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Decreased Incidence of Breast Cancer in Postmenopausal Estrogen–Progestogen Users

R. DON GAMBRELL, Jr, MD, ROBERT C. MAIER, MD, AND BARBARA I. SANDERS, RN

In a prospective study at Wilford Hall USAF Medical Center from 1975 to 1981, 5563 postmenopausal women were followed for a total of 37,236 patient-years of observation. During these seven years, 53 patients were found to have breast cancer, for an incidence of 142.3:100,000 women per year. The mean age (± SD) of the patients with cancer was 56.9 ± 8.24 years, and the mean age of the entire patient population was 56.8 ± 6.75 years. The expected incidence of breast cancer in this age group, according to the Third National Cancer Survey (1975), is 188.3:100,000 women, and for ages 55 to 59, according to the National Cancer Institute Surveillance, Epidemiology, and End-Result Reporting (NCI SEER) data (1980), is 229.2:100,000. The lowest incidence of breast cancer (67.3:100,000) was observed in the estrogen–progestogen users and was significantly lower than that of the untreated group (342.3:100,000), with $P \leq .01$. The incidence of the estrogen–progestogen users was also significantly lower than that expected from the NCI SEER data, with a relative risk of 0.3 (95% confidence interval, 0.1 to 0.8). The incidence of mammary malignancy in the estrogen users (141.0:100,000) was significantly lower than in the untreated group (342.3:100,000), with $P \leq .01$. Although the incidence in the estrogen users was not significantly lower than that expected according to the NCI SEER data (relative risk = 0.7, 0.5 to 1.1), there was a trend in that direction. These data indicate that estrogen therapy for postmenopausal women does not increase the risk of breast cancer and may afford some protection. Added progestogen to postmenopausal estrogen therapy significantly decreases the risk for this malignancy. *(Obstet Gynecol 62:435, 1983)*

The incidence of breast cancer increases throughout the female life span and will strike one in 11 women in the United States.[1,2] In this respect, the incidence of this malignancy differs from cervical, endometrial, and ovarian cancer, which peak in the 40s, 50s, and 60s, respectively, and then either decline or plateau. The sharpest increase in the frequency of breast cancer occurs between ages 30 and 50, or about the time of menopause. Then the incidence continues to rise steeply throughout the postmenopausal years, when estrogen levels are lower. Breast cancer is not only the most frequent malignancy in females (27% of all female cancers) but also the leading cause of death from cancer in women (19% of all female cancer deaths) in the United States.[3] The American Cancer Society estimated that 115,000 new cases of breast carcinoma would be diagnosed in the United States during 1983, and that 38,000 women would die from this tumor in that year.[3]

Estrogens influence the growth of normal breast tissue. The presence of estrogen receptors and, more recently, progesterone receptors in breast cancer serves as a prognostic indicator.[4] The presence of estrogen receptors is related to a longer disease-free interval and decreased mortality. It is paradoxical that some patients with metastatic carcinoma of the breast respond to endocrine ablative surgery whereas others may have a remission with estrogen therapy. The presence of both estrogen and progesterone receptors in breast tumors helps predict a 70% chance of favorable response to endocrine manipulation with either ablative surgery or antiestrogen therapy. When the estrogen–endometrial cancer controversy was renewed in the mid-1970s, interest was also aroused in the relationship of estrogen replacement therapy and breast cancer.[5–7] Long-term studies of large numbers of women have failed to incriminate exogeneous estrogen therapy for any significantly increased risk of breast malignancy. Unfortunately, none of the epidemiologic studies have looked at the possible protective effect of added progestogens for breast cancer.

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The opinions and assertions contained herein are those of the authors and are not to be construed as official or reflecting the views of the United States Air Force or the Department of Defense.

Since both the breast and endometrium are target organs for the action of hormones, attempts have been made for years to define the role of the sex steroids in the etiology of cancer in these tissues. It is now accepted that estrogen replacement therapy increases the risk of endometrial cancer.[8–11] Studies from Wilford Hall USAF Medical Center, as well as others, have shown the efficacy of progestogens in reducing the risk of endometrial cancer in estrogen-treated postmenopausal women.[12–17] With this data base of hormone usage, patients with breast cancer at this institution during the seven years of prospective study have been reviewed and comprise the basis for this report.

Materials and Methods

A prospective study was begun in 1975 to determine the incidence of breast and endometrial cancer in postmenopausal women using various hormone regimens. A postmenopausal hormone survey card was initiated at the first visit and updated at each subsequent visit. Information obtained included age, parity, blood pressure, weight, and, if previously performed, date of hysterectomy with or without adnexal surgery. Hormone therapy, if any, was recorded, including type, dosage, how taken, and for how many years. Age at menopause and age of initial estrogen treatment were listed. A total of 5563 postmenopausal women was registered in the study from 1975 through 1981.

The patients with breast and endometrial cancer were identified from the tumor registry. These records include narrative summaries, hospital chart cover sheets, surgery reports, pathology reports, tumor board decisions, radiotherapy records, Southwestern Oncology Group (SWOG) chemotherapy protocols, and copies of all follow-up visits. Once a patient is entered into this registry, outpatient records are coded so that copies of all pertinent records are forwarded for inclusion. In addition, semiannual or annual questionnaires are mailed to all patients for current status after the initial therapy, and patients are seen at least annually for a minimum of ten years.

Wilford Hall USAF Medical Center is the major Air Force hospital for the San Antonio, Texas area, so the patient population consists of female personnel on active duty and wives and other dependents of military personnel, including retired personnel from that area. Hormone therapy selected for patients was based primarily on symptoms, with one exception. Because of the recognized protection from endometrial hyperplasia and neoplasia with cyclic progestogens, this hormone was added to the therapy of more patients each year as the study progressed. The progestogen challenge test[12] was administered to women with intact uteri, including both those receiving estrogen replacement therapy and asymptomatic women presenting for annual evaluation. The progestogen administration was continued cyclicly each month as long as withdrawal bleeding resulted. Patients who had a previous hysterectomy were usually not treated with progestogens. Otherwise, treatment was based on the patient's symptoms. If the primary symptom was hot flushes, then oral estrogens were administered. Estrogen vaginal cream was prescribed to patients with atrophic vaginitis, and androgens were given to women who had contraindications for estrogen therapy.

Statistical analysis of the data was performed by the Systems and Computer Services, Medical College of Georgia, using the test for significance of differences between two proportions and the analysis of variance followed by Tukey's honestly significant difference procedure. Relative risks were estimated by the method of Mantel[18] and Haenszel. Confidence intervals were estimated using Miettinen's test-based method.[19]

Results

During the seven years of prospective study from 1975 to 1981, 53 postmenopausal women from the patient population at Wilford Hall USAF Medical Center were given a diagnosis of breast cancer. The age of these patients, in five-year intervals, is given in Table 1, along with the observed and expected incidence, according to the Third National Cancer Survey (1975) and the National Cancer Institute (NCI) Surveillance, Epidemiology, End Result (SEER) data (1980).[1,2] The Third National Cancer Survey was conducted before the onset of the present survey and the NCI SEER data were calculated toward the end of the study. The age of the patients with breast cancer ranged from 31 to 92 years, with a mean age of 56.9 ± 1.13 years. All results are expressed as mean ± standard error of the mean (SEM). The 31-year-old patient and three of the four patients in their 40s had a surgical menopause secondary to bilateral oophorectomy, from two to ten years before the breast cancer was diagnosed. At the time of the diagnosis of mammary malignancy, 35 patients were currently using hormones (66.0%), and 18 had not received any type of female sex steroids (34.0%). The mean age ± SEM for each hormone therapy group, as compared with that of the untreated women, is given in Table 2. Although there were no differences pairwise, there was a statistically significant main effect, with the untreated women (61.3 ± 2.06 years) having a higher age than the other four groups combined ($P \leq .02$).

Table 1. Age of Patient Population With Observed and Expected Incidence of Breast Cancer

Age	Patient-years of observation	Patients with breast cancer	Observed incidence per 100,000 women	Expected incidence per 100,000 women
<30	72	0		1.8–8.3
30–34	70	1	1428.6	23.0–26.7
35–39	456	0		53.3–57.3
40–44	616	3	487.0	102.8–106.1
45–49	2598	1	38.5	156.0–173.9
50–54	8812	11	124.8	168.4–196.2
55–59	13,583	16	117.8	188.3–229.2
60–64	7239	17	234.8	221.5–251.4
65–69	2335	3	128.5	227.8–283.3
70–74	875	0		254.0–302.5
75–79	467	0		290.7–337.7
80–84	99	0		297.1–349.7
85+	14	1	7142.9	302.8–376.0
Total	37,236	53	142.3	188.3–229.2

Of the patients with carcinoma of the breast, 44 were parous (83.0%), six were nulliparous (11.3%), and three had conceived but their only pregnancies terminated in abortion (5.7%). Of the 167 pregnancies for the entire group, 33 (19.8%) ended in abortion, and 44 of the 47 patients who had conceived had one or more abortions (93.6%). Mean parity for the entire group was 2.4 ± 0.24 (SEM) and there were no differences in the mean parity for each of the therapy groups when compared to the untreated women (Table 3). Age at birth of the first term child ranged from 19 to 29 years for the 44 parous women, with a mean age at first term birth of 23.9 ± 0.37 years. Sixteen of the parous women (36.4%) breast-fed one or more of their children and although the number of untreated women who nursed (20%) tended to be lower than in any of the hormone therapy groups, none of these differences were significant. There were 17 patients (32.1%) who gave a positive family history of breast cancer (mother, aunt, grandmother) without any significant differences between the various groups. Weight ranged from 46.7 to 109.8 kg, with a mean weight of 66.1 ± 1.87 kg. Although there were no differences pairwise, the mean weight of the untreated women (73.9 ± 4.34 kg) was higher with a significant main effect than that of the other four groups combined ($P \leq .04$). Systolic blood pressure ranged from 94 to 184 mmHg, with a mean of 130.4 ± 2.48, and no significant differences were observed between any of the groups. Diastolic blood pressure ranged from 50 to 108, with a mean of 80.2 ± 1.45. The mean diastolic blood pressure of the estrogen users (75.1 ± 2.12) was significantly lower than that of the untreated women (85.4 ± 2.19), with $P \leq .03$, but no other differences were observed. There were six of the 53 women that were hypertensive (11.3%), and five of these were receiving antihypertensive medication when their breast cancer was diagnosed. There was one patient with hypertension in each of the following hormone therapy groups: estrogen–progestogen users, estrogen users, and estrogen vaginal cream users. Three of the 18 untreated women were being treated with antihypertensive medication.

During the seven years of prospective study from 1975 through 1981, 53 breast cancers were diagnosed in the patients registered in the hormone use survey (Table 4). There were 5563 patients registered for a total of 37,236 patient-years of observation, so the overall incidence of breast cancer was 142.3:100,000 women per year. The lowest incidence of mammary malignancy was observed in the estrogen–progestogen users, with eight patients diagnosed with breast cancer during 11,895 patient-years of observation, for an annual incidence of 67.3:100,000 women. During 15,606 patient-years of observation, there were 22 breast cancers in the estrogen users, for an incidence of

Table 2. Mean Age of Patients With Breast Cancer

Therapy group	No. of patients	Age range	Mean age* (years)
Estrogen-progestogen users	8	52–64	55.5 ± 1.32
Estrogen users	22	40–66	54.5 ± 1.41
Estrogen vaginal cream users	3	56–61	59.0 ± 1.52
Progestogen or androgen users	2	31–60	45.5 ± 14.50
Untreated women	18	49–92	61.3 ± 2.16†
Total patients	53	31–92	56.9 ± 1.14

* Mean age ± SEM.
† $P \leq .02$.

Table 3. Other Factors That May Predispose Toward or Protect From Breast Cancer

Factors	E + P users (N = 8)	E users (N = 22)	EVC users (N = 3)	P or A users (N = 2)	Untreated women (N = 18)	Total patients (N = 53)
Mean parity	2.4 ± 0.46*	2.0 ± 0.32	5.7 ± 1.76	1.0 ± 1.00	2.5 ± 0.38	2.4 ± 0.24
Age range at birth of first term child	21–24	20–26	22–23	24	19–29	19–29
Mean age at birth of first term child	22.1 ± 0.59	23.9 ± 0.54	22.3 ± 0.33	24	25.0 ± 0.68	23.9 ± 0.37
Breast fed	2/7 (28.6%)	9/18 (50%)	1/3 (33.3%)	1/1 (100%)	3/15 (20%)	16/44 (36.4%)
Positive family history for breast cancer	3 (37.5%)	7 (31.8%)	1 (33.3%)	0 (–)	6 (33.3%)	17 (32.1%)
Weight range (kg)	47.6–68	46.7–95.2	58.9–70.3	58–68.9	47.1–109.7	46.7–109.7
Mean weight (kg)	59.1 ± 2.05	62.5 ± 1.94	65.7 ± 3.47	63.5 ± 5.44	73.9 ± 4.34†	66.1 ± 1.87
Range of systolic BP	98–158	94–184	100–180	115–140	108–178	94–184
Mean systolic BP	129.3 ± 5.77	128.4 ± 3.81	136.7 ± 23.33	127.5 ± 12.50	132.7 ± 3.80	130.4 ± 2.48
Range of diastolic BP	76–90	50–96	60–100	70–86	68–108	50–108
Mean diastolic BP	82.7 ± 1.96	75.1 ± 2.12†	80.0 ± 11.55	78.0 ± 8.00	85.4 ± 2.19	80.2 ± 1.45

E = estrogen; P = progesterone; EVC = estrogen vaginal cream; A = androgen; BP = blood pressure.
* Mean ± SEM.
† $P \leq .05$.

141.0:100,000. With 18 breast cancers during 5258 patient-years of observation, the incidence in the untreated women was 342.3:100,000. Statistical analysis of these data are given in Table 5, also comparing the present incidence rates with those expected according to the National Cancer Institute SEER (1980) data.[3] The NCI SEER data were reported toward the end of the present study and represents cancer incidence in the United States from 1973 to 1977.

The mean ages (± standard deviation) for each of the patient groups are as follows: estrogen–progestogen users = 55.2 ± 5.12 years; estrogen users = 57.1 ± 6.89 years; estrogen vaginal cream users = 59.4 ± 7.66 years; progestogen or androgen users = 53.4 ± 5.62 years; untreated women = 58.8 ± 8.16 years; and total population = 56.8 ± 6.75 years. The expected incidence of breast cancer in this age group, according to the Third National Cancer Survey, is 188.3:100; for ages 55 to 59, according to the NCI SEER data, it is 229.2:100,000. The incidence of breast cancer in the estrogen–progestogen users (67.3:100,000) was statistically significantly lower than the untreated women (342.3:100,000) with $P \leq .01$. The difference between the estrogen–progestogen users (67.3:100,000) and the estrogen users (141.0:100,000) was not significant but does indicate a trend ($P \leq .08$). The incidence of breast carcinoma in the estrogen users (141.0:100,000) was significantly lower than that of the present untreated group (342.3:100,000) with $P \leq .01$. The incidence of breast cancer in the estrogen vaginal cream users (95.8:100,000) was significantly lower ($P \leq .05$) when compared with the untreated group (342.3:100,000). When stratified for age and the observed incidence was compared to the expected incidence according to the NCI SEER data, the only significantly lower incidence of breast cancer was observed in the estrogen-progestogen users, with a relative risk of 0.3 (95% confidence interval, 0.1 to 0.8). Although the incidence in the estrogen users was not significantly lower from that expected according to the NCI SEER data (relative risk = 0.7, 0.5 to 1.1), there was a trend in that direction. The incidence of breast malignancy was significantly higher in the untreated group when compared with the NCI SEER data (relative risk = 1.4, 1.1 to 1.9). The mean age (61.3 ± 2.16 years) and the mean weight (73.4 ± 4.3 kg) of the untreated women was higher than the four therapy groups combined. This would account for some of their higher incidence of breast cancer because the expected incidence for age 60 to 64 is 251.4:100,000. However, taking into account these variables for age and weight, the statistical comparisons between the various groups remain unchanged and are still significant.

Table 4. Incidence of Breast Cancer at Wilford Hall USAF Medical Center: 1975 to 1981

Therapy group	Patient-years of observation	Patients with cancer	Incidence (per 100,000)
Estrogen–progestogen users	11,895	8	67.3
Estrogen users	15,606	22	141.0
Estrogen vaginal cream users	3130	3	95.8
Progestogen or androgen users	1347	2	148.5
Untreated women	5258	18	342.3
Total	37,236	53	142.3

Table 5. Statistical Analysis of Breast Cancer Incidence Data

Therapy group	Incidence (per 100,000)	E + P users	E users	EVC users	P or A users	Untreated women
Estrogen–progestogen users	67.3	—				
Estrogen users	141.0	$P \leq .08$	—			
Estrogen vaginal cream users	95.8	NS	NS	—		
Progestogen or androgen users	148.5	NS	NS	NS	—	
Untreated women	342.3	$P \leq .01$	$P \leq .01$	$P \leq .05$	NS	—
Total patients	142.3	$P \leq .08$	NS	NS	NS	$P \leq .01$
NCI SEER data (1980):		0.3	0.7	0.4	0.7	1.4
Relative risk (95% Confidence interval)		(0.1–0.8)	(0.5–1.1)	(0.2–1.6)	(0.3–1.5)	(1.1–1.9)

E = estrogen; P = progesterone; EVC = estrogen vaginal cream; A = androgen.

The data from the prospective study are shown graphically year by year in Figure 1. Although there was considerable variation each year, the incidence in the estrogen–progestogen users varied but little during the first four years, with a low of 80.6:100,000 in 1975 to a high of 169.5:100,000 in 1976. Seven of the breast cancers were diagnosed in the first four years of the study, with one additional carcinoma of the breast detected during the last three years (1980). The two mammary malignancies observed in progestogen users (P) occurred in 1978 and 1979. The incidence of breast cancer in the estrogen users remained relatively constant throughout the seven years with a low of 110.3:100,000 in 1979 and a high of 173.4:100,000 during 1981. Two of the three breast cancers found in the estrogen vaginal cream users (EVC) occurred in 1979 and the other in 1977. The incidence of mammary malignancy in the untreated group was also quite variable, from a low of 227.3:100,000 in 1975 to a high of 633.9:100,000 in 1979. Overall, the incidence of breast carcinoma increased slightly from 143.4:100,000 in 1975 to a high of 183.8:100,000 in 1978, followed by significant decreases to 104.2:100,000 in 1980 and 110.4:100,000 during 1981.

More detailed data on the eight estrogen–progestogen users diagnosed with breast cancer is presented in Table 6. In six of the eight patients, estrogens had been used for two to 13 years before the progestogen was added. Only one patient (case #38) had the estrogen and progestogen started at the same time, and the progestogen was given for only five days each month for five years before carcinoma was detected. In one other patient (case #18), Oracon, a sequential birth control pill containing only five days of progestogen

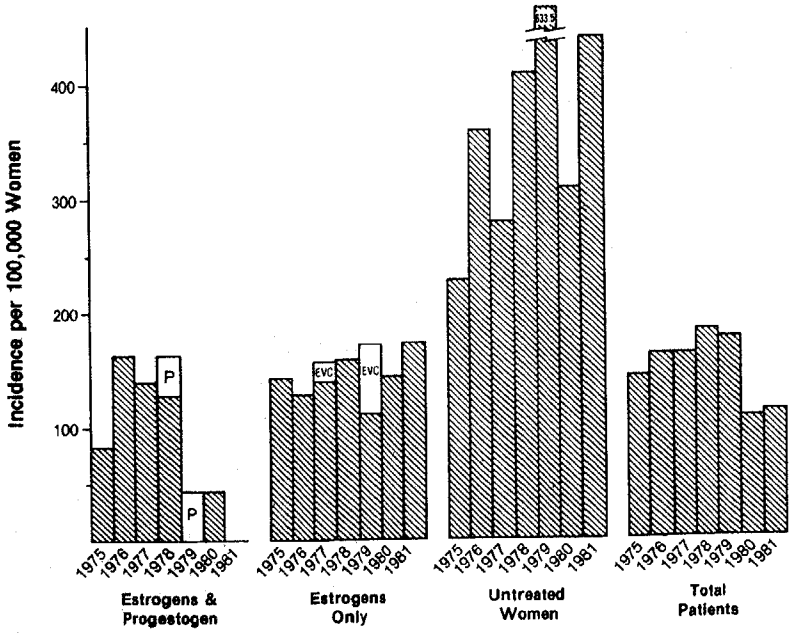

Figure 1. Incidence of breast cancer year by year from 1975 to 1981 in the hormone users compared with the untreated women. P = progestogen users; EVC = estrogen vaginal cream users.

Table 6. Breast Cancers in Estrogen-Progestogen Users

Case no.	Estrogen	Duration (yr)	Added progestogen* (cycle days)	Duration
18	Cyclic estinyl 0.02 mg		Norlutate 5 mg (19–25)	15 mo
38	Cyclic premarin 0.625 mg		Provera 10 mg (21–25)	5 yr
81	Cyclic premarin 0.625 mg	6	Norlutate 5 mg (19–25)	3 yr
103	Cyclic premarin 1.25 mg	7	Provera 10 mg (16–25)	6 mo
124	Cyclic premarin 0.625 mg	13	Norlutate 5 mg (16–25)	1 yr
145	Cyclic estinyl 0.02 mg	7	Provera 10 mg (16–25)	8 mo
152	Cyclic premarin 0.625 mg	2	Provera 10 mg (19–25)	1 yr
213	Cyclic premarin 1.25 mg	3	Norlutate 5 mg (19–25)	2 yr

* Mean Duration = 1.8 ± 0.50 yr.
† Oracon for eight yr.

each cycle, was used for eight years, and then the estrogen–progestogen combination was given for 15 months before breast cancer was diagnosed. Progestogens were prescribed for five days each month in one patient, seven days in three patients, and ten days in four of these women for six months to five years before mammary malignancy was detected. Only two of the eight women had used the progestogen for longer than two years, with a mean use duration of 1.8 ± 0.50 years.

The concept of adding progestogens to estrogen replacement therapy was introduced at Wilford Hall USAF Medical Center in 1971. Figure 2 compares the number of estrogen and estrogen–progestogen treated women to the incidence of breast cancer for the ten years from 1972 through 1981. With increased estrogen use from approximately 1320 patients in 1972 to 3940 estrogen-treated women in 1975, there was no increase in the incidence of mammary malignancy. The apparent decline in the incidence of breast cancer from 189.4:100,000 in 1972 to 143.4:100,000 during 1975 was not statistically significant. However, with ever increasing progestogen usage from approximately 9.1% of the estrogen users in 1972 to 51.1% of the estrogen users during 1981, a significant decrease in the incidence of breast cancer occurred in the ninth and tenth years of study, with an incidence of 104.2:100,000 in 1980 and 110.4:100,000 during 1981.

Discussion

It required seven years of prospective study and ten years of ever increasing progestogen use to indicate the protective effect of added progestogen to estrogen replacement therapy upon the breast, although earlier reports indicated a trend in this direction.[13,14] Apparently, it takes long-term progestogen use to reduce the risk of breast cancer in postmenopausal women. The reduction in the risk of endometrial cancer from added progestogen was confirmed in the first few years of the present study and also has been shown in several other studies.[12–17] Progestogens physically shed the endometrium each month, leaving behind fewer cells and glands to continue proliferation that may eventually lead to hyperplasia and neoplasia after several years. The increased risk of endometrial cancer from unopposed estrogen therapy is nullified within two to three years after discontinuing estrogen therapy.[11]

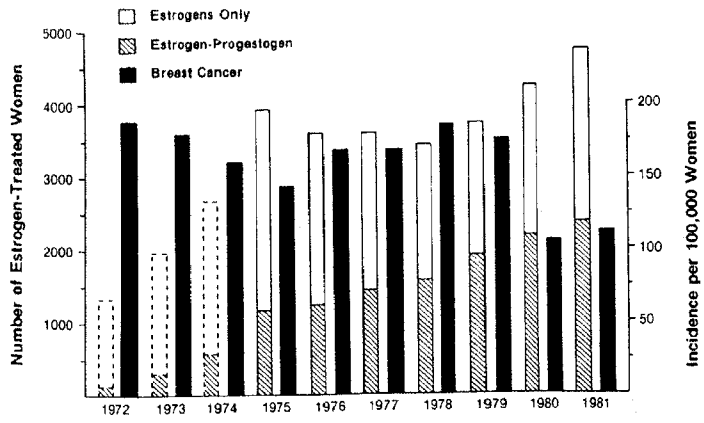

Figure 2. Comparison of the number of estrogen and estrogen–progestogen treated women and the incidence of breast cancer from 1972 to 1981. Dotted lines = estimated data from computerized pharmacy records; solid lines = data from prospective study.

Additional actions of both natural progesterone and synthetic progestogens are important in addition to the physical shedding of the endometrium. Progestogens decrease estrogen receptors in endometrial cells and induce estradiol dehydrogenase activity, which is the mechanism where the cells metabolize estrogens.[17] Because breast cells are not cyclicly shed by progesterone, the probable protective mechanism of progestogens is most likely at the intracellular level through changes in receptors and enzymatic activity. The presence of both estrogen and progesterone receptors in breast cancer tissue is related to the longer disease-free interval, decreased mortality, and more predictive of a favorable response to endocrine manipulation.[4]

It may be that progestogens alone, without adequate endogenous estrogens, are not as protective from carcinoma of the breast. Estrogens induce progesterone receptors so adequate estrogen may have to be present to induce progesterone receptors before progestogens can exert their protective effect. Although lower, there was no significant difference in the incidence of breast cancer in the estrogen–progestogen users (67.3:100,000) as compared with the progestogen users (148.5:100,000). However, two breast cancers were observed in the progestogen users whereas no endometrial cancers have occurred to date. In this respect, carcinoma of the breast may differ from adenocarcinoma of the endometrium in that both progestogens alone and added progestogen to estrogen therapy seem to protect from endometrial cancer while it takes a combination of estrogen–progestogen therapy to reduce the risk of breast cancer.

If the ever-increasing incidence of breast cancer by age is closely examined, the role of female sex steroids becomes somewhat clarified.[1,2] The greatest increase in breast cancer is between the late 30s and early 50s. What is happening at this time in a woman's life is declining production of estrogens from the ovaries as menopause is approached. Perhaps more important is the fact that more women become anovulatory in the premenopausal years, resulting in an abrupt cessation of the cyclic progesterone levels that had been present throughout the reproductive years. The incidence of breast cancer continues to increase throughout the postmenopausal years when estrogen levels are lower but not absent. However, few postmenopausal women, if any, produce progesterone. If unopposed estrogens were the cause of breast cancer, the incidence of this malignancy would peak in the 50s and 60s and decline thereafter, as does the incidence of endometrial cancer. Whatever the role of female sex steroids as cofactors or predisposing factors for mammary malignancy, progesterone deficiency seems to be more important than unopposed estrogen. The estrogen window hypothesis states that unopposed estrogens, caused by progesterone deficiency or luteal dysfunction, may provide a state favorable to the induction of breast cancer by carcinogens in the susceptible mammary gland.[20]

There is other evidence that progesterone deficiency may increase the incidence of breast cancer. In a long-term follow-up of a group of infertility patients, those with progesterone deficiency had 5.4 times the risk of premenopausal breast cancer compared with women in the nonhormone group (those whose infertility was caused by other factors).[21] Women in the progesterone deficiency group also experienced a tenfold increase in death from all malignant neoplasms compared with the nonhormone group. However, the incidence of postmenopausal breast cancer did not differ significantly between the two groups. However, another study of long-term progesterone deficiency did find an increased risk of postmenopausal breast cancer.[22] Chronic anovulation increased the risk of endometrial cancer fivefold, and the relative risk of breast cancer after the age of 55 years was 3.6. In the present 53 patients with carcinoma of the breast, nulliparity was perhaps a little higher than expected (17.0%), and the abortion rate also seemed high (19.8%). More important, 44 of 47 patients who had conceived had one or more abortions (93.7%). This could be indicative of long-term luteal dysfunction, at least in some of the patients.

Some of the potentially predisposing and protecting factors for breast cancer are related to progesterone deficiency while others are not. Protecting factors such as nulliparity and an early term pregnancy relate to periodic high progesterone production and ovulation with normal cyclic progesterone levels.[4,23,24] Nulliparity, infertility, and chronic anovulation, all progesterone deficiency states, not only predispose to endometrial cancer but also to breast cancer. Obesity is a predisposing factor for breast cancer and may also lead to anovulation. The risk factors for endometrial and breast cancer are similar, and in fact, there appears to be some association between these two cancers. Women with endometrial malignancy are more prone to develop cancer of the breast, ovaries, and large intestine. Patients with breast cancer may have a second cancer of another organ, including the uterus, ovaries, and colon. Certainly, there are other risk factors for breast cancer that are probably not related to progesterone deficiency. These include a strong family history, early menarche, and late menopause. Protecting factors not related to progesterone deficiency include breast feeding, late menarche, early menopause, and bilateral oophorectomy before age 40, which would diminish estrogen levels but deplete progesterone pro-

duction. Therefore, breast cancer must be a multifactorial disorder in which genetic traits, endocrine relationships, oncogenic factors such as viruses, and environmental factors such as chemical carcinogens all have a role.

In the ten-year double-blind study of Nachtigall et al,[15] four breast cancers were detected in the 84 placebo users and none in the 84 estrogen–progestogen users, which was statistically significant ($P \leq .05$). Several studies indicate that oral contraceptives reduce the risk of benign breast disease and there has been no evidence that birth control pills increase the risk of breast cancer.[25–30] Some studies have not found an increased risk of breast cancer in oral contraceptive users, while others observed lower rates of malignancy in those taking birth control pills. Long-term studies of large numbers of women have failed to incriminate estrogen replacement therapy as a risk factor for breast malignancy. Of the six groups that have studied both endometrial and breast cancer among estrogen users, a modest association was noted between estrogen therapy and endometrial cancer; however, in every instance the association between estrogens and breast cancer was considerably less.[5–7,13,15,16]

The present study found a decreased incidence of breast cancer in the patients that used estrogens only. Although the risk was significantly lower than in the untreated group, there was no difference when compared with the NCI SEER data; however, because the relative risk was 0.7, this indicated a trend in that direction. Hoover et al[5] observed an insignificantly increased risk of breast cancer (relative risk = 1.3) from postmenopausal estrogen use. In a later study from the same patient population, a decreased risk of breast cancer was found in estrogen users by Bland et al.[31] They followed 405 postmenopausal women (mean age 59.7 years) for three to more than 28 years with serial mammography, using xeromammography in the later years of the study. The 206 estrogen-treated women had received therapy for a minimum of 18 months (mean 6.5 years) and had a lower incidence of breast cancer than the untreated women. They concluded that long-term estrogen replacement does not significantly alter mammographic parenchymal patterns and that estrogen use does not increase the risk of breast cancer. Hammond et al[16] had four cases of breast cancer among 301 estrogen-treated women followed for five or more years, and four cases in the 309 untreated women.

Only two studies have observed any significantly increased risk of breast cancer from estrogen therapy. In neither was the risk increased in the total study population, but rather in subgroups of estrogen users. In the first by Ross et al,[6] a slightly increased risk was reported in a small subgroup of estrogen users with intact ovaries who had received a total dose of greater than 1500 mg (relative risk = 2.5; $P \leq .02$). They observed a lower relative risk of breast cancer in four other subgroups of estrogen users: those with previous oophorectomy, and those who had ever undergone estrogen treatment, relative risk = 0.8; prior oophorectomy with total milligram dose > 1500, relative risk = 0.9; prior oophorectomy with total milligram dose > 1500, relative risk = 0.7; and intact ovaries with total milligram dose < 1500, relative risk = 0.9. In the other study by Jick et al,[7] no association was observed between current estrogen use and carcinoma of the breast in women with previous hysterectomy (relative risk = 1.1). Only slightly over 50% of the women also had oophorectomy, and the rate of breast cancer in those with and without oophorectomy was similar. Although oophorectomy may lower the risk for breast cancer, it is difficult to understand why hysterectomy with conservation of the ovaries would also lower the risk. In women with a natural menopause and intact uterus, a positive association was found between current estrogen use and breast cancer (relative risk = 3.4). This association varied by age, with a relative risk of 10.2 in women aged 45 to 54 years, compared with a relative risk of 1.9 in those aged 55 to 64 years. The work of both the Ross and Jick groups can be criticized because they limited the study population to age 75 and age 65, respectively, yet the incidence of breast cancer continues to increase with each five-year increment in age. Because more women are treated with estrogens in the early menopausal years than after age 60, this alleged increased risk of breast cancer probably reflects greater estrogen use in this age group and may not be a true association at all.

In conclusion, estrogen replacement therapy does not increase the risk of breast cancer and may possibly afford some protection. Added progestogens to estrogen therapy significantly reduce the risk of mammary malignancy, so should also be given for ten days each month to patients who have had a hysterectomy. Unlike endometrial cancer, it may be that progestogens only do not help to prevent cancer, so consideration should be given for combinations of estrogen-progestogen replacement therapy when indicated for postmenopausal hormone therapy.

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