

# Breast Size, Endogenous Estrogens, and Breast Cancer: A Review with Hypothesis

STEVEN LEHRER, M.D., EVA LEVINE, MS, HEE KYUNG SONG, M.D., AND WILLIAM D. BLOOMER, M.D.

The role of endogenous estrogens in breast cancer has long been a subject of interest. The breast is much less responsive to the tumor-promoting effects of estrogens than is the endometrium; estrogens, nonetheless, appear to be necessary for breast carcinogenesis (1). We suggest that the role of endogenous estrogens is solely to increase breast size and the amount of glandular tissue susceptible to malignant transformation. In physiologic concentrations, estrogens appear to have no other carcinogenic effect. In this report, epidemiologic and experimental evidence is presented to support this hypothesis.

## Racial, Geographic, and Other Variables

There is marked variation in the rate of breast cancer in different areas of the world. In women at age 50, the incidence of breast cancer is about six times higher in the United States than in Japan or Taiwan (2). Interest in dietary fat as a possible explanation of this disparity has been stimulated by the strong correlation between national per capita consumption of fat and age-adjusted rates of breast cancer (3). However, other studies of breast cancer rates in population groups provide an inconsistent picture. For example, rates of breast cancer among orders of nuns who consume little or no meat were similar to those in the general British population of single women (4).

Furthermore, the breast cancer incidence in Japanese-American women still falls considerably below that for white women; and the rates of breast cancer for Japanese migrants and their daughters move more slowly toward the level of

the adopted country than do rates for many other forms of cancer (5).

The factor that may be responsible for the lower breast cancer incidence is breast size. Oriental women, even those living in the United States, have considerably smaller breasts than Caucasians. One brassiere manufacturer reports selling A-cup brassieres almost exclusively to orientals living on the West Coast. In contrast, the same manufacturer sells predominantly B-cup and C-cup brassieres to the Caucasian women living in the Southwest and Middle West (6).

The probability of any single cell in a population becoming malignant in a given period of time may be compared to the chance of turning up heads on the toss of a coin. If a single coin is tossed, the probability is 50%. However, if a hundred coins are tossed, the chance of one turning up heads is considerably greater than 50%. By analogy, the larger the breast, the more glandular cells and, therefore, the higher the probability that a single cell, or multiple cells, will become malignant in a given period.

This line of reasoning, of course, may also explain why men have only 1% as much breast cancer as women (1). Because they have many fewer glandular cells vulnerable to malignant transformation, one would expect their breast cancer rate to be considerably lower.

More evidence supporting the relationship between breast size and breast cancer is provided by the size difference between the left and right breasts. In most women, the left breast is larger than the right (7), and there is a 6% to 13% excess of left-sided breast cancers among premenopausal and postmenopausal patients (8). Other studies have shown that the left breast develops cancer in 52% of cases, the right breast in 47%, and in 1% the disease is bilateral (7).

But there is still considerable controversy

From the Radiation Therapy Department, Mount Sinai School of Medicine (CUNY), Box 1236, One Gustave L. Levy Place, New York, NY 10029. Address reprint requests to Dr. Steven Lehrer there.

TABLE  
*Estrogen Receptor Status and Age at Onset in a Group of Women with Breast Cancer*

	Smokers	Nonsmokers	Significance
Estrogen receptor positive	13	11	$\chi^2 = 0.02$ $p > 0.9$
negative	12	11	
Age at cancer onset (yrs)	$51.8 \pm 11.6$	$54.4 \pm 15.3$	$t = 0.65$
No. of women	25	22	$p > 0.5$

over breast size and breast cancer (7). For example, mammary fat, as well as glandular tissue, plays a substantial role in breast size (9). Yet it is logical to assume that the amount of glandular tissue is important for carcinogenesis.

### Role of Estrogen

The breast size hypothesis may explain the lack of a relationship between endogenous estrogen fluctuation and breast cancer incidence. Neither high nor low endogenous estrogens have any effect in breast carcinogenesis.

Cigarette smoking is associated with an important antiestrogenic effect. Female smokers have decreased luteal phase urinary excretion of estrone, estradiol, and estriol (10). Moreover, there is a decreased incidence of endometrial cancer in smokers (11), but no protective effect against breast cancer (12). Our own data support the latter finding. We have noted that the incidence of the tumor estrogen receptor and the age at onset of the cancer are not significantly different statistically in smokers and nonsmokers (Table).

However, urinary estrogens are no higher in women with breast cancer than in the general population. Even the hormone excretion of high-risk groups does not differ from that of normal-risk groups (2). And estrogen-secreting tumors, which promote endometrial cancer, have no effect on breast cancer (1).

Early menarche and late menopause increase the risk of breast cancer (1). Although lengthened estrogen exposure has been suggested to be the cause of this increase, it might instead be related to another hormone, prolactin, also implicated in human and rat breast cancer (13).

Like estrogen, prolactin rises sharply at menarche and falls again at menopause (14, 15). This fluctuation can explain why premenopausal castration protects against breast cancer, whereas smoking does not. The explanation is that smoking causes only decreased estrogens, whereas castration induces premature menopause, which also lowers prolactin levels.

Thus, the only role of endogenous estrogens in breast cancer may be their promotion of breast enlargement and increased amounts of glandular tissue. In physiologic quantities, endogenous estrogens probably have no other effect.

### Summary

Endogenous estrogens probably promote breast cancer only by increasing the amount of glandular tissue within the breast. For this reason, diminished estrogen production in smokers does not protect against breast cancer, though it does protect against uterine cancer. Castration before menopause diminishes breast cancer risk because it reduces prolactin levels as well as estrogen levels.

### References

1. Thomas DB. Do hormones cause breast cancer? *Cancer* 1984; 53:595-604.
2. Lippman ME. Endocrine responsive cancers of man. In: Wilson JD, Foster DW, eds. *Textbook of Endocrinology*, 7th ed. Philadelphia: WB Saunders, 1985, 1309-1326.
3. Willett WC, MacMahon B. Diet and cancer—an overview. *N Engl J Med* 1984; 310:697-701.
4. Kinlen LJ. Meat and fat consumption and cancer mortality: a study of strict religious orders in Britain. *Lancet* 1982; 1:946-949.
5. Buell P. Changing incidence of breast cancer in Japanese-American women. *J Nat Cancer Inst* 1973; 51:1479-1483.
6. Reuben Lewis, Classique, Inc. Miami, Florida. Personal communication, November 1986.
7. Vorherr H. *Breast Cancer: epidemiology, endocrinology, biochemistry, and pathology*. Baltimore, Munich: Urban & Schwarzenberg, 1980, 70-72.
8. Blot WJ, Fraumeni JF, Young JL. Left sided breast cancer. *Lancet* 1977; 2:762-763.
9. Valaoras VG, MacMahon B, Trichopoulos D, Polychronopoulou A. Lactation and reproductive histories of breast cancer patients in greater Athens. *Int J Cancer* 1969; 4:350-363.
10. MacMahon B, Trichopoulos D, Cole P, Brown J. Cigarette smoking and urinary estrogens. *N Engl J Med* 1982; 307:1062-1065.
11. Michnovicz JJ, Herschcopf RJ, Naganuma H, Bradlow HL, Fishman J. Increased 2-hydroxylation of estradiol as a possible mechanism for the anti-estrogenic effect of cigarette smoking. *N Engl J Med* 1986; 315:1305-1309.
12. Brinton LA, Schairer C, Stanford JL, Hoover RN. Cigarette smoking and breast cancer. *Am J Epidemiol* 1986; 123:614-622.
13. Levin PA, Malarkey WB. Daughters of women with breast cancer have elevated mean 24-hour prolactin (PRL) levels and a partial resistance of PRL to dopamine suppression. *J Clin Endocrinol Metab* 1981; 53:179-183.
14. Yen SSC. Prolactin in human reproduction. In: Yen SSC, Jaffee RB, eds. *Reproductive endocrinology*, 2nd ed. Philadelphia: WB Saunders, 1986, 237-263.
15. Berman RL. Current perspectives in gynecology. *Clin Symp* 1985; 37(1): 2-32.

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