood circulation.[40,41] Three diterpenoids from the root of salvia have been identified as inhibitors of platelet aggregation.[42]

White peony, which is also said to help circulate the blood, has demonstrated vasodilator effects on aortic rat endothelium.[43] Additionally, white peony contains polysaccharides that possess immunological properties.[44]

Similar to turmeric, ginger is also known to possess significant antioxidant, antiinflammatory, and cardioprotective properties.[45-47] Ginger is also widely used to promote digestion.

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