

Cruciferous Vegetables and Human Breast Cancer: An Important Interdisciplinary Hypothesis in the Field of Diet and Cancer

Ron Jevning
Los Angeles International
University—Irvine

Mark Biedebach
California State University

Rajen Anand
Center for Nutrition Policy
and Promotion

Very early progress in cancer treatment and prevention was based primarily on a basic understanding of genetic changes in genes at cellular and biochemical levels. Today, however, an interdisciplinary approach from complementary research tracks is possible in the understanding of cancer treatment and prevention. Such an approach is particularly important for its potential to increase our knowledge about diet and cancer because it may lead to sounder dietary guidance. This interdisciplinary approach is well illustrated by a hypothesis linking cruciferous vegetables to breast cancer prevention. The hypothesis links indole-3-carbinol, a specific component of brassica vegetables, such as broccoli or cauliflower, to a beneficial effect on human breast cancer (estrogen metabolism). In addition to its value for preventing human breast cancer, the biologic elements of the hypothesis have specific implications for research on other cancers and for other diets.

Cancer: Trends, Complexity, and Research

All have concerns about cancer. Because of the incidence and devastating effects of cancer, its burden of suffering and death throughout the world is huge. In English-speaking countries, the incidence of cancer appears to be increasing at an alarming rate (26). However, because it takes several years to collect and analyze sufficient data to establish trends, the trend in English-speaking countries is only probable. For example, the incidence of prostate cancer increased from 27,000 to 41,000 per year in the 8 years preceding 1991 (2). In 1992, 180,000 new cases of breast cancer were reported in American women, compared with 142,000 in 1989 (20). There also seems to be a steady increase in mortality from most cancers in recent years, with the most rapid increase

occurring in steroid-related cancers (see table). Both these projections—increased incidence and increased mortality—are supported by a recent review on the topic (26).

Cancer is a very complex disorder; hence, research on its cure and prevention has had to use several approaches. Early researchers tried almost exclusively to understand cancer by studying biochemical and genetic effects of such cancer-causing emissions as X rays, ultraviolet radiation, radioactive emanations, and the effects of chemical agents (5,9,11,24). However, later scientists began to use statistical or epidemiological¹ approaches to examine whether environmental factors such as diet or lifestyle may affect cancer risk (7,10,15).

¹“Epidemiological” refers to the study of diseases within particular groups or populations.

Cancer deaths per year from the most deadly types

Types	1992			1996 (estimated)			Percent increase of total over 4 years
	Male	Female	Total	Male	Female	Total	
Lung	91,400	54,500	145,900	94,400	64,300	158,700	8.8
Pancreas and colo-rectal	41,100	42,400	83,500	41,600	42,300	83,900	0.5
Steroid-involved (Breast, ovary, and prostate)	34,200	56,500	90,700	41,400	59,100	100,500	10.8

Source: Boring, C.C., Squires, J.S., and Tong, T. 1992. *Cancer statistics. Cancer Journal for Clinicians* 42:19-35. Estimates are projections from 1990-1992 trends.

These latter approaches have led many to conclude that diet has a likely role in cancer. In particular, Doll and Peto (9) in the United States and a group of researchers in Sweden (5) believe that the disease could be reduced by as much as 35 percent by practical dietary means.

One of the problems with these statistical methods is that they do not provide precise understanding of what about the diet may be associated with change of cancer risk (22,25). For example, investigators are fairly certain that diet change can reduce the risk of breast cancer. But is fat the culprit in breast cancer? Is the relatively higher concentration of fruits and vegetables in improved diets responsible? Complementing these statistical approaches with biochemical and genetic data is an indispensable input into providing more sound dietary guidance. In this article we describe a specific theory about diet and breast cancer that illustrates the advantages of such a combined approach for practical dietary guidance.

Diet-Estrogen Link to Breast Cancer

In steroid-related cancers, the tissues affected are those associated with reproduction. Epidemiologically, changes in incidence of these cancers correlate directly with dietary change (12). In particular, the incidence of breast cancer in English-speaking countries is between 10 and 15 times the incidence in poorer countries such as Thailand or Ecuador, a fact attributed by some researchers to difference in diet (7) (see figure). However, a serious problem with these correlational studies is that we often do not know or control for risk factors related to breast cancer—including both low parity (small number of offspring) and late age at first birth—other than diet that operate in developed countries. In this commentary, we maintain that a better understanding of the physiology of breast cancer can help clarify what it is about the diet that may affect breast cancer.

Early physiologically based research has suggested a role for estrogen² in

breast cancer (1,19). Much later, research has suggested that diet probably influenced the levels of blood estrogen (19,20,23). In 1996, Beatson noted that removal of the ovaries containing the estrogen-releasing cells was beneficial in some cases of breast cancer (1). In 1990, Key et al. found that compared with British women, rural Chinese women had lower estrogen levels and one-fifth the incidence of breast cancer (15).

At the same time, strong biochemical evidence links estrogen to cancer of reproductive tissue. Estrogen activates the parts of the chromosome (DNA) that promotes cell division. We know, however, that more than one form of estrogen exists: estradiol, the form normally secreted, promotes cell division in a well-controlled manner, while 16-hydroxyestrogen (C-16), another form of estrogen, seems to promote cell division in an uncontrolled manner that can lead to cancer in affected tissue (23).

²Estrogen is a steroid hormone that acts during the menstrual cycle to prepare the uterine and mammary tissues for possible pregnancy.

C-16 is one of the metabolites of normal estrogen, from which it differs only by the presence of a hydroxyl group on the number 16 carbon atom; C-2, the alternative estrogen metabolite, is a “safe” (inactive) substance.

Finally, we know that women with a family history of breast cancer have elevated blood C-16 (4); and the anti-estrogenic prescription drug 4-hydroxy tamoxifen (or simply tamoxifen) lowers blood C-16 and reduces both the incidence of breast cancer and the growth rate of existing breast cancer cells (13,14,21).

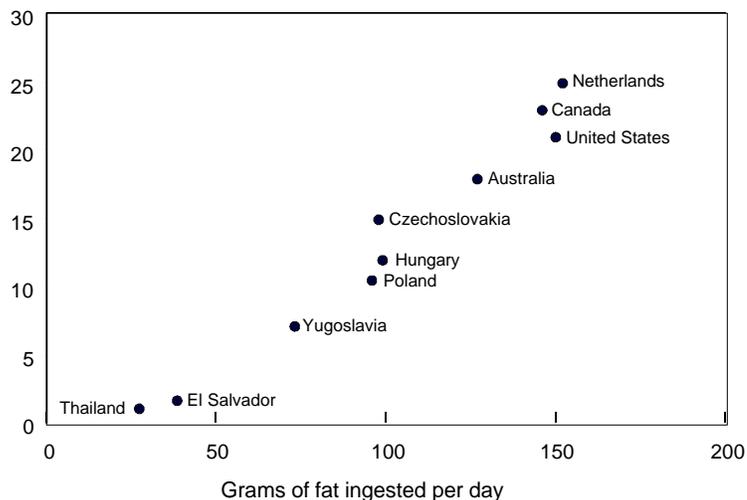
A Biochemically and Physiologically Based Breast Cancer-Diet Hypothesis

In the 1970's, Wattenberg reported that a diet of cruciferous (specifically brassica) vegetables³ was associated with an anti-breast cancer effect in animals (24). Wattenberg also identified a chemical compound in the vegetables, indole-3-carbinol (i-3-C), as the main contributor to their anti-cancer effect. Later authors have reported decreased formation of C-16 associated with increased vegetable diets (5). Such findings as these and those we discussed above led Michnovicz to hypothesize that cruciferous vegetables or purified i-3-C may reduce breast cancer initiation or the C-16/C-2 ratio by decreasing C-16 in the metabolism of estrogen (19,20). While there is already some experimental support for this hypothesis (3,19), larger clinical studies of i-3-C are necessary and are in progress (20).

³Among these types of vegetables are cabbage, broccoli, cauliflower, and Brussels sprouts.

Cancer death rate versus fat intake

Death rate
(per 100,000,
age adjusted)



Importance of Breast-Diet Hypothesis

Scientifically based references such as the *Food Guide Pyramid* or the *Dietary Guidelines for Americans*, published by the U.S. Department of Agriculture, exemplify bodies of knowledge relating to dietary guidance that may change with time. Therefore, on the basis of much research (some of which we have described), we know that Americans should probably choose a diet low in fat and cholesterol and one with plenty of vegetables and grains. However, much of our knowledge lacks specificity. For example, are there *particular* diets that may protect against cancer?

The possible link among crucifers, estrogen, and breast cancer illustrates how change in our knowledge will probably occur. Therefore, even if the details of this hypothesis prove wrong, its epidemiological, physiological, and biochemical basis has already stimu-

lated new research and discoveries. To exemplify this, we first note that net C-16 removal is mediated by representatives of a particular enzyme group known as “mixed function oxidases” (MFO’s) (24) and that i-3-C activates these enzymes (8). MFO’s have a generalized tissue function of rendering toxic substances harmless (including many otherwise carcinogenic compounds). Questions important for cancer in general then have arisen that include “what other substances than i-3-C can activate the C-16 removing MFO’s? In what other tissues can general MFO activity be increased?” For example, it has been reported that ascorbigen, a vitamin-C group compound (6), activates MFO and that there is marked synergy in MFO activation by administration of both i-3-C and ascorbigen (even though ascorbigen is a nucleoside that itself contains i-3-C) (5,16,17). McDanell also reports MFO activation or a synergistic effect of joint i-3-C and ascorbigen on MFO

activity in a wide variety of tissues, including small intestine, large intestine, liver, and lung (17). We can then reasonably ask this: "Are there cancer prevention or treatment implications of i-3-C or ascorbigen for tissues other than breast tissue? Is MFO activation operative in the reported anti-cancer effect of a vegetable diet on a wide variety of these tissues? Can benefits be enhanced by combination i-3-C/ascorbigen supplementation or administration?"

General principles of the hypothesized beneficial linkage between crucifers and breast cancer may also be relevant to other diets or dietary aspects. Therefore, the central role of estrogen suggests that a fiber-rich diet may be protective, because dietary fiber increases removal and decreases reabsorption of stool estrogen. This biologic rationale complements some epidemiologic evidence that fiber is important, although epidemiologic assessment has been compromised by scarcity of data on the fiber content of individual foods (25). Similarly, suggestive data, indicating protection for a soy diet, have a biologic rationale in the ability of soy isoflavones to interfere with estrogen receptors (18). Finally, selection for future evaluation from the enormous number of phytochemical possibilities can be guided, in part, by knowledge of which chemicals affect estrogen content or biochemistry.

The possible cruciferous vegetable and estrogen linkage exemplifies how more sound and more specific guidance can result from combining pieces of the dietary puzzle from a variety of scientific disciplines. While we focused on only breast cancer here, the possible linkage between cruciferous vegetables and estrogen may have far wider significance for other diets and other cancers, because the principles discussed here are generally applicable.

References

1. Beatson, G.T. 1996. On the treatment of inoperable cases of carcinoma of the mamma: Suggestions for a new method of treatment with illustrative cases. *Lancet* 2:104-107.
2. Boring, C.C., Squires, J.S., and Tong, T. 1992. Cancer statistics. *Cancer Journal for Clinicians* 42:19-35.
3. Bradfield, C.H. and Bjeldanes, L.F. 1984. Effect of dietary indole-3-carbinol on intestinal and hepatic monooxygenase, glutathione S-transferase and epoxide hydrolase activities in the rat. *Food and Chemical Toxicology* 22:977-987.
4. Bradlow, H.L. and Michnovicz, J.J. 1989. A new approach to the prevention of breast cancer. *Proceedings of the Royal Society, Edinburgh* 95B:77-86.
5. Byers, T. and Graham, S. 1984. The epidemiology of diet and cancer. *Advances in Cancer Research* 41:1.
6. Cameron, E. and Pauling, L. 1979. Ascorbic acid and cancer: A review. *Cancer Research* 39:663.
7. Cohen, L.A. 1987. Diet and cancer. *Scientific American* 257:42-50.
8. Dashwood, R.H., Arbogast, D.N., Fong, A.T., et al. 1988. Mechanism of anticarcinogens by indole-3-carbinol: Detailed in vivo DNA binding dose-response studies after dietary administration with aflatoxin B1. *Carcinogenesis* 9:427-432.
9. Doll, R. and Peto, R. 1981. The causes of cancer: Quantitative estimates of avoidable risks of cancer in the United States today. *Journal of the National Cancer Institute* 66:1191-1308.
10. Frisch, R.E., Wyshak, G., Witschi, J., et al. 1987. Lower lifetime occurrences of breast cancer and cancers of the reproductive system among former college athletes. *International Journal of Fertility* 32:217-225.
11. Gerhardsson, J.D. and Donahue, L. 1988. Aflatoxin, a human carcinogen: Determination in foods and biological samples by monoclonal antibody affinity chromatography. *Journal of the Association of Official Analytical Chemists* 71:861-867.
12. Haenszel, L. and Kurihara, M. 1968. Studies of Japanese migrants. I. Mortality from cancer and other diseases among Japanese in the United States. *Journal of the National Cancer Institute* 40:43-49.
13. Han, X. and Liehr, J.G. 1992. Induction of covalent DNA adducts in rodents by tamoxifen. *Cancer Research* 52:1360-1363.

-
14. Harris, J.R., Lippman, M.E., Veronesi, U. 1992. *New England Journal of Medicine* 327:389-398.
15. Key, T.J.A., Chen, J., Wang, D.Y., et al. 1992. Sex hormones in women in rural China and in Britain. *British Journal of Cancer* 62:631-636.
16. Kutacek, M., Prochazka Z., and Valenta, M. 1962. The metabolism of glucobrassicine and other indole derivatives in brassica, in naturally occurring goitrogens, thyroid function. Symposium, Smolensk, Czechoslovakia. pp. 49-56.
17. McDanell, R., McLean, A.E.M., Hanley, A.B., et al. 1987. Differential induction of mixed-function oxidase (MFO) activity in rat liver and intestine by diets containing processed cabbage: Correlation with cabbage levels of glucosinolates and glucosinolate hydrolysis products. *Food and Chemical Toxicology* 25:363-368.
18. Messina, M. and Barnes, S. 1991. The role of soy products in reducing risk of cancer. *Journal of the National Cancer Institute* 83:541-546.
19. Michnovicz, J.J., Adlercreutz, H., and Bradlow, H.L. 1997. Changes in levels of urinary estrogen metabolite after oral indole-3-carbinol treatment in humans. *Journal of the National Cancer Institute* 89:718-723.
20. Michnovicz, J.J. and Klein, D.S. 1994. *How to Reduce Your Risk of Breast Cancer*. Warner Books, New York.
21. Nayfield, S.G., Karp, J.E., Ford, L.G., et al. 1991. Potential role of tamoxifen in prevention of breast cancer. *Journal of the National Cancer Institute* 83:1450-1459.
22. Steinmetz, K.A. and Potter, J.D. 1991. Vegetables, fruit and cancer. I. Epidemiology. *Cancer Causes and Control* 2:325-357.
23. Telang, N.T., et al. 1997. Inhibition of proliferation and modulation of estradiol metabolism; novel mechanisms for breast cancer prevention by the phytochemical indole-3-carbinol. *Proceedings of the Society of Experimental Biology and Medicine* 215:246-254.
24. Wattenberg, L.W. 1997. An overview of chemoprevention; current status and future prospects. *Proceedings of the Society of Experimental Biology and Medicine* 216:133-155.
25. Willett, W.C. and Hunter, D.J. 1992. Dietary fat and fiber in relation to breast cancer. *Journal of the American Medical Association* 268:2034-2044.
26. World Cancer Research Fund/American Institute for Cancer Research. 1997. *Food, Nutrition & the Prevention of Cancer; a global perspective*. Washington, DC.