Estrogens, Phytoestrogens, Xenoestrogens

and the Risk of Breast Cancer

by

Richard A. Hansen, M.D.

Phone calls from concerned patients, letters and e-mails, and other inquiries from concerned health-minded friends, have raised new questions about the risks and the benefits of soy products. Cooked soybean dishes such as the Japanese delicacy *edamame*, soy milk beverages, tofu and other soy protein concentrates have long been held as beneficial for the prevention of heart disease 1,2 as well as cancer 3,4. However, in recent years a growing cadre of soy critics have published books, written articles in prominent health publications, and uploaded their anti-soy ammunition on the internet. Hence, we find the soybean in a new and mostly undeserved crossfire of controversy. One of the major soy issues pertains to the plant estrogenic action of soybeans, and other legumes. Theories abound concerning their risk to human health, as well as the soybean’s demonstrated or potential benefits, particularly helping lower the risk of heart disease, osteoporosis, and resisting cancer.

Most physicians and American women are increasingly aware that estrogen is a much more complicated substance that we originally believed. In fact, it is not a single entity at all, but a mixture of three biochemically distinct molecules, which the body produces naturally. Additionally, there is also a growing family of synthetic estrogens, used in hormone replacement therapy (HRT) as well as birth control pills. The natural human hormones are called estrone (E1), estradiol (E2), and estriol (E3). These will be the subject of this article, along with several plant products which have estrogen-like activity, called appropriately phytoestrogens. Then, we will consider other environmental chemicals which also are reported to have an estrogen-like action on the body.

It is widely believed that cumulative estrogen exposure is a most critical breast cancer risk factor. Breast cancer risk in women increases with early menarche, late menopause, long-term use of birth control pills, and estrogen replacement therapy. 5 When women grow taller, gain weight, have fewer children, and have them later in life, they increase their lifetime exposure to estrogen and its associated risks.

Researchers are gaining new insights into the processes through which E1, E2, and E3 are metabolized, detoxified, and excreted. These three estrogens break down or are detoxified into estrogen metabolites—daughter compounds, if you please—called 2-hydroxyestrone, 4-hydroxyestrone, and 16-hydroxyestrone. These metabolites can have stronger or weaker estrogenic activity, depending on where the hydroxyl part of the reaction is attached. And thus, the woman’s risk of breast, uterine, and other cancers will be either enhanced or diminished, as her estrogen is changed before being excreted by the kidneys. 6

It is known that the various pathways of estrogen metabolism depend on three factors: first, a woman’s genetic makeup; second, her lifestyle and diet; and third, a number of environmental factors. This knowledge provides the basis for cancer risk reduction, especially through modifying lifestyle and dietary choices. In other words, the ultimate risk of breast and uterine cancer is not fixed by heredity or birthplace, but is the result of a lifetime of choices at the pharmacy for medication use, at the dinner table with food selection, as well as those factors that contribute to a person’s weight such as exercise, stress, and motherhood.

**Estrogen Metabolism**

In premenopausal women, the ovaries primarily produce the estrogen estradiol (E2), which then converts into estrone (E1), both of which must eventually be broken down and excreted from the body. This metabolic pathway occurs primarily in the liver, and the excreted compounds flow out in the bile or urine. Estradiol and estrone undergo this breakdown through a process called hydroxylation, an enzymatic reaction in which the parent estrogen is transformed by the addition of a hydroxyl (OH) group at specific positions on the estrogen’s molecular ring.

Estrogen molecules are composed of four linked ring structures where the carbon atoms are named sequentially by the numbers 1 to 17. Estradiol has 17 carbon atoms and can be hydroxylated at particular points on that ring. Considerable research has shown that major metabolites of estradiol and estrone are those hydroxylated at either the C-2 or the C-16 positions. Hydroxylated metabolites at the C-4 position also exist, but in lesser amounts. We could look at these estrogenic ‘daughters’ as good daughters and bad ones. What makes an estrogen metabolite turn out ‘good’ or bad’? The answer has to do with the biological activity, or potency, of that estrogen.

Estrogens are important in a host of cellular activities that affect growth and differentiation in various target cells. This is normally beneficial, but too much estrogenic stimulation can have adverse effect. Therefore, properly metabolizing and excreting estrogens becomes crucial. Let me explain how the daughter compounds differ in their potency, also called biological activity. If a woman’s normal estrogens are metabolized into the 2-hydroxylated estrone and estradiol, they lose much of their cell proliferative and estrogenic activity, and are hence termed ‘good’ estrogen metabolites. 7 Studies show that when 2-hydroxylation increases, the person resists breast or uterine cancer, and that when 2-hydroxylation decreases, cancer incidence increases. 8

However, the C-4 and C-16 estrogen and estrone metabolites are different from the C-2 variety, because these metabolites have *more* estrogenic activity than their mother compound. Research strongly suggests that women who metabolize a larger proportion of their estrogens down the C-16 pathway, as opposed to the C-2 pathway, have elevated breast cancer risk. 9 Further, the daughter estrogens metabolized down the C-16 route may be associated with direct genotoxic effects and carcinogenicity!

**Predicting Cancer Risks**

In one recent study of 10,786 premenopausal women at the State University of New York at Buffalo, researchers found that those who went on to develop breast cancer had significantly less 2-hydroxyestrone and more 16-alphahydroxyestrone metabolites than women who did not. Following women for 5.5 years, they found that participants with increased levels of 2-hydroxyestrone had a 40 percent decrease in the occurrence of breast cancer. 10

In a longer study on postmenopausal women, those with the highest C-2:C16 ratio (a higher ratio means more C-2 and less C-16, proportionally) had 30 percent less risk of developing breast cancer than women with lower ratios. 11 With this information it would seem useful to discover what, if any, dietary or lifestyle modifications could guide estrogens down the healthier C-2 pathway. In other words, if the proportion of C-16-alpha-hydroxyestrone can be decreased, while the C-2-hydroxyestrone is increased, we will likely see a considerable reduction in the risk of breast and/or uterine cancer in American women.

**Nutrition and Estrogen**

In Asian countries where soy is a dietary mainstay, epidemiological studies have indicated that soy protein is quite protective in breast cancer, both in Chinese and Japanese women. 12 While soy protein is a complex mixture of nutrients and phytochemicals, it appears that part of its benefit is related to the isoflavones genistein and daidzein. Studies suggest that they change the way estrogens are metabolized, therefore changing favorably the C-2:C-16 ratio. Both premenopausal women and postmenopausal women have been studied in this regard, demonstrating that isoflavones increase the beneficial 2-hydroxyestrone at the expense of the 16-hydroxyestrone, therefore increasing the C-2:C-16 ratio. 13

It appears that isoflavones found in other plants might also have beneficial effects. Kudzu (*Pueraria lobata*), a vine found in the southern United States, contains unique isoflavones. One of them, puerarin, induced cytochrome P450 enzymes 1A1 and 1A2 among others, which pushed estrogen breakdown toward the beneficial 2-hydroxylation metabolic pathway. 14

Lignans found in fiber-rich foods such as seeds and grains, and in particularly high concentration in flaxseeds, contain phytochemicals that, when acted upon by bacteria in the gut, are converted to metabolites called enterolactone and enterodiol which appear to have similar effects as isoflavones. Researchers have demonstrated in animal and cell (*in vitro*) studies that lignans have chemoprotective effects, and they may favorably influence estrogen metabolism. 15 Other studies have shown that women with breast cancer, or who are at risk for breast cancer, have low excretion levels of urinary lignans. In cell-culture studies, lignans have been shown to inhibit estrogen-sensitive breast cancer cell proliferation. When flax was supplemented in five and ten grams per day for three seven-week periods in a group of 28 postmenopausal women, the levels of 2-hydroxyestrone increased in the urine, which increased the ratio of C-2:C-16. This suggests that flax may also have a beneficial effect on estrogen metabolism and thereby help to reduce the risk of breast cancer.

Cruciferous vegetables, such as broccoli, Brussels sprouts, cabbage, cauliflower, kale, kohlrabi, mustard greens, rutabaga and turnips have also been shown to lower the rate of breast cancer. 16 And, it is not surprising to find that diets high in these vegetables can increase the C-2:C-16 estrogen ratio. These phytochemicals seem to have a specific estrogen modulating effect. Cruciferous plants are particularly rich in indoles. A special form, called indole-3-carbinol (I3C) may be the most important phytonutrient in this regard. 17

Eating broccoli, kale, or other crucifers releases I3C, which when transported to the stomach, is converted into many active compounds, one of which is diindoylmethane (DIM). Both of these indole metabolites have estrogen-modulating activity, and promote the formation of 2-hydroxyestrone, a well-documented key to breast cancer prevention. 18 Current research studies are under way, studying I3C intake and women at increased risk of breast cancer. 19 Meanwhile we can eat these indole-containing foods with confidence and gustatory satisfaction.

**Xenoestrogens and the Environment**

A principal reason for our concern about environmental chemicals and toxins pertains to the epidemic proportion breast cancer has reached, not only in the U.S.A. but in countries around the world. For example, the possibility that a woman in North America will contract the disease has risen from one chance in twenty in 1950 to the current rate of one in eight. Today, breast cancer is the most prevalent type of cancer in women, and is the leading cause of death among women between the ages of 40-55. Every year 182,000 American women will be diagnosed with breast cancer; while 46,000 women die of the disease annually. There is hardly a family that has not been affected by such tragedies.

While much research and publicity has been given to the breast cancer genotype, and not a little attention to the risks of hormone replacement therapy, we have more difficulty processing and analyzing a woman’s lifetime exposure to estrogen, and its risk to breast disease. The dramatic increase in breast cancer over the last fifty years cannot be entirely accounted for by the use of estrogenic drugs, nor genetic factors, nor family choices such as the age of childbearing or infant breast-feeding practices. 20

In 1990, two environmental specialists – Elihu Richter and Jerry Westin – from Hebrew University’s Hadassah School of Medicine discovered a surprising glitch in otherwise depressing breast cancer statistics. 21 They found that in the decade between 1976 and 1986, Israel was unique among 28 countries surveyed in that it actually registered a significant drop in breast cancer mortality. This was in spite of increasing risk factors in the Israeli population, such as per capita fat intake, increasing patterns of delayed pregnancy, alcohol intake, and previous Israeli breast cancer rates that paralleled the international epidemic. As Westin noted, “All and all, we expected a rise in beast cancer mortality of approximately 20 percent overall, and what we found was that there was an eight percent drop, and in the youngest age group, the drop was 34 percent, as opposed to an expected 20 per cent rise. So, if we put those two together, we are talking about a difference of about 50 percent, which is enormous!”

Westin and Richter eventually connected this drop in breast cancer mortality to a 1978 Israeli ban on the use of three organochlorine pesticides (a ban, by the way, which was opposed by the Israeli cancer establishment). Prior to 1978, alpha-benzene hexachloride (BHC), gamma benzene hexachloride (lindane), and DDT were used heavily in Israeli cowsheds. As a result, the three pesticides heavily contaminated milk and milk products, at rates between 100 and 1,000 times greater than in the U.S.A. National public outcry resulted in legislation prohibiting these three pesticides.

Critics quickly challenged this suggested connection between breast cancer mortality and pesticide exposure, claiming that since most environmentally-induced cancers take at least twenty years to develop, the drop in mortality happened too quickly to associate any data with the prohibition of the three pesticides. Westin and Richter, in reply, explained that organochlorine pesticides are ‘complete’ carcinogens, which both initiate and promote tumor growth, and whose presence (or absence) can change cancer statistics quite rapidly.

Actually, animal experiments conducted back in the 1960s proved that organochlorine pesticides cause breast cancer in rats. 22 Like so many other animal studies, however, the results and their implied human parallel were totally ignored when they proved economically inconvenient to the burgeoning agro-industrial consortium. Also demonstrated, was the fact that organochlorine pesticides concentrate in animal and human fat tissue. As early as 1981, one research study concluded that organochlorine pesticides ‘might be considered possible contributors to the high incidence of breast cancer among women.’ 23

Such pesticides as DDT, dioxin, and atrazine are called ‘organochlorines’ because they are organic compounds containing chlorine bonded to carbon. Organochlorines are also produced in the manufacture of many herbicides, petrochemicals such as polychlorinated biphenyls (PCBs), PVC plastics and even certain paper products. In animals, including humans, organochlorines are stored in fat tissue, being inefficiently metabolized, and accumulate in the body for years. In Hamburg, Germany, an analysis of chemical plant workers showed a two-fold increase in breast cancer among women workers who had been exposed to dioxin contamination. Significantly higher incidence of breast cancer has been found in separate studies of women living near organochlorine chemical plants in Minnesota and Long Island. 24 Other studies have revealed elevated breast cancer mortality among professional chemists, among hairdressers, and users of hair dye. 25

Organochlorines are not only overtly toxic; some also possess estrogenic activity. In other words, these pesticides and chemicals mimic estrogen. Called xenoestrogens (literally ‘foreign estrogens’) these chemicals move into the nucleus of a receptor cell and disrupt the cell’s growth and division. 26 Xenoestrogens are known to exaggerate the carcinogenic effects of radiation, and may increase the breast cancer risk among women who were subjected to prenatal exposure to these substances. As mentioned already, the metabolic pathway of natural estrogens is modified beneficially by many phytochemicals, like indoles in cruciferous vegetables, lignans in flax, and isoflavones (genistein and daidzein) in soy bean products. Synthetic xenoestrogens, in contrast, block the 2-hydroxylation pathway and promote the more threatening 16-hydroxyestrone metabolic pathway. Some reports have even suggested that xenoestrogenic material is able to leach out of polycarbonate plastics, used in much of the food storage and cosmetic packaging industry. Back to nature, and a simpler country life is the watchword, both for eating and food preservation.

As we look at these cancer risk factors, with a desire to prevent disease and without economic or academic bias, it is not hard to discover the lifestyle which will prove most likely to avoid the ravages of breast cancer with its attendant suffering, worry, and pain. Soybean intake has not proven any risk at all in regard to breast cancer, with the possible theoretical exception of a high intake of soy protein isolates. And, it is not rational to extract a chemical for such testing, and then condemn the whole legume for a risk, unless there is a financial incentive for such advice. In careful study of the sources of this misinformation concerning the soy issue, such conflict-of-interest does appear prominently. Two of the authors who have written such soy-condemning articles are advocates of raw milk, meat, and high-protein intakes, while professing philosophical ideology which could best be described as New Age or pantheistic. Such ideas are blended in the articles which raise a false warning flag against soy milk and tofu, while making it appear that a vegetarian who uses these plant substances might be eating nothing else than soy, and thus merit the charge of food fanaticism.

Finally, in researching the scientific data concerning plant food dietaries, I have become more convinced than ever, that soy in the diet is not only healthful, but perhaps one of the best food sources of protein. 27 It should, though, be balanced in the diet with a wide variety of other fruits, vegetables, nuts, and legumes. There is little reason for a person to succumb to breast cancer, unless high genetic risk, previous unwise dietary choices, prior alcohol intake, obesity, or persistent use of meat and dairy products overwhelms the normal immune defenses, thus making even the use of soy and cruciferous vegetables insufficient to fight off carcinogenic toxins, tumor viruses, or as yet undiscovered cancer inducers. What we are up against is the challenge to preserve health in the face of growing environmental destruction with toxins that cannot be seen or avoided. This growing scientific confirmation of the value of a plant-based diet and natural lifestyle is cheering, to say the least, since it shows that our Creator’s original plan for human life on planet Earth was an all-wise provision for our longevity. If one has not begun to experiment with such choices, the time for decision and change is now.

**REFERENCES**

1 Lo GS, Goldberg AP, Lim A, et al. Soy fiber improves lipid and carbohydrate metabolism in primary hyperlipidemic subjects. *Atherosclerosis* 1986;62:239-248.

2 Sirtori CR, Lovati MR, Manzoni C, et al. Soy and cholesterol reduction: clinical experience. *J Nutr* 1995;125(suppl):598S-605S.

3 Kolonel, L.N., Hankin, J.H., Whittemore, A.S., Wu, A.H., Gallagher, R.P., Wilkens, L.R., et al (2000) Vegetables, fruits, legumes and prostate cancer: a multiethnic case-control study. *Cancer Epidemiol Biomarkers* Prev. 9: 795-804.

4 Witte, J.S., Longnecker, M.P., Bird, C.L., Lee, E.R., Frankl, H.D. and Haile, R.W. (1996) Relation of vegetable, fruit, and grain consumption to colorectal adenomatous polyps. *Am J Epidemiol*. 144: 1015-1025.

5 Shu, X.O., Jin, F., Dai, Q., Wen, W.Q., Potter, J.D., Kushi, L.H., et al (2001) Soyfood Intake during Adolescence and Subsequent Risk of Breast Cancer among Chinese Women. *Cancer Epid Biomarkers* Prev. 10: 483-488.

6 Zheng, W., Dai, Q., Custer, L.J., Shu, X.O., Wen, W.Q., Jin, F. and Franke, A.A. (1999) Urinary excretion of isoflavonoids and the risk of breast cancer. *Cancer Epidemiol Biomarkers* Prev. 8: 35-40.

7 Bradlow HL, et al. 2-hydroxyestrone: the 'good' estrogen. *J Endocrinol* 1996;150 Suppl:S259-65.

8 Gupta M, et al. Estrogenic and antiestrogenic activities of 16 alpha- and 2-hydroxy metabolites of 17 beta-estradiol in MCF-7 and T47D human breast cancer cells. *J Steroid Biochem Mol Biol* 1998;67(5-6):413-9.

9 Kabat GC, et al. Urinary estrogen metabolites and breast cancer: a case-control study. *Cancer Epidemiol Biomarkers Prev* 1997;6(7):505-9.

10 Muti P, et al. Estrogen metabolism and risk of breast cancer: a prospective study of the 2:16 alpha-hydroxyestrone ratio in premenopausal and postmenopausal women. *Epidemiology* 2000;11(6):635-40.

11 Meilahn EN, et al. Do urinary oestrogen metabolites predict breast cancer? Guernsey III cohort follow-up. *Br J Cancer* 1998;78(9):1250-5.

12 Xu X, et al. Effects of soy isoflavones on estrogen and phytoestrogen metabolism in premenopausal women. *Cancer Epidemiol Biomarkers Prev* 1998;7(12):1101-8.

13 Xu X, et al. Soy consumption alters endogenous estrogen metabolism in postmenopausal women. *Cancer Epidemiol Biomarkers Prev* 2000;9(8):781-6.

14 Guerra MC, et al. Comparison between Chinese medical herb Pueraria lobata crude extract and its main isoflavone puerarin antioxidant properties and effects on rat liver CYP-cataly-sed drug metabolism. *Life Sci* 2000;67(24):2997-3006.

15 Haggans CJ, et al. Effect of flaxseed consumption on urinary estrogen metabolites in postmenopausal women. *Nutr Cancer* 1999;33(2):188-95.

16 Fowke JH, et al. Brassica vegetable consumption shifts estrogen metabolism in healthy postmenopausal women. Cancer *Epidemiol Biomarkers Prev* 2000;9(8):773-9.

17 Liu H, et al. Indolo[3,2-b]carbazole: a dietary-derived factor that exhibits both antiestrogenic and estrogenic activity. *J Natl Cancer Inst* 1994;1758-65.

18 Wong GY, et al. Dose-ranging study of indole-3-carbinol for breast cancer prevention. *J Cell Biochem Suppl* 1997;29:111-6.

19 Telang NT, et al. Inhibition of proliferation and modulation of estradiol metabolism: novel mechanisms for breast cancer prevention by the phytochemical indole-3-carbinol. *Proc Soc Exp Biol Med* 1997;216(2):246-52.

20 Davis, Devra Lee and H. Leon Bradlow. "Can Environmental Estrogens Cause Breast Cancer?" *Scientific American*, October 1995, 166-172.

21 Westin, J.B. & Richter, E., The Israeli breast-cancer anomaly. *Ann. N. Y. Acad. Sci.* **609**, 269−79 (1990).

22 Greene, Gayle and Vicki Ratner. "A Toxic Link to Breast Cancer?" *The Nation*, 20 June 1994, 866-869.

23 Wolff, Mary S., et al. "Blood Levels of Organochlorine Residues and Risk of Breast Cancer." *Journal of the National Cancer Institute* 85: 648-652 (1993).

24 Gammon MD, Santella RM, et al, Environmental toxins and breast cancer on Long Island. I Polycyclic aromatic hydrocarbon DNA Adducts. II. Organochlorine Compound Levels in Blood. *Cancer Epidemio Biomarkers Prev* 2002 Aug; 11 (8): 677-697.

25 Iscan M, Coban T et al, The organochlorine pesticide residues and antioxidant enzyme activities in human breast tumors: Is there any association?, *Breast Cancer Res Treat* 2002 Mar; 72(2):173-182.

26 Epstein, Samuel S. "Environmental and Occupational Pollutants are Avoidable Causes of Breast Cancer." *International Journal of Health Services* 24:145-150 (1994).

27 **The Simple Soybean And Your Health** by Mark Messina, Ph.D. and Virginia Messina, RD (Avery Publishing Group, New York, 1994).