The Role of Estrogens in Mastopathy and Mammary Cancer in Perimenopausal Women

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Fibrocystic disease of the breast (FCD) is an exaggeration of the normal physiologic response to cyclic estrogen and progesterone stimulation. The disorder can persist, with much less severity, in the menopausal woman. Whether FCD predisposes to mammary cancer remains moot. A new steroidal agent, danazol, can eliminate nodosities in the majority of women with FCD. Thermography may identify women who are at greater risk because of increased heat production. Mammography should be employed in women with persistently abnormal thermograms, even though no suggestive breast masses are palpable. Needle biopsy or surgical biopsy should be undertaken whenever a firm indurated mass is palpated, regardless of negative findings with a thermogram or mammogram. In a series of 1548 women treated for 10,715 women-years, the incidence of breast cancer after prolonged estrogen therapy was not increased. Although estrogens and prolactin have been incriminated in the etiology of mammary cancer, no hard facts exist to confirm such allegations.

Fibrocystic breast disease (FCD), so prevalent during the reproductive years, may persist after the onset of the menopause. Kramer and Rush examined the breasts of 70 women older than 70 who died of causes other than cancer of the breast; they found cysts in 89 per cent, apocrine metaplasia in 80 per cent, and intraductal hyperplasia in 68 per cent.[1] The incidence of cystic breast disease in breast cancer patients has been reported as double (43 vs 22 per cent) that in a normal population.[2] Several experienced investigators have alleged that FCD predisposes to cancer or is unusually common in breasts in which malignant tumors subsequently develop.[3–5] A relationship between FCD and breast cancer is not universally accepted, and according to Azzopardi, the evidence at best is tenuous.[6]

Menopausal women in whom benign breast disease (BBD) develops following estrogen therapy are alleged to have a sevenfold greater risk of breast cancer,[7] but Bulbrook could not establish any such risk.[8] That heredity, nutrition, and environment

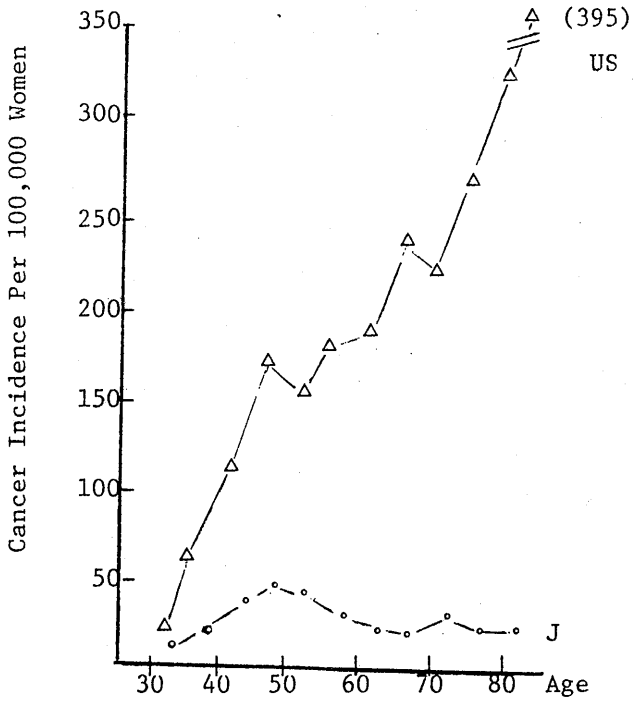

Figure 1. Age-related curves of breast cancer in Japan and the United States. After the age of 35, breast cancer incidence rises rather steeply until ages 45–50, followed by a temporary plateau. After ages 55–60, in the United States, the incidence of mammary cancer rises steeply. Notice the pronounced difference in breast cancer incidence between US and Japanese women. (Modified from Vorheer H, Messer RH: Breast cancer: Potentially predisposing and protecting factors. Am J Obstet Gynecol 130:335, 1978.)

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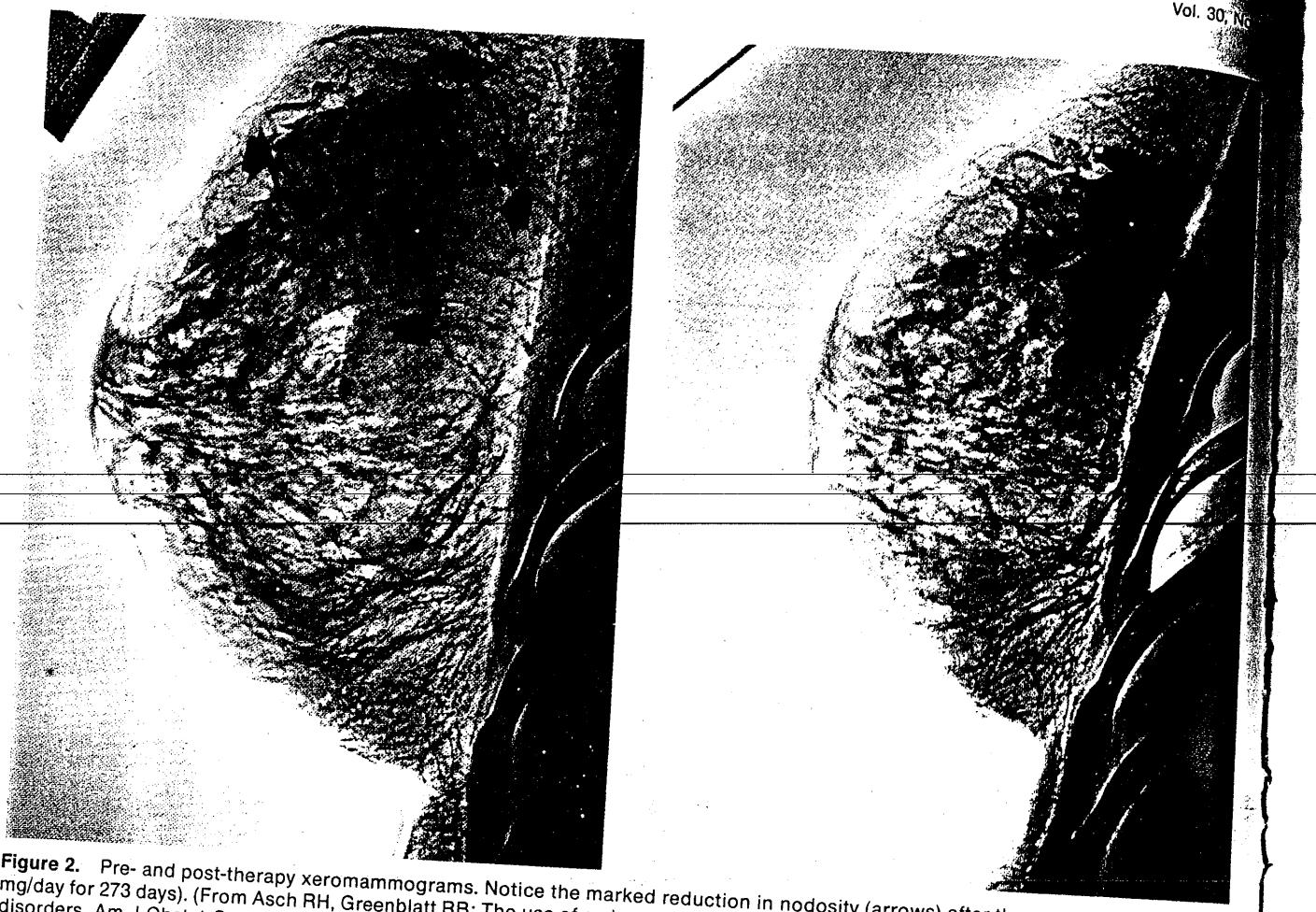

Figure 2. Pre- and post-therapy xeromammograms. Notice the marked reduction in nodosity (arrows) after therapy with danazol (200 mg/day for 273 days). (From Asch RH, Greenblatt RB: The use of an impeded androgen—danazol—in the management of benign breast disorders. Am J Obstet Gynecol 127:130, 1977.)

probably play a greater role in mammary cancer than do hormones is suggested by the fact that Japanese women living in Hawaii show a far greater incidence of breast cancer than those living in Japan. Moreover, Japanese women show a much lower incidence of breast cancer than do Occidental women (Fig. 1).[9] The incidence of breast cancer quickly rises between the ages of 25 and 45, reaching a plateau between tha ages of 45 and 55; thereafter, the curve of incidence resumes its original steep upward course.[10]

One of 11 women in the United States will have mammary cancer in her lifetime. The horrendous mortality from this disease has not lessened in the past 40 years despite improved surgical techniques, radiation, and chemotherapy.

This paper attempts to answer several questions. What role does past and present benign mastopathy play in the development of breast cancer? Do estrogens play a significant role in the development of BBD and mammary cancer?

THE ETIOLOGY OF FIBROCYSTIC BREAST DISEASE (FCD)

FCD occurs in ovulatory women and is believed to result from an inappropriate tissue response to cyclic estrogen and progesterone stimulation, or from an imbalance between the growth-promoting effects of estrogens and the growth-limiting properties of progesterone. Although it is true that anovulatory women with persistent estrogen production (e.g., Stein-Leventhal syndrome) rarely have breast mastopathy, fibroadenomas and the histologic changes of fibrocystic mastopathy have been observed in men working with stilbestrol.[11] On the other hand, Bonte quotes the surveys by Gray et al (1971), Sartwell et al. (1973), and the Boston Collaborative Drug Survey Program (1974) showing that estrogen is not a significant factor in BBD, whereas Fechner (1972) and Nomura (1976) both claimed a significant association.[12] The epidemiologic studies of Ory indicate that users of the oral contraceptive pill for two or more years have less FCD, fibroadenomas, and mammary cancer than do nonusers of the pill.[13] As to the relationship between mastopathy and cancer, Bloodgood believed so strongly that FCD predisposes to cancer that he advocated mastectomy for severe disease. However, when old in years and after mature reflection, he admitted to one of us (RBG) that he removed "far, far too many breasts."[14]

ROLE OF ESTROGENS IN BREAST CANCER

What is the role of estrogens in breast cancer? Estrogens have been incriminated as increasing the

risk of cancer. Based on animal studies in rodents and on certain retrospective human studies, Hoover et al found that there was a 1.3–2.0 increased risk in postmenopausal women who had been taking estrogens for 10 to 15 years.[7] However, when Bland et al reviewed the same series along with their own cases, they came to a different conclusion, i.e., that there was a slight decrease in cancer incidence.[15] Burch et al concluded from a study of 511 estrogen-treated women followed up for nine or more years that the incidence of breast cancer was essentially the same as in a peer control group, but that the malignancies occurred 10 years later.[16] For Burch et al, this was a decided plus in favor of estrogen administration. Gambrell et al found less mammary cancer in estrogen or estrogen-progestogen treated women than in nonhormonally treated women.[17] Although estrogens have been employed to advantage in treating postmenopausal women with metastatic breast cancer, anti-estrogens (tamoxifen) have proved equally or even more effective. In subhuman species, Geschicter et al failed to induce mammary cancer in monkeys by giving extremely high doses of estrogen for seven years and seven months.[18]

TABLE 1
*Evaluation of Breast Nodularity in 40 Patients with Benign Cystic Breast Disease, after Danazol Therapy (100 mg/day)**

Breast nodules	Evaluation After				
	6 mo	12 mo	24 mo	36 mo	48 mo
Elimination	26	25	26	27	7
Partial resolution	13	14	13	7	1
Unchanged	1	1	0	0	0
Totals	40	40	39	34	8

* From Nezhat C, Asch RH, Greenblatt RB: Am J Obstet Gynecol 137:604, 1980[5]

TABLE 2
*Evaluation of Breast Nodularity in 35 Patients with Benign Cystic Breast Disease after Danazol Therapy (400 mg/day)**

Breast nodules	Evaluation After				
	6 mo	12 mo	24 mo	36 mo	48 mo
Elimination	28	28	25	20	19
Partial resolution	7	6	8	10	7
Unchanged	0	1	0	0	0
Totals	35	35	33	30	26

* From Nezhat C, Asch RH, Greenblatt RB: Am J Obstet Gynecol 137:604, 1980[5]

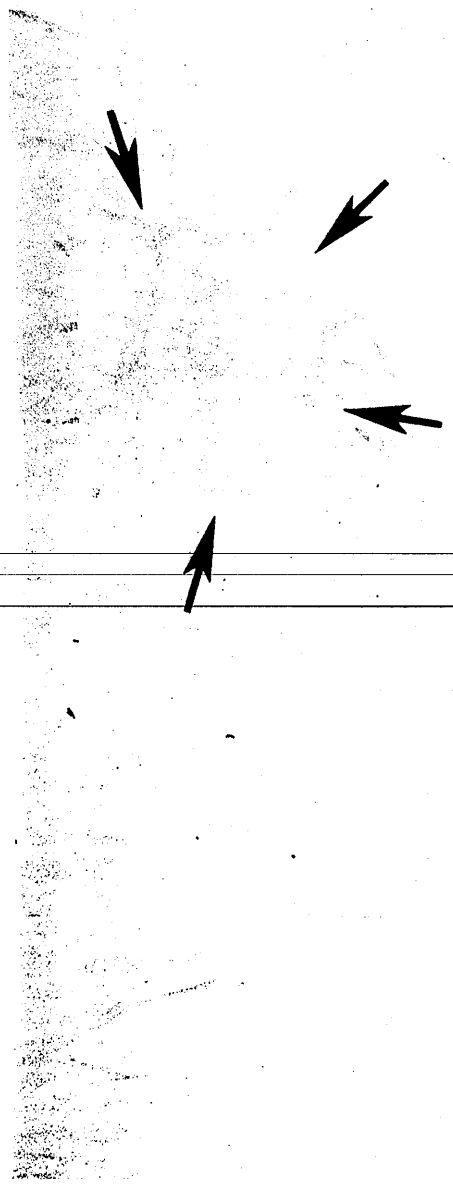

Figure 3. Xeromammogram revealing a mass in the upper lateral quadrant of the left breast in a 53-year-old woman with an abnormal thermogram. No lymph node involvement was found at operation. (From Greenblatt RB, Samaras C, Vasquez J: Benign breast disease. Contemp Surg 18:27, 1981.)

ROLE OF PROLACTIN IN MAMMARY CANCER

1. In rats, the administration of prolactin before the administration of carcinogenic agents diminishes the incidence of tumor formation, but if prolactin is given after the carcinoma is induced, the tumor will grow rapidly. However, if prolactin is rapidly withdrawn, complete regression may take place.[19]

2. In a mammary-cancer strain of rats, the administration of estrogen increases tumor frequency, but if the rodent undergoes hypophysectomy, cancer fails to occur. Evidently prolactin is essential to tumor growth.[20]

TABLE 3

Age-Related Breast Cancer Incidence in Women Receiving Continuous Estrogen Therapy for 10,715 Women-Years

Age (years)	No. of Women Treated	No. of Mammary Cancers	Cancer Incidence	Expected Incidence*
15–19	24	0	0:100,000	0.2:100,000
20–24	82	0	0:100,000	1.1:100,000
25–29	95	0	0:100,000	8.4:100,000
30–34	94	0	0:100,000	26.7:100,000
35–39	134	0	0:100,000	57.3:100,000
40–44	61	0	0:100,000	106:100,000
45–49	255	3	155:100,000	174:100,000
50–54	263	1	50:100,000	196:100,000
55–59	259	3	152:100,000	229:100,000
60–64	136	2	194:100,000	251:100,000
65–69	95	2	277:100,000	283:100,000
>70	50	0	0:100,000	303:100,000
Totals 47.8	1,548	11	69:100,000	136.3:100,000

* Cutler SJ, Young JL Jr: Third National Cancer Survey: Incidence data. National Cancer Institute Monograph 41, 1975

3. Bromocriptine, an antiprolactin, will prevent the appearance of spontaneous mammary tumors when administered to a cancer strain of mice.[21]

4. Pituitary ablation in women with metastatic breast cancer is often followed by remarkable, though temporary, regression of metastases, which is believed to be due to the elimination of prolactin production.[22]

Before prolactin is indicted as a causative agent, it is well to consider that parous women have less cancer than nonparous ones, despite the fact that prolactin values are elevated during pregnancy. Japanese women have higher nocturnal levels of prolactin during the winter and spring than do American women, yet have fewer mammary cancers.[23]

TREATMENT OF FCD THROUGH HORMONAL MANIPULATION

Estrogens and/or progestogens, as well as androgens, have been used to advantage in the management of FCD. A new steroidal agent, danazol, seems quite effective.[24] Doses of 100–400 mg/day, depending upon the severity of the disease, are administered for three to six months. Tables 1 and 2 are from a study by Nezhat, Asch and Greenblatt.[25] Untoward reactions, such as hot flashes, leg cramps, and weight gain, were frequent but minor. A few women were unable to take the drug because of nervousness, depression, or nausea. It is hoped that by the elimination or marked reduction of nodosities, fewer breast biopsies will be necessary and women will be less predisposed toward the development of mammary cancer (Fig. 2). Hormonal manipulation appears to be of some value, since oral contraceptives lessen the incidence of BBD and breast cancer. Other modes of treatment have been suggested in the management of FCD, e.g., alpha tocopherol,[26] elimination of methylxanthines,[27] bromocriptine,[28] and antiestrogens.[29] The effects of such regimens need further confirmation.

IDENTIFYING WOMEN AT GREATER RISK

Contact thermography, which measures heat production, is based on the ability of liquid cholesterol crystals to change their color under the influence of infrared rays. The human skin emits infrared radiation. Florid FCD may be identified by abnormal thermograms.[30] Gautherie and Gros found that in women with persistent abnormal thermograms, mammary cancer developed more frequently than in women with normal thermograms.[31] Abnormal thermograms are also obtained in women with rapidly proliferating breast carcinoma, whereas slow-growing sclerotic lesions emit less heat and the thermograms in such instances are normal. Women with abnormal thermograms that fail to revert to normal, or in whom the degree of heat production is not reduced on hormonal manipulation, (e.g., administration of danazol, androgens, or progestogens), should be studied further by mammography. Mammograms often reveal an irregular density with or without characteristic calcification, even before a mass in palpable (Fig. 3). Whenever a suspicious mass is noted, fine-needle biopsy for cytologic evaluation or surgical biopsy for histologic study is indicated, regardless of negative findings with a thermogram or mammogram.[32–34] Cystic masses should be aspirated and the material sent to the pathologist. Smears should be taken of all serous and discolored discharges from the nipple (except frankly milky ones) and sent to the pathologist for diagnosis.

INCIDENCE OF MAMMARY CANCER FOLLOWING ESTROGEN ADMINISTRATION

One of us (CN), who had been indoctrinated to believe that estrogens increased the risk of breast cancer, undertook to review the case histories of 1548 women in our clinic who had received estradiol pellets for 10,715 women-years. Table 3 indicates the number of women, by age groups, in relation to the development of mammary cancers; 11 cancers occurred among 1548 women. According to National Cancer Survey statistics, the incidence should have been about doubled. Even if an equal number of cases were lost to follow-up, it appears that the frequency was no greater than in the general population. The alleged relationship between exogenous estrogens and mammary cancer remains to be proved.

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