GYNECOLOGIC ONCOLOGY **65,** 89–93 (1997)
ARTICLE NO. GO974621

Estrogen Replacement Therapy in Women with Prior Diagnosis and Treatment for Breast Cancer

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Received July 8, 1996

We followed 49 women who underwent a minimum of 2 years estrogen replacement therapy (ERT) after diagnosis and treatment for localized breast cancer. Forty-three women were treated with oral ERT. In this group, the median age at the time of cancer diagnosis was 46 years (range 26 to 66 years), and ERT was begun a median of 84 months after diagnosis (range 0 to 286 months). The patients were followed for a median of 144 months after cancer diagnosis (range 46 to 324 months), and the median duration of ERT was 31 months (range 24 to 142 months). For six women, ERT was administered as a vaginal cream application. In this group, the median age at time of cancer diagnosis was 46 years (range 38 to 57 years), and ERT was begun a median of 49 months after diagnosis (range 24 to 61 months). The patients were followed for a median of 95 months after cancer diagnosis (range 72 to 154 months), and the median duration of ERT was 47 months (range 27 to 80 months). One patient experienced disease recurrence; she had received surgery for a stage I, estrogen receptor (ER)-positive lesion. The patient began ERT 30 months after cancer diagnosis and developed a recurrent ER-negative tumor 56 months after initiation of ERT. She remained alive without evidence of disease for 10 years since initial diagnosis of breast cancer. Despite the inherent limitations of retrospective experiential data and the need for prospective, randomized trials to assess the safety of ERT, the present observations suggest that ERT does not appear to have a pronounced adverse effect on cancer outcome. Nevertheless, until appropriate clinical trials determine that ERT is safe, caution is needed.

INTRODUCTION

Estrogen replacement therapy (ERT) after a diagnosis of breast cancer is a controversial topic both within the medical community and among women with the disease. ERT has generally been omitted in this setting, but the validity of current practices is increasingly being questioned [1–14]. With screening programs, breast cancer is being diagnosed at an earlier stage and with improved therapy, survival durations are increasing. Adjuvant chemotherapy is being increasingly incorporated into the treatment program for localized disease, but it can accelerate the arrival of menopause. Thus, more and younger women with excellent survival prognoses will experience early menopause after treatment for early-stage breast cancer. These women face several decades of estrogen deficiency because current concerns regarding the safety of ERT have caused physicians to limit the use of this treatment.

Whether and for which subgroups of breast cancer patients ERT may be used safely to correct climacteric symptoms and prevent cardiovascular and skeletal morbidities cannot be clearly defined without carefully designed and executed prospective trials. While our own prospective study is ongoing [15] and plans for related trials are being prepared by several investigators, results will not be available for a number of years. In the meantime, there is mounting pressure to obtain some information regarding ERT in this growing population of postmenopausal women. To address this need, a number of retrospective analyses, including the present report, are being published to provide some information about the potential safety of ERT [16–19].

MATERIALS AND METHODS

Patient Population

Estrogen is not generally prescribed for women with a history of breast cancer. However, up to 10% of prior patients receive ERT for relief of menopausal health problems [12, 19]. The patients in the present report were followed at the University of Texas M. D. Anderson Cancer Center after treatment for breast cancer and have either: (a) received ERT through their community physicians and requested surveillance at our institution or (b) joined our prospective study and been assigned to the ERT arm. All women included in the study had received ERT for a minimum of 2 years. Treatment was administered orally or as a vaginal cream application. Most women received conjugated estrogen only; the dose was quite variable due to the unselected, retrospective character of the population.

At the time of breast cancer diagnosis, 18 women were

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TABLE 1
Characteristics of Women Who Receive ERT after Breast Cancer

Orally administered ERT (43 women)

	Age-dx[a]	Start ERT[b]	Duration ERT	Overall F/U[c]
Median	46 years	84 months	31 months	144 months
(range)	(26 to 66)	(0 to 286)	(24 to 142)	(46 to 324)
Mean ± SEM	47 ± 1.5	94 ± 10	47 ± 4.9	146 ± 10

Stage		ER status		Nodal status	
I	22[d]	(+)	7[d]	neg	28[d]
II	19	(−)	20	pos	8
In situ	2	NA	16	NA	7

Vaginal ERT (6 women)

	Age-dx[a]	Start ERT[b]	Duration ERT	Overall F/U[c]
Median	46 years	49 months	47 months	95 months
(range)	(38 to 57)	(24 to 61)	(27 to 80)	(72 to 154)
Mean ± SEM	46 ± 2.7	46 ± 6.0	47 ± 8.1	101 ± 12

Stage		ER status		Nodal status	
I	3[d]	(+)	2[d]	neg	3[d]
II	2	(−)	2	pos	3
III	1	NA	2		

Note. NA, information not available.
[a] Age at the time of breast cancer diagnosis.
[b] Interval between cancer diagnosis and initiation of ERT.
[c] Period of observation following initial diagnosis of breast cancer.
[d] Number of patients in each group.

postmenopausal (median age, 45 years; range, 31 to 59 years), 16 were premenopausal, 8 were perimenopausal, and information was not available for the other 7 patients. Estrogen deficiency was induced by gynecologic surgery in 15 women, by chemotherapy in 5, and as a natural result of menopause in 24 (information was unavailable for the other 5 patients). During the observation period, the patients had regular evaluations with history and physical examination every 3 to 6 months and annual mammograms, cervical cytologies, and electrocardiograms.

All patients had surgery for treatment of breast cancer. Twelve women had surgery alone; 20 had surgery plus radiotherapy; 10 had surgery plus chemotherapy; and 7 had surgery, radiotherapy, and chemotherapy.

RESULTS

Patients on Oral ERT

Forty-three women received oral ERT (Table 1). Their median age at the time of cancer diagnosis was 46 years (range, 26 to 66 years; mean ± SEM, 47 ± 1.5 years). The disease was classified as stage I in 22 women, stage II in 19, and *in situ* in 2. Estrogen receptor (ER) status was negative in 20 women, positive in 7, and unavailable in 16. Node status was negative in 28 women, positive in 8, and unavailable in 7.

ERT was instituted after a median interval of 84 months following the diagnosis of breast cancer (range, 0 to 286 months; mean ± SEM, 94 ± 10 months). Median duration of ERT was 31 months (range, 24 to 142; mean ± SEM, 47 ± 10 months). Median period of follow-up was 144 months after diagnosis (range, 46 to 324 months). Three postmenopausal women were receiving ERT at the time of cancer diagnosis and continued to receive estrogen throughout the duration of their treatment. At their last evaluations these patients still had no evidence of disease at 24, 96, and 106 months, respectively.

One patient with coexisting infertility, thyroid cancer, and type I diabetes mellitus experienced breast cancer recurrence. At the age of 42 years, this patient presented with a 1.5-cm left breast mass; excision biopsy showed infiltrating lobular carcinoma and she underwent a modified radical mastectomy. At surgery, 31 axillary lymph nodes were negative and ER was 16.8 fm/mg. A simple right mastectomy

and latissimus dorsi dorsal myocutaneous flap reconstructions were performed during the following months. ERT was prescribed 30 months later. A 1-cm mass was found in the left breast, just above the flap reconstruction 56 months after initiation of ERT; wide local excision was performed and recurrent lobular carcinoma was found. Postoperatively she was treated with six cycles of chemotherapy (5-FU, Adriamycin, and cyclophosphamide) and radiotherapy (50 Gy), followed by Tamoxifen (10 mg twice daily) for 2 years. She was disease-free at the time of last evaluation, 34 months after the diagnosis of recurrence, 10 years after the initial diagnosis of breast cancer.

Patients on Vaginal ERT

Six women received ERT as a vaginal cream application (Table 1). Their median age at the time of cancer diagnosis was 46 years (range, 38 to 57 years; mean ± SEM, 46 ± 2.7 years). Their disease was classified as stage I in 3 women, stage II in 2, and stage III in 1. ER status was negative in 2 women, positive in 2, and unavailable in 2. Node status was negative in 3 women and positive in the other 3.

ERT was instituted after a median interval of 49 months following the diagnosis of breast cancer (range, 24 to 61 months; mean ± SEM, 46 ± 6.0). The median duration of ERT was 47 months (range, 27 to 80 months; mean + SEM, 47 ± 8.1 months). Median period of follow-up was 95 months after diagnosis (range, 72 to 154 months). There have been no cancer recurrences in this patient group.

DISCUSSION

With successful screening programs, detection of breast cancer at an early stage (including lesions *in situ*) is becoming more prevalent. Accordingly, we anticipate that treatment of limited disease will result in higher rates of disease-free and overall survival. As a result, an ever-increasing number of prior breast cancer patients will join the growing population of aging women. However, women with a history of breast cancer are exposed to estrogen deficiency more often and for longer periods of time than women in the general population. Natural menopause is frequently accelerated by chemotherapy [20, 21] which is increasingly being incorporated in treatment protocols for localized disease. Furthermore, women with prior surgical menopause are urged to discontinue ERT at the time of breast cancer diagnosis. This practice stems from deep-seated concerns that ERT may precipitate cancer recurrence.

TABLE 2
Outcome of Women Receiving ERT after Breast Cancer

Patient characteristics	Powles[a]	Wile[a]	DiSaia[b]	Eden[b]	M. D. Anderson[b]
No. of pts	35	25	77	90	43[c]
Stage, No. of pts	T1, 12	*In situ*, 2	*In situ*, 6	Local	*In situ*, 2
	T2, 14	Stage I, 13	Stage I, 43		Stage I, 22
	T3, 9	Stage II, 7	Stage II, 17		Stage II, 19
ER status, No. of pts	NA	NA	Pos, 28	Pos, 12	Pos, 7
			Neg, 12	Neg, 10	Neg, 20
			NA, 37	NA, 68	NA, 16
Node status, No. of pts	Neg, 12	NA	Neg, 58	Neg, 18	Neg, 28
	Pos, 10		Pos, 13	Pos, 72	Pos, 8
	NA, 13		NA, 6		NA, 7
Age at diagnosis	51 years	51 years	50 years	47 years	46 years
	(41–70)	(39–67)	(26–80)	(24–71)	(26–67)
ERT initiation[d]	31 months	26 months	24 months	60 months	84 months
	(0–215)	(0–180)	(0–324)	(0–300)	(0–286)
ERT duration	15 months	35 months	27 months	18 months	31 months
	(1–238)	(6–78)	(1–233)	(4–144)	(24–142)
Overall F/U[e]	43 months	35 months[f]	59 months	84 months	144 months
	(1–238)	(24–84)	(10–425)	(4–360)	(46–342)
No. of recurrences	2/35	3/25[g]	7/77	7/90	1/43

Source. Adapted from: Powles *et al.,* Lancet 342: 60–61, 1993; Wile *et al.,* Am J Surg 165:372–375, 1993; DiSaia *et al.,* Lancet 342:1232, 1993; Eden *et al.,* Menopause 2:67–72, 1995.

[a] Time intervals, mean (range).

[b] Time intervals, median (range).

[c] Data for oral ERT users only.

[d] Initiation of ERT in months after the diagnosis of breast cancer.

[e] Total available follow-up since initial cancer diagnosis.

[f] Observation while on ERT only.

[g] All three cases started ERT within 24 months of cancer diagnosis.

The controversy surrounding the potential impact of ERT on the development of breast cancer has been extensively discussed in the literature [22–38]. Similarly, the efficacy of ERT in preventing cardiovascular [39–42] and skeletal [43–46] morbidities and in correcting climacteric symptoms are also well described. In addition, accumulating evidence indicates that women who develop breast cancer while they are receiving ERT have a favorable prognosis with respect both to tumor grade and to final clinical outcome [47–51].

The emerging skepticism about current standards of ERT practice in women with a history of breast cancer is highlighted in several recent editorials and commentaries [1–14] and clinical studies directly addressing this problem are emerging [15]. While such information is being gathered, however, it is important to consolidate available data regarding the outcomes of the women who have receive ERT. Physicians and patients have expressed concern about the lack of information regarding the safety or ERT for their particular cancer circumstance [12]. Recognizing the limitations of descriptive, retrospective analyses, useful insights can be gained from available clinical experience to help practitioners and patients to address menopause-related health decisions.

An outline of available studies is provided in Table 2. The clinical outcome of 270 women who received systemic ERT (with or without progesterone) has been described in five recent studies [16–19] including the present report. In general, the patients had localized disease but were not restricted with respect to ER or node status. There is wide fluctuation with respect to the interval between diagnosis and ERT initiation (on average within the first 5 years), ERT duration (on average 2 years), and the overall observation period (range 1 to 425 months). Given the retrospective and uncontrolled nature of available data, it is difficult to derive statistically meaningful conclusions about the potential impact of ERT on disease recurrence. Available studies [52–56] suggest that recurrence-free survival ranges between approximately 70 and 90% within the first 10 years after diagnosis and treatment for localized and regional breast cancer. With the caveat that great caution should be applied to any comparisons, the results of these retrospective analyses do not appear to deviate from expected outcome data for recurrence. Overall, it is reasonable to conclude that ERT does not appear to have a pronounced adverse effect on cancer outcome. As the number of women successfully treated for localized breast disease increases, it becomes important to determine whether their exclusion from the established benefits of ERT is appropriate.

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