Estrogen replacement therapy in patients with early breast cancer

Puthugramam K. Natrajan, MD, and R. Don Gambrell, Jr, MD

Augusta, Ga

OBJECTIVE: Most physicians believe that estrogen replacement therapy is contraindicated once a patient is diagnosed with breast cancer. Recently, several studies have shown that estrogen replacement therapy may be safely used in patients with early breast cancer that has been treated successfully. These women can have severe menopausal symptoms and are at risk for osteoporosis. We reviewed the current status of women in our practice with breast cancer who received estrogen replacement therapy, who did not receive hormone replacement therapy, and who did not receive estrogenic hormone replacement therapy.

STUDY DESIGN: The study group consisted of 123 women (mean age, 65.4 ± 8.85 years) who were diagnosed with breast cancer in our practice, including 69 patients who received estrogen replacement therapy for ≤32 years after diagnosis. The comparative groups were 22 women who used nonestrogenic hormones for ≤18 years and 32 women who used no hormones for ≤12 years. The group who did not receive estrogenic hormone replacement therapy received androgens with or without progestogens (such as megestrol acetate). Of the 63 living hormone users, 56 women are still being treated in our clinic, as are 15 of the 22 subjects who receive nonestrogenic hormone replacement therapy. Follow-up was done through the tumor registry at University Hospital; those patients whose tumor records were not current were contacted by telephone.

RESULTS: There were 18 deaths in the 123 patients: 6 patients who received estrogen replacement therapy (8.69%), 2 patients who received nonestrogenic hormone replacement therapy (9.09%), and 10 patients who received no hormone replacement therapy (31.25%). Of the 18 deaths, 9 deaths were from breast cancer (mortality rate, 7.3%); 3 deaths were from lung cancer; 1 death was from endometrial cancer; 1 death was from myocardial infarction; 1 death was from renal failure; and 3 deaths were from cerebrovascular accidents. The 9 deaths from breast cancer included one patient who received nonestrogenic hormone replacement therapy (mortality rate, 4.5%), 6 patients who received no hormone replacement therapy (mortality rate, 11.3%), and 2 patients who received estrogen replacement therapy (mortality rate, 4.28%). The 9 non–breast cancer deaths included 4 patients who received estrogen replacement therapy (endometrial cancer [1 death], lung cancer [1 death], cerebrovascular accident [1 death], and renal failure [1 death]), 1 patient who did not receive estrogenic hormone replacement therapy group (myocardial infarction), and 4 patients who used no hormones (lung cancer, 2 deaths; stroke, 2 deaths). Carcinoma developed in one patient in the estrogen replacement therapy group in the contralateral breast after 4 years of hormone replacement therapy; she is living and well 2.5 years later with no evidence of disease. Metastatic breast cancer developed in one patient after 8 years of hormone replacement therapy; she is living with disease.

CONCLUSION: Estrogen replacement therapy apparently does not increase either the risk of recurrence or of death in patients with early breast cancer. These patients may be offered estrogen replacement therapy after a full explanation of the benefits, risks, and controversies. (Am J Obstet Gynecol 2002;187:289-95.)

Key words: Breast cancer, estrogen replacement, progestogens, nonestrogenic hormone replacement

Breast cancer is being diagnosed in early stages because of the increasing use of mammograms (≤60% of women >50 years old) and greater public awareness of the disease. It is the most common malignancy in the United Stated, comprising 31% of all female cancers, and 15% of all cancer deaths, second only to lung cancer.[1] Mortality rates from breast cancer has been on the decline over the past few years, down from 46,000 deaths in 1995 to 40,200 in 2001 and 39,600 in 2002. The frequency of breast cancer increases throughout the life span of women. Most physicians assume that estrogens promote carcinoma of the breast, hasten recurrence, and increase the risk for metastasis. However, there is no direct evidence to indicate that female hormones worsen the prognosis of this malignancy. In a recent report, Bush et al[2] came to the conclusion that estrogen replacement ther-

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Reprint requests: P. K. Natrajan, MD, Reproductive Endocrinologists, 903 15th St, Augusta, GA 30910.

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Table I. Estrogen therapies for patients with breast cancer

Therapy	*No. of patients*	*No. of patients who used other hormone therapies*	*Megestrol acetate Tamoxifen*	*Medroxyprogesterone acetate*	*Norethindrone acetate*
Testosterone 150 mg, estradiol 50 mg	14	1	3	3	6
Testosterone 150 mg, estradiol 25 mg	14	3	1	5	5
Testosterone 75 mg, estradiol 50 mg	12	1	2	3	5
Testosterone 75 mg, estradiol 25 mg	6	2	2	1	2
Testosterone 225 mg, estradiol 25 mg	2			1	1
Testosterone 75 mg, oral estrogen	4		3		1
Testosterone 150 mg, oral estrogen	2		1		1
Estradiol 50 mg	2			1	1
Estradiol 75 mg, testosterone 75 mg	1				1
Esterified estrogen-methyl testosterone	5	1	2	2	1
Oral estrogen	3		1		2
Estrogen vaginal cream	2	1	1		
Testosterone 75 mg, transdermal estradiol	1		1		
Transdermal estradiol	1			1	
Total	69	9	17	17	26

Table II. Cause of death in women who received estrogen therapy

Subject No.	*Age (y)*	*Year of diagnosis*	*Year of death*	*Length of HRT before diagnosis (y)*	*Length of HRT before death (y)*	*Cause of death*
1	71	1989	2000	18	10	Endometrial cancer
2	73	1986	1994	6	4	Breast cancer
3	62	1995	1996	16	1	Breast cancer
4	79	1994	2000	10	5	Lung cancer
5	65	1980	2001	—	6	Stroke
6	71	1978	1999	7	18	Renal failure

Table III. Cause of death in women who received nonestrogenic hormone therapy

Subject No.	*Age (y)*	*Year of diagnosis of breast cancer*	*Year of death*	*Length of treatment before death (y)*	*Cause of death*
1	51	1992	1995	3	Myocardial infarction
2	54	1988	1991	1	Breast cancer

apy (ERT) and hormone replacement therapy (HRT) do not increase the risk, and estrogen users are less likely to die of breast cancer than nonusers. Women with breast cancer can have severe menopausal symptoms and are at risk for osteoporosis.

Premenopausal women in whom breast cancer develops continue to produce endogenous estrogens but are denied ERT when they reach menopause.[3] Early breast cancer is defined as stage I disease with ≤3 positive axillary lymph nodes. The 5-year survival rate for early breast cancer has increased from 72% in the 1940s to 97% today.[4] There have been several studies that have addressed the use of ERT and HRT after early breast cancer to treat menopausal symptoms and protect against osteoporosis.[5-18] In our earlier report, we had 75 patients with early breast cancer of whom 50 women had used ERT and HRT for many years; this group had a much lower mortality rate than the no treatment group.[17]

Material and methods

The study group consisted of 123 patients who ranged in age from 39 to 91 years (mean age, 65.4 ± 11.58 years) and were diagnosed with early breast cancer. All of the patients are included, except for 18 women whose diagnosis of breast cancer was made in the 1970s and 1980s and who have been lost to follow-up. Three patients who had used estrogen for 21.5 years, 24 years, and 32 years were already receiving estrogen after previous carcinoma of the breast when we joined our current practice. There were 69 patients who received ERT/HRT for 1 to 32 years, 22 patients who received nonestrogenic hormonal therapy (including progestogens such as megestrol acetate, testosterone, and/or tamoxifen) for 1 to 18 years, and 32 patients who presumably were convinced by their surgeon or oncologist that they should never use estrogen.

The mean age in the ERT group was 65.2 ± 11.45 years, in the nonestrogenic hormone group it was 64.1 ± 12.08

Table IV. Alternative hormone therapies to estrogen

Therapy	*Patients (No.)*	*Range (y)*	*Mean duration ± SD (y)*
Testosterone pellets 150 mg, megestrol acetate	7	1.5-11	3.9 ± 3.32
Testosterone pellets 150 mg	4	2-18	7.5 ± 7.19
Testosterone pellets 75 mg, megestrol acetate	1	1	
Testosterone pellets 75 mg, tamoxifen	2	2-5	3.5 ± 2.12
Tamoxifen	6	1-6	3.2 ± 1.94
Megestrol acetate	1	11	
Tamoxifen, raloxifene	1	5	
Total	22	1-18	5.6 ± 4.80

Table V. Cause of death in women who did not receive HRT

Subject No.	*Age (y)*	*Length of HRT before diagnosis (y)*	*Year of diagnosis*	*Year of death*	*Cause of death*
1	57	21	1990	1999	Breast cancer
2	65	5	1988	1999	Breast cancer
3	91	32	1991	2000	Stroke
4	82	11	1992	1993	Lung cancer
5	60	11	1990	1993	Breast cancer
6	80	34	2001	2001	Lung cancer
7	75	31	1998	2000	Breast cancer
8	85	26	1990	1993	Stroke
9	74	41	1990	1991	Breast cancer
10	67	18	1991	2000	Breast cancer

years, and in the nonuser group it was 66.8 ± 11.23 years. The mean age among the 6 patients in the ERT group who died was 70.2 ± 6.01 years, of the 2 patients in the nonestrogenic group who died it was 52.5 years, and of the 4 patients in the nonusers group who died it was 73.6 ± 11.18 years. Progestogens such as megestrol acetate were used in 55 of the 63 patients (87.3%) who used estrogens. Receptor status was known in 23 patients, 16 patients with positive estrogen receptors and 7 patients who also had positive progesterone receptors. All of the patients had stage I disease at the start of HRT, with one exception; 8 women each had 1 positive lymph node, and 4 women each had 3 positive axillary lymph nodes. In the ERT group, there were 3 patients each with 1 positive lymph node and 2 patients each with 3 positive lymph nodes. In the nonestrogen hormone group, 3 patients had positive estrogen receptors; 2 patients each had 1 positive lymph node; and 2 patients each had 3 positive nodes. In the nonuser group, there are 2 patients who were living and who each had 1 positive lymph node, 1 patient had positive estrogen receptors, and 1 patient had positive progesterone receptors. Of the patients who died, 1 patient had 1 positive lymph node, and 2 patients had positive estrogen receptors. Of the 63 patients who received HRT and are living, 56 patients are still being seen in our clinic; of the 22 patients who did not receive ERT and are living, 15 patients are still attending our clinic. None of the 32 patients who did not use HRT returned, and 10 patients have died. Follow-up of all the patients who did not return to our clinic was done by personal telephone calls or through the tumor registry at University Hospital. Patients were counseled in detail before the onset of therapy, and informed consent was obtained from all patients.

Results

Mean age at diagnosis of breast cancer was 57.0 ± 12.23 years, and the follow-up of those who received ERT after a diagnosis of breast cancer was from 1 to 32 years, with a mean duration of 6.4 ± 5.84 years. Of a total of 69 patients who received ERT after a diagnosis of breast cancer, there are 63 patients still living, with a mean age of 64.73 ± 11.76 years. The estrogen and other therapies used in these 69 women are listed in Table I. Cancer developed in the contralateral breast of 1 patient after 9 years of ERT; mastectomy was performed, and she is living and well 2.5 years later with no evidence of disease. Metastases have developed in 1 patient who is living and is being treated with aromatase inhibitors 2 years later. Six patients have died (mean age, 70.17 ± 6.01 years). They were treated with ERT for 12 months to 18 years. Two patients have died of breast cancer; 1 patient has died of endometrial cancer, 1 patient has died of renal failure, 1 patient has died of cancer of lung, and 1 patient has died of stroke (Table II).

In the group of 22 patients who used nonestrogenic HRT, 20 patients are still living (mean age, 64.09 ± 12.08

Table VI. Postmenopausal estrogen therapy in survivors of breast cancer

	No.		*Duration (mo)*	
Study	*Users*	*Nonusers*	*Mean*	*Range*
Stoll and Parbhoo, 1988[7]	50	—	≥24	—
DiSaia et al, 1993[8]	77	—	27	1-233
Wile et al, 1993[9]	25	—	32.5	24-82
Powles et al, 1993[10]	35	—	14.6	1-44
Eden et al, 1995[6]	90	180	18	4-144
DiSaia et al, 1996[11]	41	82	68.9	12-108
Dew et al, 1998[17]	167	1,305	19.2	4-264
Vassilopoulou-Sellini et al, 1999[15]	39	280	—	—
Ursic-Vrcaj and Bebar, 1999[18]	21	42	28	3-72
Natrajan et al, 1999[16]	50	26	5.5	6-384
DiSaia et al, 2000[12]	125	362	22	1-357
O'Meara et al, 2001[13]	174	696	44	

*Per 1000 woman-years.

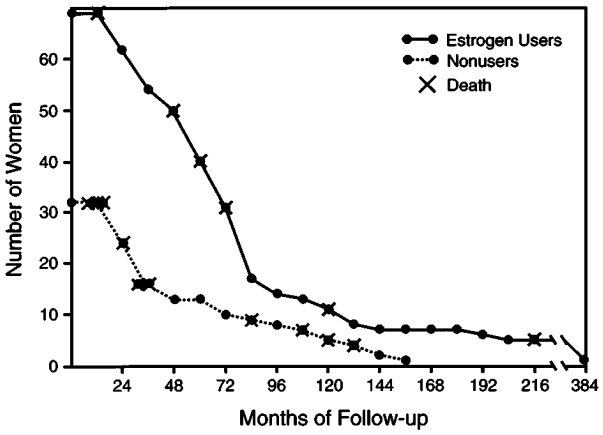

Figure. The number of patients with breast cancer who were treated with ERT compared with patients who were not treated with ERT, the length of follow-up, and when death occurred in each group.

years). Two patients have died, one patient from breast cancer and one patient from myocardial infarction (Table III). Of the 20 patients, 10 patients are still receiving testosterone, 8 patients are using tamoxifen, 1 patient is using megestrol acetate only, and 8 patients are using megestrol acetate with testosterone pellets (Table IV).

Of the nonuser group, 22 patients are still living (mean age, 63.7 ± 10.02 years), and 10 patients have died (mean age, 73.6 ± 11.18 years: breast cancer (6 patients), lung cancer (2 patients, and cerebrovascular accidents (2 patients; Table V). The Figure compares the 69 who received ERT after a diagnosis of breast cancer with the 32 nonusers, indicates the length of follow-up, and shows when the deaths occurred.

Comment

The association between ERT and breast cancer has been very controversial and has received much attention in the past few decades. There have been numerous epidemiologic studies and meta-analyses that have tried to unravel this association, but so far none have given us a definite answer. Bush et al[2] compared the unadjusted or age-adjusted risk estimates for breast cancer among patients who had ever received ERT compared with patients who had not received ERT from 45 previously published articles that assessed ERT and breast cancer risk and from 20 articles that assessed HRT and breast cancer risk. In addition, 11 studies were assessed for risk estimates for death from breast cancer and for breast cancer survival. They found little consistency in the studies that estimated the risk of breast cancer in patients who received HRT versus patients who had not, but there was a consistently lower risk of death from breast cancer in patients who received HRT than patients who had not received HRT. Most of the studies reported a relative risk at 0.9 to 1.1 for the development of breast cancer; none of these studies had a relative risk of >2.0. In the HRT group, there were 2 studies that showed a higher risk, 2 studies that found a protective effect, and 1 study that observed no increased risk in patients who received combined HRT therapy. The risk estimates for deaths from breast cancer in patients who received HRT was consistently <1.0 when compared with patients who had not received HRT. The authors came to the conclusion that the association between estrogen therapy and breast cancer is inconsistent (the risk hovers around 1.0) nor is there any increase in risk for patients who receive HRT. The data are consistent that patients who receive combined HRT are less likely to die of breast cancer than patients who do not receive HRT. The data also suggest that patients who receive ERT are less likely to die of breast cancer than patients who do not receive ERT.[19-21]

Breast cancer is frequently diagnosed in the early stages because of increased public awareness and the routine use of mammograms; most cases of breast cancer are

Recurrence (No.)		*Deaths (No.)*	
Users	*Nonusers*	*Users*	*Nonusers*
0	—	0	—
7	—	3	—
3 (12%)	—	1 (4.0%)	—
2 (5.7%)	—	—	—
7 (7.8%)	31 (17.2%)	0	11 (6.1%)
6 (14.6%)	7 (8.5%)	2 (4.8%)	6 (7.3%)
RR = 0.64	RR = 1.0	2 (1.2%)	167 (12.8%)
1 (2.6%)	14 (5.0%)	0	0
4 (19.0%)	5 (11.9%)	0	1 (2.4%)
3 (6%)	9 (34.6%)	3 (6%)	7 (26.9%)
—	—	15 (12%)	134 (37%)
17*	30*	5*	15*

treated successfully. Most of these women are denied ERT/HRT because of the concerns of recurrence although they have severe symptoms. The survival rates have increased to >97% in the last few decades, and many of these women have menopausal symptoms and are at a high risk for osteoporosis.[4] Although definitive prospective studies, which may take 10 to 20 years to complete, are currently being done to show that estrogens are safe in survivors of breast cancer, there are at least 12 studies to support its safety (Table VI). O'Meara et al[13] compiled data from 2755 women aged 35 to 74 years who were diagnosed with breast cancer to evaluate the impact of HRT in the 174 users after diagnosis on recurrence and mortality rates. The rate of breast cancer recurrence was 17 per 1000 woman-years in women who received HRT after diagnosis and 30 per 1000 woman-years in women who did not receive HRT (relative risk, 0.5; 95% CI, 0.3-0.85). Breast cancer mortality rates were 5 per 1000 woman-years in HRT users and 15 per 1000 woman-years in nonusers (relative risk, 0.34; 95% CI, 0.3-0.91). They concluded that HRT after breast cancer has no adverse impact on recurrences and does not increase mortality risk. In a cohort study of 125 hormone users who were matched to 362 control subjects who were observed for 1 to 375 months, there were 15 deaths in the HRT group (12%) compared to 134 deaths in the non-HRT group (37%).[12] Another study compared breast cancer events in users and nonusers who had been treated previously for localized breast cancer.[15] One new breast cancer occurred in the 39 ERT users (2.5%) compared with 14 new or recurrent breast cancers in the 280 nonusers (5%).

In our clinic, the use of ERT/HRT after a diagnosis of early breast cancer has changed over the years. In the 1980s estrogens were discontinued, and nonestrogenic hormones were recommended for 5 years. Androgens such as testosterone and progestogens were given for menopausal symptoms. After 5 years of nonestrogenic HRT, ERT was advised. During the 1990s, as more evidence accumulated that estrogens did not increase the risk, particularly in HRT users, HRT was resumed earlier.[22,23] Although recent studies have questioned the protection from breast cancer with added progestogen and even may have shown an elevated risk with HRT, it is still our practice to add progestogen to ERT, particularly megestrol acetate.[24,25]

Our present study has found similar results to other studies with ERT/HRT after breast cancer (Table VI). The mortality rates from breast cancer for the ERT users was 4.28% compared with 11.3% in the nonusers. The death rate from nonestrogen HRT was 4.5%, similar to the estrogen group. In our practice, patients in whom early breast cancer developed or those patients with previous breast cancer who are referred to us are offered HRT/ERT for treatment of menopause. The benefits and risks are discussed with them in a detailed fashion. Informed consent is obtained; the patients are offered ERT, usually with a progestogen, and the patients are encouraged to make the decision.

Women with early breast cancer who have menopausal symptoms and especially those who are at risk for osteoporosis should be offered ERT/HRT after a thorough discussion of all the benefits, risks, and controversies.

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Discussion

Dr Charles B. Hammond, Durham, NC. The authors present a retrospective, descriptive study that evaluates the impact of HRT for women with early breast cancer. The study group comprises 123 women with breast cancer. Outcomes for women who had received ERT (69 women), nonestrogenic HRT (22 women), or no hormone therapy (32 women) were reported. The authors conclude that ERT does not increase the risk of recurrence or death in patients with early breast cancer. The authors clearly have contributed to this important area through the years, and the present study is a further addition to that literature. The question is an important one because it is well documented that many women who have had breast cancer have acute symptoms and problems related to the menopausal transition. Current dogma suggests that these patients are not candidates for HRT.

Through 2000 there were at least 11 reports in the literature that addressed the concern of the administration of estrogen after a diagnosis of early breast cancer and as to whether estrogen had any negative impact on the risk of recurrence of that disease.[1-11] Most of the studies were retrospective, but at least 4 of the studies were prospective. None of the studies have been the gold standard randomized, placebo-controlled trial. To date, none of these reports have shown a recurrence risk after ERT to be any greater than in patients who did not receive ERT. The present study shows a similar result.

As one looks at retrospective and even prospective trials of the sort I have described, we have to realize that weaknesses may exist because of small numbers, potential selection bias, and nonrandomization.

Unfortunately, I have some concerns about this paper which reflect those potential concerns:

1. The title describes the study group as "patients with early breast cancer," yet there is no description of the actual stages of the patients who are included or what the authors consider to be early breast cancer.

2. The description of two of the most significant prognostic indicators for this disease (that is, nodal and estrogen receptor/progesterone receptor status) is incomplete and confusing. The authors must state the precise number of tumors for which receptor status was available, not just describe the number with positive status for estrogen and progesterone.

3. None of the 32 patients who did not receive HRT returned to the clinic for a follow-up visit. The authors should define the reasons for this and whether it limits the interpretation of data from this group.

4. No statistical manipulation of data is described in the "Material and methods," "Results," or "Comment" sections of the article. Without such analysis, including probability values, the authors will find it difficult to draw any conclusions from the descriptive comparisons of the 3 groups.

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Dr Natrajan (Closing). Patients with early breast cancer were those with stage I cancer with ≤3 positive axillary lymph nodes.

Receptor status was known in 23 patients: 16 patients with positive estrogen receptors and 7 patients with positive estrogen and progesterone receptors.

The 32 patients were those patients in whom breast cancer developed while they were being treated in our clinic over the years and after the diagnosis of the breast cancer chose not to continue the ERT. These patients were observed with personal phone calls or through the tumor registry at University Hospital in Augusta.

No statistical analysis was done because the control subjects were not matched to the estrogen users. Conclusions are valid because of the long duration of estrogen use after breast cancer and the length of follow-up of the nonuser group, with great differences in the mortality rates (4.28% vs 11.3%).