Reducing the Risk of Breast Cancer: Nutritional Strategies

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Breast cancer is the most common cancer among women and the leading cause of death in women aged 40 to 55 years. In North America, the lifetime odds of developing breast cancer for women are one in eight. Understandably, breast cancer is a condition that creates stress and worry in many women. Women turn to healthcare professionals for guidance as to how they can minimize their risk. The scientific literature is rich with information on preventive strategies, and many of the recommendations fall into the nutritional domain.

Reducing estrogen exposure is a first-line approach. One strategy would be to consume more phytoestrogens—presumably displacing some 17-β-estradiol at estrogen receptors. Asian populations consume approximately 10 to 50 grams of soy foods compared with one to three grams for Americans; their estradiol levels are 40% lower than those found in Caucasian women.[1] Epidemiologic studies have linked soy consumption to a reduced risk for breast cancer.[2] However, breast cancer chemoprevention using dietary phytoestrogens may be dependent on consumption before puberty when the breast is still developing.[3] The human clinical trial data on soy for prevention of breast cancer in adulthood are limited, and the results are mixed.

Alcohol can act as a cocarcinogen by increasing estradiol levels. Metaanalysis of existing studies reveals a 30% to 40% increased risk of breast cancer in women who consume at least 30 grams of alcohol daily compared with women who do not drink alcohol.[4] (30 grams is equivalent to 1.5 alcoholic drinks, 3 glasses of wine, or 2 cans of beer.) Exogenous estrogen is another source of exposure that can be reduced. The hormones fed to cattle may be found in their meat and milk.[5] Consuming hormone-free milk and meat are recommended.

Another approach to reducing risk is to alter the metabolism of estrogen to its less risky metabolites. Estrogen is metabolized along two competing pathways to form 2-hydroxylated and 16-α-hydroxylated metabolites. Women with an elevated 2:16-α-hydroxyestrone ratio are hypothesized to be at a decreased risk of breast cancer.[6] Flaxseed supplementation significantly increases 2-hydoxyestrone excretion and the urinary 2:16-hydoxyestrone ratio.[7,8] The lignans within flaxseed are known to stimulate sex hormone binding globulin synthesis, inhibit aromatase activity, reduce breast tumor initiation, and inhibit the growth of human breast tumor cells. Flaxseed supplementation in mice has been shown to inhibit breast cancer growth and metastasis.[9] Dietary intake of l0 grams (1 tablespoon) of ground flaxseed per day is recommended. (Flaxseed oil does not contain lignans (unless bits of the seeds are left) or fiber and is significantly more expensive than ground seed.)

The phytochemicals in cruciferous vegetables (broccoli, Brussells sprouts, cabbage, cauliflower, and kale) are not estrogenic. They act by modulating the activity of cellular enzymes responsible for estrogen metabolism. Increasing cruciferous vegetable intake leads to an increase in the 2:16-hydroxyestrone ratio.[10] Cruciferous vegetables contain isothiocyanates and other glucosinolate derivatives capable of inducing phase II enzymes and apoptosis, altering steroid hormone metabolism, regulating estrogen receptor response, and stabilizing cellular proliferation.[11] One study recommended a high-fiber diet including the consumption of 50 g cabbage or 100 g broccoli twice weekly.[12]

After hydroxylation, estogen metabolites are conjugated with glucuronate or sulfate, or methylation occurs prior to excretion in urine. Some of the conjugated and unconjugated metabolites pass into bile in which they may be reabsorbed in the enterohepatic circulation. High-fiber diets and lignans contribute to lower intestinal reuptake rates of these metabolites.[10]

High-fat diets have been associated with breast cancer.[13] As for other health issues, the type of fat is proving to be critical. Case control trials have examined the hypothesis that omega-3 fatty acids protect against breast cancer. Breast biopsy specimen, adipose tissue fatty acid composition in women with invasive breast carcinoma is compared with the adipose tissue of women with benign breast disease. The breast biopsy specimens revealed an inverse association between breast cancer risk and omega-3 fatty acid levels.[14-16]

Possible mechanisms of the protective effect of omega-3 fatty acids include modulation of estrogen metabolism and estrogen-receptor binding. Increased 2-hydroxylation of estradiol occurs in human breast cancer cells grown with omega-3 fatty acids.[17] Conversely, omega-6 fatty acids (linoleic acid and arachidonic acid) increase 16-α hydroxylation.[18] Docosahexaenoic acid, an omega-3 fatty acid, reduces binding of estradiol to the estrogen receptor.[19] Omega-3 fatty acids can be increased in the diet by eating more cold northern fish (wild Alaskan salmon, albacore tuna, sardines, mackerel) walnuts, flaxseed, omega-3-enriched eggs, and purslane.

Avoiding exposure to carcinogens in the diet is another area women can control. Cooking meats at high temperatures produces heterocyclic amines and polycyclic aromatic hydrocarbons.[20] The reaction is triggered when food from animal muscle—beef, pork, poultry, and fish—is cooked at high temperatures (300°-400°F.) Frying, broiling, and barbecuing and longer cooking times generate the most heterocyclic amines. Well-done meat poses the greatest risk.[21] Other studies have not confirmed this risk factor.[22]

Contamination of food with xenoestrogens exposes women to carcinogens. Xenoestrogens mimic naturally occurring estrogens. They are in pesticides including DDT and in polychlorinated biphenyls (PCBs.)[21] They can also enter the body by exposure to plastics (as when food is microwave cooked in plastic.)

Following the principles of a healthy, antiinflammatory diet is a broad strategy for preventing cancer and heart disease.[23] This diet is rich in antioxidants, has a low glycemic load, a favorable omega-3: omega-6 fatty acid ratio, and favors whole foods over refined and processed foods.

Probably the most important recommendation for all women is to eat more fruits and vegetables. Epidemiologic evidence supports this recommendation.[24] For breast cancer prevention, cruciferous vegetables are particularly important. It is important to explain serving size to patients—otherwise nine servings a day seems overwhelming. A large banana or apple contains two servings, and most salads served at restaurants contain four to five servings.

A multitude of other phytonutrients is being investigated for cancer chemoprevention. Ginger and turmeric act as COX-2 inhibitors. COX-2 is highly expressed in ductal carcinoma in situ and in perineoplastic benign epithelium as well as approximately 40% of human breast cancers.[25] Other beneficial foods include berries, citrus fruits, garlic, ginseng, green tea, and tomatoes.[26] Although they have not been studied specifically (or extensively) in breast cancer chemoprevention, they are being actively investigated.

Many questions remain. Mixed data exist for fiber's ability to prevent breast cancer. For example, although a metaanalysis of 12 studies revealed a 15% decrease in breast cancer risk when 20 g dietary fiber were consumed,[27] the Nurse's Health Study did not reveal a relationship between dietary fiber and breast cancer risk.[28] The relationship of obesity to breast cancer risk has also proven to be complex. There is a positive association of obesity in postmenopausal women and an inverse association in premenopausal women. Undernutrition in laboratory animals reduces breast cancer; however, this may be related to the stage of breast development. Severe caloric restriction in humans may confer protection from invasive breast cancer; an intriguing retrospective study revealed that women with anorexia have lower rates of breast cancer.[29]

The role of organic foods in cancer chemoprevention continues to emerge. In addition to the absence of hormones (stressed above), organically grown fruit was shown to have more antioxidant vitamins (α- and γ-tocopherols and β-carotene) and phenolic compounds (total polyphenols, phenolic acids, flavonols) compared with conventionally grown foods.[30] Dietary supplements, such as fish oil, indole-3 carbinol, and turmeric, may also prove to play a role in chemoprevention, especially for those women who are unable to consume sufficient amounts of these nutrients in their diets. Genetic polymorphism may explain some of the variability found in nutrition studies; ongoing work in nutritional genomics may soon allow us to target specific dietary recommendations for specific women (soy and cruciferous vegetables are currently being studied).

It has been estimated that up to 40% of cancers could be prevented through dietary strategies.[31] Women can alter their diets effectively to enhance their health in general and to reduce their risk of breast cancer. This review, and the abundant literature, can help the primary care provider partner with their women patients to develop nutritional approaches to reducing their personal risk of breast cancer.

REFERENCES

1. Peeters PH, Keinan-Boker L, van der Schouw YT, Grobbee DE. Phytoestrogens and breast cancer risk. Review of the epidemiological evidence. *Breast Cancer Res Treat.* 2003;77:171-183.
2. Adlercreutz H. Phytoestrogens: epidemiology and a possible role in cancer protection. *Environ Health Perspect.* 1995;103:103-112.
3. Limer JL, Speirs V. Phyto-oestrogens and breast cancer chemoprevention. *Breast Cancer Res.* 2004;6:119-127.
4. Smith-Warner SA, Spiegelman D, Yaun SS, et al. Alcohol and breast cancer in women: a pooled analysis of cohort studies. *JAMA.* 1998;279:535-540.
5. Hartmann S, Lacorn M, Steinhart H. Natural occurrence of steroid hormones in food. *Food Chem.* 1998;62:7-20.
6. Muti P, Bradlow HL, Micheli A, et al. Estrogen metabolism and risk of breast cancer: a prospective study of the 2:16 α-hydroxyestrone ratio in premenopausal and postmenopausal women. *Epidemiology.* 2000;11:635-640.
7. Haggans CJ, Hutchins AM, Olson BA, Thomas W, Martini MC, Slavin JL. Effect of consumption on urinary estrogen metabolites in postmenopausal women. *Nutr Cancer.* 1999;33:188-195.
8. Haggans CJ, Travelli EJ, Thomas W, Martini MC, Slavin JL. The effect of flaxseed and wheat bran consumption on urinary estrogen metabolites in premenopausal women. *Cancer Epidemiol Biomarkers Prev.* 2000;9:719-725.
9. Chen J, Stavro PM, Thompson LU. Dietary flaxseed inhibits human breast cancer growth and metastasis and down-regulates expression of insulin-like growth factor and epidermal growth factor receptor. *Nutr Cancer.* 2002;43:187-192.
10. Lord RS, Bongiovanni B, Bralley JA. Estrogen metabolism and the diet-cancer connection: rationale for assessing the ratio of urinary hydroxylated estrogen metabolites. *Altern Med Rev.* 2002;7:112-129.
11. Fowke JH, Chung FL, Jin F, et al. Urinary isothiocyanate levels, brassica, and human breast cancer. *Cancer Res.* 2003;63:3980-3986.
12. Bradlow HL, Telang NT, Sepkovic DW, Osborne MP. 2-hydroxyestrone: the "good" estrogen. *J Endocrinol.* 1996;150:S259-S265.
13. Prentice RL, Sheppard L. Dietary fat and cancer: consistency of the epidemiologic data, and disease prevention that may follow from a practical reduction in fat consumption. *Cancer Causes Control.* 1990;1:81-97, discussion 99-109.
14. Maillard V, Bougnoux P, Ferrari P, et al. N-3 and N-6 fatty acids in breast adipose tissue and relative risk of breast cancer in a case-control study in Tours, France. *Int J Cancer.* 2002;98:78-83.
15. Simonsen N, van't Veer P, Strain JJ, et al. Adipose tissue omega-3 and omega-6 fatty acid content and breast cancer in the EURAMIC study. European Community Multicenter Study on Antioxidants, Myocardial Infarction, and Breast Cancer. *Am J Epidemiol.* 1998;147:342-352.
16. Bagga D, Anders KH, Wang HJ, Glaspy JA. Long-chain n-3-to-n-6 polyunsaturated fatty acid ratios in breast adipose tissue from women with and without breast cancer. *Nutr Cancer.* 2002;42:180-185.
17. Telang NT, Bradlow HL, Osborne MP. Molecular and endocrine biomarkers in non-involved breast: relevance to cancer chemoprevention. *J Cell Biochem Suppl.* 1992;16G:161-169.
18. Bartsch H, Nair J, Owen RW. Dietary polyunsaturated fatty acids and cancers of the breast and colorectum: emerging evidence for their role as risk modifiers. *Carcinogenesis.* 1999;20:2209-2218.

19. Borras M, Leclercq G. Modulatory effect of nonesterified fatty acids on structure and binding characteristics of estrogen receptor from MCF-7 human breast cancer cells. *J Recept Res.* 1992;12:463-484.
20. Mitra AK, Faruque FS, Avis AL. Breast cancer and environmental risks: where is the link? *J Environ Health* 2004;66:24-32, 40.
21. Zheng W, Gustafson DR, Sinha R, et al. Well-done meat intake and the risk of breast cancer. *J Natl Cancer Inst.* 1998;90: 1724-1729.
22. Holmes MD, Colditz GA, Hunter DJ, et al. Meat, fish and egg intake and risk of breast cancer. *Int J Cancer.* 2003;104:221-227.
23. Donaldson MS. Nutrition and cancer: a review of the evidence for the anti-cancer diet. *Nutr J.* 2004;3:19.
24. Block G, Patterson B, Subar A. Fruit, vegetables, and cancer prevention: a review of the epidemiological evidence. *Nutr Cancer.* 1992;18:1-29.
25. Howe LR, Dannenberg AJ. COX-2 inhibitors for the prevention of breast cancer. *J Mammary Gland Biol Neoplasia.* 200;8:31-43.
26. Park EJ, Pezzuto JM. Botanicals in Cancer Chemoprevention. *Cancer Metastasis Rev.* 2002;21:231-255.
27. Howe GR, Hirohota T, Hislop TG, et al. Dietary factors and risk of breast cancer: combined analysis of 12 case-control studies. *J Natl Cancer Inst.* 1990:82:561-569.
28. Willett WC, Hunter DJ, Stampfer MJ, et al. Dietary fat and fiber in relation to risk of breast cancer. An 8-year follow-up. *JAMA.* 1992;268:2037-2044.
29. Karin B, Ekbom A. Caloric restriction and incidence of breast cancer. *JAMA.* 2004; 291:1226-1230.
30. Lombardi-Boccia G, Lucarini M, Lanzi S, Aguzzi A, Cappelloni M. Nutrients and antioxidant molecules in yellow plums (*Prunus domestica L.*) from conventional and organic productions: a comparative study. *J Agric Food Chem.* 2004;52:90-94.
31. World Cancer Research Fund/American Institute for Cancer Research. *Food, Nutrition and the Prevention of Cancer: A Global Perspective.* Washington, DC: WCRF/ AICR, 1997

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