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Estrogen Replacement Therapy After Breast Cancer: A 12-Year Follow-Up

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Background: In the United States, estrogen replacement therapy (ERT) is discouraged in breast cancer survivors because of concerns that hormones may reactivate the disease. Because ERT can improve quality of life and decrease morbidity from osteoporosis and cardiovascular disease, however, this policy is increasingly being challenged.

Methods: From February to August 1995, 607 breast cancer survivors were interviewed concerning ERT usage. Sixty-four patients indicated they received some form of ERT after their breast cancer diagnosis. Medical records for these patients were analyzed for disease stage, surgical treatment, adjuvant treatment, estrogen and progesterone receptor status, date of initiation of ERT, type of ERT, recurrence, and final outcome. Patients receiving ERT were followed prospectively.

Results: Eight patients were excluded because they had used only vaginal cream ERT. The remaining 56 received ERT as conjugated estrogens, an estradiol patch, estropipate, or birth control pills. The median follow-up from diagnosis was 12.8 years (range, 4.7–38.9 years). The median time on ERT since diagnosis was 6.4 years (range, 1.0–20.9 years); 38% of the patients initiated ERT within 2 years of diagnosis. Estrogen receptors were positive in 28 (74%) of the 38 cases with available information. Pathological disease stage at time of diagnosis and treatment was 0 in 15 cases (27%), I in 27 (48%), and II in 14 (25%). Twenty-six patients (47%) received adjuvant chemotherapy or hormonal therapy. One local recurrence and one contralateral breast cancer occurred during the follow-up period (13.5 and 9.6 years, respectively), with no regional or distant recurrences, for a 15-year actuarial disease-free survival rate of 92.5%. There were no breast cancer deaths.

Conclusions: Use of ERT in a cohort of breast cancer survivors with tumors of generally good prognosis was not associated with increased breast cancer events compared with non-ERT users, even over a long follow-up period.

Key Words: Breast cancer—Recurrence—Estrogen replacement therapy—Prognosis.

Use of estrogen replacement therapy (ERT) by postmenopausal women has become widespread. Two centuries ago, less than 30% of women lived long enough to reach menopause, but today 90% of women reach the climacteric. In the United States, more than 30 million women have an average postmenopausal life expectancy of 28 years.[1] In addition to its beneficial effects on the vasomotor symptoms of the climacteric and on the urogenital epithelium, ERT has been associated with reductions in cardiovascular mortality and in the morbidity associated with osteoporosis. There is increasing evidence that ERT further protects against colorectal carcinoma, the clinical consequences of rheumatoid arthritis, and even deterioration of cognitive function.[2–8]

Because of concerns that ERT may reactivate the disease, ERT usually is not recommended for women who reach menopause after treatment of breast cancer. It is also not recommended in women who are postmenopausal and then develop breast cancer. This policy is being challenged with increasing frequency, because greater patient awareness, mammography screening, and

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the use of adjuvant therapy have resulted in earlier diagnosis of breast cancer and a greater probability of long-term survival. Because breast cancer is now being detected at an earlier stage and because adjuvant chemotherapy may cause ovarian failure in 53% to 89% of patients, an increasing number of women are postmenopausal at a younger age as a result of treatment of their breast cancer.[9] These women are exposed to estrogen deficiency more often and for a longer time than those in the general population. With an average age at diagnosis of 60 years, coupled with a 25-year expected survival, it is estimated that the number of breast cancer survivors in the United States is nearly 2.5 million women. The short-term effects of estrogen deficiency (e.g., vasomotor instability and urogenital atrophy) and long-term consequences (e.g., osteoporosis and cardiovascular disease) are important quality-of-life and health issues for breast cancer survivors.[10]

To define the prevalence of ERT usage in our patient population and determine whether there were any adverse risks, in 1995 we surveyed our patients and began a prospective follow-up of patients receiving ERT. This article describes the clinical outcomes of these patients with respect to the development of new or recurrent disease.

MATERIALS AND METHODS

Between February and August 1995, 607 breast cancer survivors were interviewed concerning ERT usage after the diagnosis and treatment of their breast cancer. All patients were treated and followed by a single surgeon at Baylor University Medical Center and The University of Texas Southwestern Medical Center at Dallas. After initial identification of breast cancer patients using ERT, their clinical outcome was prospectively observed for a minimum of 60 months. The observation period was from the date of identification of these patients in 1995 until their last follow-up visit in 2000.

Based on concerns that ERT may reactivate disease, all patients were informed during diagnosis and treatment that ERT usually is not recommended for women who reach menopause after successful treatment of breast cancer. However, prior studies have documented that up to 10% of breast cancer survivors use ERT for relief of menopausal symptoms.[11] Sixty-four patients who received some form of ERT after their diagnosis of breast cancer were identified in our series. All patients received ERT through their primary care physicians for quality-of-life issues or health concerns surrounding estrogen deficiency. Because of the controversy concerning the absorption or lack of absorption of vaginal creams, 8 patients who used only this form of ERT were excluded from the study.

Medical records for these patients were analyzed for stage of disease, surgical treatment, adjuvant treatment, estrogen receptor and progesterone receptor (ER/PR) status, date of initiation of ERT relative to date of diagnosis, duration of ERT usage, recurrence, and final outcome. All patients were under the care of an oncologist and received routine surveillance. During the observation period after treatment, patients had regular follow-up evaluations, with history and physical examinations every 3 to 6 months, annual mammograms and chest radiographs, and evaluation of liver chemistries at each visit.

RESULTS

Fifty-six (9%) of the 607 breast cancer survivors interviewed between February and August in 1995 received ERT. The preferred ERT regimen was conjugated estrogen (Table 1). Dosages were variable. At the time of breast cancer diagnosis, the median age of these women was 49 years (range, 29–76 years), and the median disease-free interval before initiation of ERT was 46.7 months (range, 0–448 months). Forty-nine patients initiated ERT after diagnosis. Twenty-one patients (38%) initiated ERT within 2 years of diagnosis. Six patients continued their ERT and one patient continued her birth control pills during diagnosis and treatment of their initial breast cancers. One patient initiated ERT 37 years after diagnosis of her breast cancer. The median follow-up from diagnosis was 12.8 years (range, 4.7–38.9 years), and the median number of years on ERT since breast cancer diagnosis was 6.4 years (range, 1.0–20.9 years) (Table 2).

All patients had surgery: 45% had breast conservation, 50% had modified radical mastectomy, and 5% had radical mastectomy. Twenty-six patients (46%) received adjuvant chemotherapy or hormonal therapy. Twenty patients (36%) had radiotherapy. All patients were disease-free after initial therapy.

Pathological disease stage is shown in Table 3. Among those with stage 0 disease, there were 10 cases of ductal

TABLE 1. *Type of estrogen replacement therapy after breast cancer diagnosis and treatment*

Hormone	No. patients
Conjugated estrogens	24
Conjugated estrogen and medroxyprogesterone acetate	20
Estradiol	10
Estropipate	1
Birth control pills	1

TABLE 2. *Characteristics of and follow-up times for 56 patients who received hormone replacement therapy after breast cancer diagnosis and treatment*

Variable	No. years	
	Median	Range
Patient age	49	29–76
DFI at entry (initiation of ERT)	3.9	0–37.3
Follow-up from initial diagnosis	12.8	4.7–38.9
Follow-up on ERT	6.4	1.0–20.9

DFI, disease-free interval; ERT, estrogen replacement therapy.

carcinoma in situ and five cases of lobular carcinoma in situ. Only seven patients (13%) had lymph nodes that were positive for metastatic disease. Estrogen receptors were positive in 28 (74%) of the 38 cases for which assays were available (Table 4). The predominant pathological histology was infiltrating ductal carcinoma, in 38 cases.

Events that occurred during the follow-up period are shown in Table 5. One patient who was stage IIA and ER+/PR+ developed a local recurrence 13.7 years after initial diagnosis of her breast cancer. She had been on ERT for 3.8 years at the time of local recurrence. She is now disease-free at 3 years after treatment of her local recurrence and not on ERT. A second patient who was stage 0 and ER+/PR+ developed a contralateral ductal carcinoma in situ (DCIS) 9.6 years after her initial diagnosis of DCIS. She was on ERT for 90 months. She is now disease-free at 1.4 years after treatment of her second primary carcinoma. There have been no regional or distant recurrences and no breast cancer deaths, for a 15-year actuarial disease-free survival of 92.5% (Fig. 1).

Of the eight patients who have used only vaginal cream ERT, median follow-up from diagnosis was 11.4 years, and median time on ERT since diagnosis was 4.0 years. There have been no contralateral breast cancers; no local, regional, or distant recurrences; and no cancer deaths in this group.

DISCUSSION

The potential benefits of ERT have become entangled in the controversy over the association of ERT with increased breast cancer risk.[12–16] Most physicians and patients, however, remain extremely cautious about the routine use of estrogens in women who have been treated for breast cancer. Appropriately designed prospective, randomized studies of ERT in this subgroup, such as the HABITS trial, are beginning or are already underway, but results will not be available for several years. Potential participants often are reluctant to join ERT studies, making recruitment for randomized trials difficult.[10,17–20] One article concerning potential participation in an ERT clinical study reported that 38% of respondents had no interest in such a study; 33% were afraid of potential risks; and 17% gave other reasons for declining, such as a physician or spouse who discouraged them.[20]

Despite the lack of information from randomized trials, there is growing pressure to obtain some information and develop recommendations regarding the role of ERT in breast cancer survivors. It is, therefore, important to obtain and consolidate currently available data regarding the outcomes of breast cancer survivors currently on ERT. Until data from randomized trials can be obtained, and while recognizing the limitations of retrospective studies, useful information can still be obtained from such studies to assist physicians and patients in making decisions concerning ERT usage.[11]

Our study shows that ERT in this cohort of breast cancer survivors with generally good-prognosis tumors was not associated with increased recurrences, even over a long follow-up period. With a median follow-up of 12.8 years and a median ERT usage of 6.4 years, there were no excess cancer events. Disease tended to be localized (71% were stage 0-I), yet a large number of these patients (74%) demonstrated estrogen receptor ac-

TABLE 3. *Stage of cancer at diagnosis for 56 patients who received hormone replacement therapy after breast cancer diagnosis and treatment*

AJCC stage	No. patients (%)
0	15 (27)
I	27 (48)
II	14 (25)

AJCC, American Joint Commission on Cancer.

TABLE 4. *Results of estrogen/progesterone assay for 38 patients who received hormone replacement therapy after breast cancer diagnosis and treatment*

Result	No. patients (%)
ER+/PR+	24 (63)
ER+/PR−	4 (11)
ER−/PR+	3 (8)
ER−/PR−	7 (18)

ER, estrogen receptor; PR, progesterone receptor.

TABLE 5. *Events among 56 patients who received hormone replacement therapy after breast cancer diagnosis and treatment*

Event	No. patients
Local recurrence	1
Contralateral breast cancer	1
Cardiac death	3

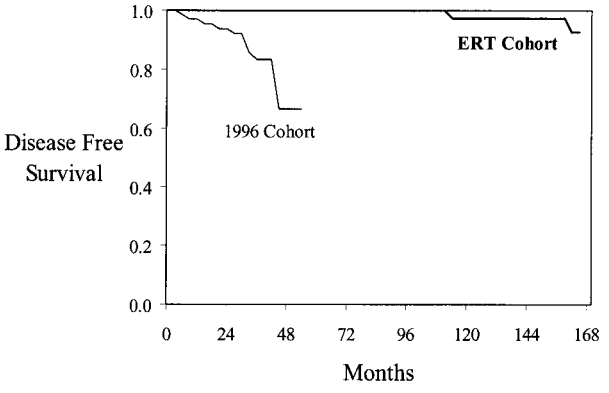

FIG. 1. Life table analysis of disease-free survival for 56 stage 0–II breast cancer patients who took HRT after a breast cancer diagnosis (ERT cohort) and 74 stage 0–II breast cancer patients from the same practice diagnosed in 1996 (1996 cohort).

tivity. Only two patients (4%) developed either recurrent or new disease. To date, our study provides the longest follow-up of breast cancer survivors on ERT with the longest duration of ERT usage.

Our results are consistent with those of other small retrospective and observational studies in women with breast cancer receiving ERT (Table 6).[11,21–31] These studies also show that ERT usage in 656 breast cancer survivors does not adversely affect breast cancer outcome. Furthermore, duration of ERT usage does not appear to affect outcome adversely, although it may be a determinant with further follow-up. On average, the patients tend to be younger, mostly with localized disease and with a low incidence of breast cancer events (2%–9%) during observation. In the study with the smallest number of patients,[21] a higher incidence of recurrence (19%) was reported. Only two studies reported death due to disease, with an incidence of 1.7% and 2%, respectively.

Twelve-year follow-up data of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 protocol provides the only comparable results for our ERT group. The estimate of overall survival at 12 years is 63%; disease-free survival is 50%; and local recurrence for the group treated by lumpectomy and breast irradiation is 10%.[32]

For comparison, disease-free survival was calculated for a cohort of 74 stage 0-II breast cancer patients from our practice who were diagnosed and treated in 1996. These women ranged in age from 36 to 82 years (mean, 61 years). There were 9 stage 0 (12%), 40 stage I (54%), and 25 stage II (34%) patients. After a median follow-up of 37 months, disease-free survival was 67% for the 1996 cohort as compared to 100% for the ERT cohort ($P = .029$, Fig. 1). Because half of the patients in our group started ERT nearly 4 years after diagnosis, our ERT patients are likely to be self-selected for good-prognosis tumors, because patients with poor-prognosis tumors would have died of breast cancer earlier, in the first few years after diagnosis. No appropriate comparison groups are available, therefore, and comparisons with NSABP or unselected patients from our practice could be misleading.

The results of retrospective analyses do not appear to reveal any unexpected excessive recurrent breast cancer events. As we await the results of ongoing randomized trials, it is reasonable to conclude that ERT does not appear to have an adverse effect on cancer outcome. Physicians and patients need to determine whether it is

TABLE 6. *Summary of eight studies of estrogen replacement therapy after breast cancer*

Study	No. patients	Age at diagnosis (y)	ERT duration (y)	Overall follow-up (y)	Breast cancer new/recurrence No. (%)	Systemic relapse No. (%)	Deaths No. (%)
Vassilopoulou-Sellin et al.[11]	49				1 (2)	0 (0)	0 (0)
Median (range)		46 (26–66)	2.6 (2–11.8)	12 (3.8–27)			
Powles et al.[22]	35				2 (5.7)	0 (0)	0 (0)
Median (range)		51 (41–70)	1.4 (0.1–19.8)	3.6 (NA)			
Eden et al.[25]	90				6 (7)	0 (0)	0 (0)
Median (range)		47 (24–71)	1.5 (0.3–12.0)	7 (0.3–30)			
Decker et al.[26]	114				4 (3)	3 (2.6)	2 (1.7)
Median (range)		51.8 (29.8–77.6)	2.5 (0.1–17.3)	6.36 (0.27–24.5)			
Bluming et al.[29]	146				4 (2.8)	0 (0)	0 (0)
Median (range)		NA	2.3 (0.1–4.3)	NA			
Ursic-Vrscaj et al.[30]	21				4 (19)	0 (0)	0 (0)
Median (range)		42 (30–53)	2.3 (0.25–6)	NA (2.3–19.5)			
Brewster et al.[31]	145				13 (9)	NA	3 (2)
Median (range)		50 (26–88)	3.3 (0.25–22)	NA			
Peters (current study)	56				2 (4)	0 (0)	0 (0)
Median (range)		49 (29–76)	6.4 (1.0–20.9)	12.8 (4.7–38.9)			

NA, not available.

appropriate to continue excluding breast cancer survivors from the benefits of ERT while there is not enough information to substantiate a negative effect associated with ERT therapy with these patients. Physicians should inform patients of the well-established benefits and theoretical risks of ERT to help them make a reasoned decision.

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