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Estrogen replacement therapy in breast cancer survivors: a matched-controlled series

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Abstract

Objective: We prospectively administered estrogen replacement therapy (ERT) to control estrogen deficiency symptoms in breast cancer survivors as part of our clinical practice. We report the consequences of ERT compared with a historical matched-control group.

Design: Two hundred seventy-seven disease-free survivors received ERT. Controls were matched for exact stage, a recurrence-free period similar to the period to ERT initiation in the ERT group, approximate age, and duration of follow-up. The mean time from breast cancer diagnosis to initiation of ERT was 3.61 (± 0.25) years, with a median of 1.88 years. The mean duration of ERT was 3.7 (± 3.01) years, with a median of 3.05 years.

Results: Hot flashes were relieved in 206 of 223 women (92%), dyspareunia/vaginal dryness in 149 of 167 women (89%), and reactive depression/anxiety/mood change in 111 of 126 women (88%). Univariate analysis demonstrated no statistical differences between the groups for age, stage, pathology at diagnosis, progesterone receptor status, local therapy, breast at risk, prior chemotherapy, and duration of follow-up. The ERT group was more likely to be estrogen receptor negative ($P = 0.01$), to have received prior ERT ($P < 0.001$), and to have received no adjuvant tamoxifen ($P < 0.001$). There was no significant difference between the ERT and control groups in ipsilateral primary/recurrence (5/155 v 5/143; $P = 0.85$), contralateral breast cancers (10/258 v 9/260; $P = 0.99$), or systemic metastasis (8/277 v 15/277; $P = 0.13$). Noncause-specific deaths in the control group numbered 15 (of 277), and in the ERT group, 7 (of 277) ($P = 0.03$). Overall survival favored the ERT group ($P = 0.02$).

Conclusions: In these selected patients, ERT relieved estrogen deficiency symptoms and did not increase the rate or time to an ipsilateral recurrence/new primary, contralateral new primary, local-regional recurrence, or systemic metastases.

Key Words: Estrogen replacement therapy – Breast cancer – Estrogen deficiency symptoms.

Estrogen deficiency symptoms (EDS) are a major problem for breast cancer survivors and can have a significant impact on quality of life. Hot flashes have been reported in 65% of patients, vaginal dryness in 48%, night sweats in 44%, difficulty sleeping in 44%, feeling depressed in 44%, and dyspareunia in 26%.[1] Concerns about osteoporosis and heart disease are also common.[2] Nonhormonal interventions to control hot flashes and vaginal dryness offer modest clinical benefit.[3-7] For some women, the only means of controlling EDS is estrogen replacement therapy (ERT).

Estrogens have traditionally not been administered to breast cancer survivors. It has been assumed that ERT would increase a breast cancer survivor's rate of relapse and decrease the time to relapse. This assumption is based on estrogen deprivation therapy in premenopausal breast cancer patients, laboratory evidence, epidemiological studies, and recently, a

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randomized trial of ERT in healthy women.[8-11] On the other hand, conjugated equine estrogen (CEE) was the treatment of choice for postmenopausal women with estrogen receptor-positive metastatic breast cancer before the antiestrogen era.[12] The use of estrogens to control EDS is also supported by several small, published series of survivors receiving ERT without a subsequent increase in recurrences.[13-25]

For breast cancer survivors in our clinical practice who have uncontrolled EDS, we have administered ERT and followed them prospectively. We have published an uncontrolled series of these patients and subsequently presented a smaller series with a matched control group.[26,27] This paper reports the consequences of ERT in 277 patients with comparison to a historically matched-control group.

METHODS

Two hundred seventy-seven patients free of breast cancer prospectively received ERT and were followed from approximately 1984 to March 1, 2000. We initiated ERT in 252 of them, and 25 patients followed by us had their ERT initiated by other physicians. Patients receiving ERT were not part of a prospective clinical trial. The ERT patients had failed other nonestrogen interventions for EDS. Patients who had received ERT for at least 3 months before June 1, 2000, were included in the ERT group. All patients had a prior biopsy-confirmed ductal carcinoma in situ or infiltrating breast cancer. Before starting ERT, patients did not routinely undergo extensive radiologic or blood testing to exclude metastatic disease. Patients receiving ERT plus concurrent tamoxifen, vaginal estradiol ring (Estring, Pfizer, New York, NY, USA), or vaginal estradiol suppositories (Vagifem, Pfizer) were excluded. Patients receiving vaginal estrogen creams without concurrent tamoxifen were included. Patients placed on ERT received extensive information concerning the known risks and benefits. This information included a review of published medical literature and national guidelines. Patients received a letter at their request concerning the known risks and benefits. Human Investigation Committee approval to review the records was obtained. We followed 273 patients in the ERT group and 271 in the control group until June 1, 2000, or death.

Before initiation of ERT, the patients were asked by one of the authors to give their reasons for using ERT. The reasons included hot flashes, vaginal dryness/painful intercourse, depression/anxiety/mood change, fear of osteoporosis, and fear of cardiovascular disease. After the initiation of ERT, and at each return office visit, the patients were asked whether the hot flashes, vaginal dryness/painful intercourse, and depression/anxiety/mood change had improved. Estrogen deficiency symptoms were considered improved if the symptoms were no longer of clinical significance requiring further intervention. This information was collected retrospectively on the 25 patients who were started on ERT by other physicians. Patients were followed in a routine fashion with physical examinations, yearly mammograms, and other testing as necessary.

The duration of ERT was defined as the time between initiation of ERT and either discontinuation or June 1, 2000. Time to initiation of ERT was defined as the time from the first biopsy-proven breast cancer to the initiation of ERT. Breast recurrence is a biopsy-proven cancer in the remaining ipsilateral or contralateral breast any time after completion of local therapy without evidence of other systemic disease. A breast at risk for recurrence/relapse is a remaining ipsilateral or contralateral breast present at the time of ERT initiation. Local-regional recurrence is the development of ipsilateral chest wall or regional nodal disease.

The control group consisted of an equivalent number of patients identically matched for stage of disease at the time of diagnosis from our patient records. Controls had to be free of recurrent cancer for an interval of time that was at least the same interval as their ERT match from diagnosis to initiation of ERT. Controls were matched within approximately 1 year for age and within 1 year of their date of breast cancer diagnosis and duration of follow-up. Information on EDS was not consistently available from the records of the controls.

Comparisons between groups were analyzed by the independent t test if the measures were continuous in nature. Alternatively, the Mann-Whitney signed rank test was employed if the groups had a small sample sizes. χ^2 tests were employed for comparison if the measures were nominal in nature. The Fisher's exact tests were used if the cell frequencies were small. Differences in survival or failure rates were analyzed by the log-rank test that is computed by the Kaplan-Meier method. Estimated times of events were presented as mean (± SD). All testing significances were selected at an α level of 0.05. Ipsilateral disease-free survival was defined as follows: (ipsilateral failure date − date of initial breast cancer diagnosis)/365.25. Contralateral disease-free survival was defined as follows: (contralateral failure − date of initial breast cancer diagnosis)/365.25. Overall survival and duration of follow-up was defined as follows: (last follow-up date, or date of death, or June 1, 2000 − date of initial breast cancer diagnosis)/365.25.

The prognostic and clinical characteristics of the ERT group and the control group are listed in Table 1. Mean age is the age at diagnosis of breast cancer. The staging system of the American Joint Committee on Cancer Staging was used. Staging was predominantly pathologic. One patient in the control group had only LCIS in the breast with axillary metastases, and one patient in the ERT group had only DCIS+LCIS in the breast with axillary metastases. The known tumor grade, estrogen receptor (ER), and progesterone receptor (PR) are listed, with the remainder being unknown. ER and PR were not determined in all cases because many of these were too small for the previously used dextran-coated charcoal assay. Local therapy consisted of mastectomy, excision and radiation, or excision only. The breast at risk for the development of cancer would be both, contralateral, ipsilateral, or no breast for those with prior bilateral mastectomies. Prior ERT refers to those receiving ERT at the time of breast cancer diagnosis. Prior chemotherapy consisted primarily of combinations of cyclophosphamide, methotrexate, 5-fluoruricil, prednisone, vincristine, and doxorubicin.

Fifty-six patients taking ERT at the time of their breast cancer diagnosis continued on ERT or resumed it within 2 months after the initial breast cancer diagnosis. The other patients taking ERT at the time of their breast cancer diagnosis discontinued their ERT and reinitiated ERT more than 2 months later. The mean (± SD) and median time from diagnosis to initiation of ERT was 3.61 (± 0.25) and 1.88 years. The minimal time to initiation of ERT was 0 years; maximal time, 23.53 years; and mode, 0 years.

The mean and median duration of ERT was 3.7 (± 3.01) and 3.05 years. Seventy-five patients have been taking ERT longer than 5 years. The duration of ERT ranged from 0.3-21.06 years. Follow-up from the time of diagnosis to June 1, 2000 was 7.41 (± 4.72) years for the control group and 7.75 (± 4.96) years for the ERT group.

The type of ERT and other combinations of additive hormones given to the ERT group are listed in Table 2. Estrogens were administered either as single agents or in combination. Route and dose were adjusted to control EDS. The type of estrogen therapy and route was individualized. Table 2 lists the estrogens the patients were taking as of June 1, 2000, at the time of their recurrence, or when they stopped ERT. Typically, the current estrogen replacement regime was also the estrogen therapy of longest duration.

Estrogens were administered orally in 240 patients, transdermally in 26 patients, as vaginal creams in 9, and parentally in 2. Standard doses of ERT were used. The

TABLE 1. *Prognostic and clinical characteristics of participants*

	Control group[a]		ERT group[a]		
Variable	*n*	%	*n*	%	*P* value
Stage					
DCIS	84	30	84	30	1.00
I	124	45	124	45	
IIA	47	17	47	17	
IIB	19	7	19	7	
IIIA	3	1	3	1	
Pathology					
DCIS	79	29	83	30	0.28
LCIS	1	0.5	0	0	
DCIS + LCIS	5	2	2	1	
Infiltrating ductal cancer	153	55	149	55	
Infiltrating lobular cancer	12	4	13	5	
Infiltrating ductal and lobular cancer	7	2.5	2	1	
Mucinous	7	2.5	9	3	
Tubular	4	1.5	7	2	
Medullary	2	1	2	1	
Spindle	0	0	1	0.5	
Atypical medullary	1	0.5	4	1.5	
Other	4	1.5	0	0	
Tumor grade					
I	24	15	27	16	0.94
II	91	58	102	43	
III	41	27	41	41	
Estrogen receptor status					
Positive	121	78	100	65	0.01
Negative	35	22	54	35	
Progesterone receptor status					
Positive	73	63	63	58	0.38
Negative	42	37	46	42	
Local therapy					
Mastectomy	124	46	122	44	0.6
Excision plus radiation	131	49	146	47	
Excision alone	12	5	9	9	
Breast at risk					
Both breasts	141	51	151	55	0.64
Contralateral	119	43	107	39	
Ipsilateral	2	1	4	1	
No breast	15	5	15	5	
Prior ERT					
No	230	83	126	45	<0.001
Yes	47	17	151	55	
Prior chemotherapy[b]					
CMF	15	33	21	36	0.63
CMFP	4	9	3	5	
CMFVP	14	30	19	32	
CA	6	13	9	15	
CAF	3	7	6	10	
CAFM	2	4	1	2	
Other	2	4			
Prior tamoxifen					
No	158	57	209	75	<0.001
Yes	119	43	68	25	

ERT, estrogen replacement therapy; DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ.

[a]Age at diagnosis (mean ± SD) was as follows: control group, 55.35 ± 11.85 y; ERT group, 53.79 ± 11 y. $P = 0.1$.

[b]Coded as follows: C, cyclophosphamide; M, methotrexate; F, 5-fluoruricil; P, prednisone; V, vincristine; A, doxorubicin.

TABLE 2. *Hormone replacement agents*

Estrogen replacement	Other additive hormones			Total (%)
	None	Progestin	Methyltestosterone	
Conjugated estrogens	85	106	2	193 (70)
Esterified estrogens	7	4	4	15 (5)
Estradiol	37	19	0	56 (20)
Estrone (estropipate)	6	5	0	11 (4)
Estrone/estradiol/ estriol	0	2	0	2 (1)
Total	135	136	6	277

most frequent regimen was oral conjugated estrogen (0.625 mg; either single agent or in combination), administered in 153 patients; cutaneous estradiol (0.05 mg), in 15 patients; oral estradiol (0.5 mg), in 11 patients; estropipate estrone (1.25 mg), in 4 patients; and esterified estrogens (1.25 mg) in 4 patients.

The most common reason for administering ERT was hot flashes, followed by dyspareunia/vaginal dryness (see Table 3). The majority of these patients had failed other treatments to control hot flashes and dyspareunia/vaginal dryness. The depression/anxiety/mood change seemed to be secondary to the decreased quality of life from the hot flashes and the dyspareunia/vaginal dryness. Most patients had more than one EDS or reason for taking ERT.

RESULTS

Hot flashes were relieved in 206 of 223 patients (92%), with inadequate relief in 7 cases and an unknown response in 10 cases (see Table 4). Dyspareunia/vaginal dryness was relieved in 149 of 167 patients (89%), with no relief in 13 cases and an unknown response in 5 cases. Depression/anxiety/mood change was relieved in 111 of 126 patients (88%), with no relief in 10 cases and an unknown response in 5 cases.

Fifty-five patients (19.9%) without recurrence stopped ERT after a mean duration of 2.0 (± 0.27) years, with a median of 1.1 years. The duration of ERT in these patients ranged from a minimum of 0.28 years to a maximum of 8.1 years. The most common reasons for stopping ERT were fear concerning recurrent breast cancer, breast tenderness, and vaginal bleeding, with lack of benefit in their quality of life being less common.

Univariate analysis demonstrated no statistical differences between the groups for age, stage, pathology at diagnosis, PR status, local therapy, breast at risk,

TABLE 3. *Estrogen deficiency symptoms before estrogen replacement therapy*

Symptom	Present (%)	Absent (%)	Unknown
Hot flashes	223 (81)	50 (19)	4
Vaginal dryness/dyspareunia	167 (60)	106 (40)	4
Fear osteoporosis	147 (53)	106 (47)	24
Depression/anxiety	126 (46)	147 (54)	4
Fear cardiovascular disease	123 (44)	129 (56)	25

prior chemotherapy, and duration of follow-up. There were significant differences, with patients in the ERT group being more ER negative ($P = 0.01$), having received prior ERT ($P < 0.001$), and having received no prior tamoxifen ($P < 0.001$; see Table 1).

Of the 155 patients receiving ERT with an ipsilateral breast at risk, five new primary or ipsilateral breast recurrences (3%) were observed (see Table 5). In the control group, five new primary or ipsilateral breast recurrences (4%) in the 143 patients with an ipsilateral breast at risk were observed ($P = 0.85$). There was no significant difference in the time from initiation of ERT to an ipsilateral breast failure between the two groups. The estimated mean time of an ipsilateral breast failure in the control group was 6.02 (± 3.29) years, whereas that of the ERT group was 6.36 (± 3.18) years. The Kaplan-Meier mean survival for the ipsilateral breast failure patients was 24.31 (± 0.31) years in the control group and 27.22 (± 0.36) years in the estrogen replacement group ($P = 0.96$). Mean survival is reported instead of the median because the survival/event curves for both groups did not fall below 0.50.

Ten (4%) of 258 patients in the ERT group with a contralateral breast at risk have developed a contralateral breast cancer (see Table 5). In the control group, 9 contralateral primary breast cancers in 260 patients (4%) were observed ($P = 0.99$). There was no significant difference in the time from initiation of ERT to a contralateral breast failure between the groups. The estimated mean time of a contralateral breast failure in the control group was 4.90 (± 2.32) years, whereas that in the hormone group was 5.11 (± 1.76) years. The overall Kaplan-Meier mean survival for the contralateral breast failure patients was 23.85 (± 0.35) years in the control group and 26.67 (± 0.42) years in the estrogen replacement group ($P = 0.88$).

Local-regional recurrence was observed in 7 of 277 patients (3%) in the estrogen replacement group and 6 of 277 (2%) in the control group (see Table 5; $P = 1.00$). The estimated mean time of a local-regional recurrence was 7.09 (± 6.09) years in the control group and 10.53 (± 4.91) years in the ERT group. The Kaplan-Meier mean survival for the local-regional recurrence patients

TABLE 4. *Symptom response to estrogen replacement therapy*

Symptom	Patients with symptom (%)	ERT improved (%)	ERT not improved	ERT response unknown
Hot flashes	223 (81)	206 (92)	7	10
Dyspareunia/vaginal dryness	167 (60)	149 (89)	13	5
Depression/anxiety	126 (46)	111 (88)	10	5

TABLE 5. *Recurrence and survival comparison control versus estrogen replacement therapy (ERT) group*

	Control group		ERT group		
Variable	n^a	%	n^a	%	*P* value
Ipsilateral breast relapse					
Absent	138		150		
Present	5	4	5	3	0.85
Time to relapse (mean ± SD) in y	6.02 ± 3.29		6.36 ± 3.18		
Contralateral breast relapse					
Absent	251		248		
Present	9	4	10	4	0.99
Time to relapse (mean ± SD) in y	4.90 ± 2.32		5.11 ± 1.76		
Chest wall relapse					
Absent	271		270		
Present	6	2	7	3	1.00
Time to relapse (mean ± SD) in y	7.09 ± 6.09		10.53 ± 4.91		0.28
Metastatic disease					
Absent	262		269		
Present	15	5	8	3	0.13
Time to relapse (mean ± SD) in y	7.66 ± 4.71		6.51 ± 3.87		0.56
Death					
Alive	260		270		
Dead	17	6	7	3	0.03
Time to death in y (mean ± SD)	21.83 ± 0.79		26.29 ± 0.79		
Time to death in y (median ± SD)	24.92		—		0.02

All outcomes remained statistically nonsignificant ($P > 0.05$) after adjustment for age, tumor grade, estrogen receptor, prior ERT, and prior tamoxifen. The total number of death events has greatly been reduced from 24 to 9 for both groups because of the adjustments, thereby lessening the statistical power to draw any meaningful significance from the events.

[a]Unless otherwise indicated.

was 23.48 (± 0.81) years in the control group and 25.65 (± 1.05) years in the estrogen replacement group ($P = 0.93$).

Metastatic disease was observed in 8 of 277 patients (3%) in the estrogen replacement group and 15 of 277 (5%) in the control group (see Table 5; $P = 0.13$). The estimated mean time to metastatic disease in the control group was 7.66 ± 4.71 years, whereas that in the hormone group was 6.51 (± 3.87) years. The Kaplan-Meier mean survival was significantly better for the ERT group, 21.98 (± 0.85) years, compared with the case of the control group, 26.65 (± 0.50) years ($P = 0.02$).

There were significantly more deaths in the control group. Deaths were observed in 17 of 277 (6%) of the controls and 7 of 277 (3%) of the ERT patients ($P = 0.03$). These deaths were not all breast cancer related. Nine of the 17 deaths (53%) in the control group were due to breast cancer and 8 to other causes. The other deaths were predominantly a result of other cancers and cardiovascular disease. Five of the 7 deaths (71%) in the ERT group were due to breast cancer and 2 to other causes.

The estimated mean time to death was 9.85 (± 5.72) years in the control group and 8.15 (± 5.21) years in the ERT group. The difference in survival time between the control and ERT groups was statistically significantly different ($P = 0.02$). The Kaplan-Meier mean survival for all patients was 21.83 (± 0.79) years in the control group and 26.29 (± 0.79) years in the ERT group (see Fig. 1).

DISCUSSION

The frequency of EDS in our patients and their reasons for considering ERT are consistent with published surveys of survivors.[1,2] These patients received ERT primarily for symptoms of hot flashes and dyspareunia/vaginal dryness. They were less concerned about depression/anxiety/mood change or the prevention of osteoporosis and cardiovascular disease. Most patients had more than one EDS.

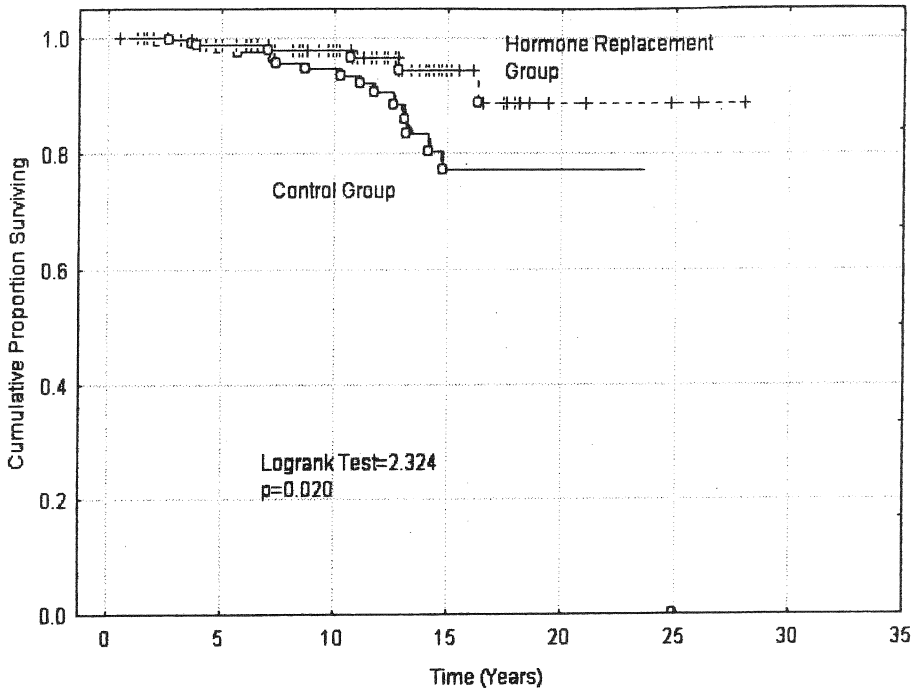

FIG. 1. Survival Hormone Replacement and Control Group

ERT relieved, to the patient's satisfaction, the hot flashes, vaginal dryness/painful intercourse, and depression/anxiety/mood changes in about 90% of instances. Our observation agrees with the reported effect of ERT in relieving EDS in up to 90% of healthy postmenopausal women.[28,29] The observed benefit was undoubtedly a consequence of the ERT and not an error in assessment. Although a detailed survey of responses to EDS as reported in prospective randomized trials was not conducted, our method of determining response seems reliable.[5-7] There are no published data suggesting that a large percentage of patients would deceive their physician about their EDS or any subsequent benefit from ERT. Some of the observed benefit of ERT may have been a placebo effect.[3-7] The placebo effect is observed in about 20% of patients.[3-7]

The hypothesis that ERT would increase the rate of an ipsilateral new primary/recurrence, contralateral breast cancer, or death from breast cancer is not supported by this study. Our results are consistent with those of the published literature. There has been one small, randomized study; several case-controlled studies; and a few small, published series.[13-25] There have been no published reports of an adverse outcome from ERT in breast cancer survivors. Indeed, some of these reports suggest a survival benefit in those patients taking ERT. These reports have methodological problems and are not definitive evidence supporting ERT for all breast cancer survivors with EDS. There may have been a selection process that biases survival in favor of the ERT patients. The number of patients is small, with the largest series including only 174 patients. The primary endpoint has been survival and not necessarily ipsilateral new primary/recurrence or contralateral breast cancer incidence. Patients were started on ERT after a disease-free survival of about 5 years in most of the case-controlled series. Patients have received ERT for an average of only about 2 years, with a short follow-up of 2 to 3 years. Most of the studies were not prospective or randomized. In some of the case-controlled studies, it is not clear that the controls were alive without disease at a time when the ERT patient would have started ERT. Finally, deaths were not reported as cause specific.

Although not intentional, we undoubtedly selected patients. The ERT-treated group contained more patients with ER-negative breast cancer. Estrogen receptor-negative patients and their physicians may accept ERT more readily, believing their tumor is not hormone responsive. More patients in the control group received adjuvant tamoxifen. This is a reflection of the increased number of ER-positive patients in the control group. There were more patients in the ERT group who were on ERT at the time of breast cancer diagnosis.

The rate of an ipsilateral new primary/recurrence or contralateral breast cancer in the ERT group was not significantly different from that in the matched-control group. Furthermore, there was no suggestion that ERT hastened a recurrence, as there was no significant difference in the disease-free survival rates between the

groups. However, this does not exclude an increased risk of an ipsilateral new primary/recurrence or contralateral breast cancer in the ERT group. The Women's Health Initiative recently reported that CEE and medroxyprogesterone acetate (MPA) increase the risk of breast cancer by 26% in otherwise healthy women (mean follow-up, 5.2 years).[11] Intuitively, for breast cancer survivors with a 5% 5-year risk of developing an ipsilateral or contralateral breast cancer, a 26% increase in this risk would translate to an absolute increase in risk of 1% over 5 years. If ERT increases a breast cancer survivor's risk by only 1%, this risk could easily be missed in a small series of patients. The absolute number of patients in our series receiving ERT or only CEE and MPA may be too small to identify an absolute increase in risk of only 1%. Furthermore, the duration of ERT in the present series [mean, 3.7 ± 3.01 years] may not be long enough to observe an increase in the risk of an ipsilateral new primary/recurrence or contralateral breast cancer.

There was no significant difference in the rate of metastatic breast cancer or time to develop metastasis between our ERT and control groups. An improved overall survival in the ERT group was observed. A survival advantage with ERT use has also been reported in other case-controlled series. Possible explanations of the survival advantage include estrogens controlling occult metastasis with prevention of breast cancer death or patient selection. Unintentional selection bias was present in both our ERT and control groups. The controls may have been selected with a higher mortality rate from other causes. Our control group had a larger percentage of non-breast cancer related deaths than did the ERT group. In any historically controlled series, it is impossible to identically match the patients for all known prognostic variables. Finally, ERT at the time of breast cancer diagnosis is associated with a favorable prognosis.[30,31]

As with ipsilateral new primary/recurrence or contralateral breast cancer, it is possible that with larger numbers of patients or longer duration of ERT, an increased rate of metastases may be observed. The number of patients with breast cancer who were at high risk (ie, high-stage disease) for metastases in this series was relatively small. The mean time on ERT of 3.7 (± 3.01) years is most likely long enough to observe a clinically apparent increase in system relapse. Unlike the development of a primary breast cancer that may take 5 years of exposure to ERT, a much shorter time of ERT may be sufficient to result in clinically apparent metastatic disease from occult metastases. One of the arguments against ERT has been the rapid growth stimulation of MCF-7 cell line when exposed to low doses of estrogen.[32] Because this stimulation is rapid, it would seem reasonable to conclude that occult metastatic disease would become clinically detectable during a 3.7-year (± 3.01 years) period of time.

The theory that low-dose ERT would activate occult metastasis has seemed inconsistent with our historical clinical experience. Estrogen was the standard systemic hormonal therapy for postmenopausal women with estrogen receptor-positive metastatic breast cancer before tamoxifen.[12,33,34] Both low and high doses of estrogens were accepted therapies. CEE at a dose as low as 2.5 mg daily was a recommended treatment.[12] This dose of CEE was inexpensive and relatively free of side effects. Like low doses of CEE, low doses of diethylstilbestrol (1.5 mg per day) improve metastatic disease, with responses similar to those of higher doses of diethylstilbestrol (15 mg).[33] The response rates and survival for diethylstilbestrol (3 or 15 mg/day) and tamoxifen are similar,[34,35] with one study demonstrating a survival advantage for the 15-mg diethylstilbestrol.[36] Tamoxifen became the preferred therapy for metastatic breast cancer primarily because of its side-effect profile. The use of adjuvant estrogen is suggested by one small, randomized trial comparing adjuvant tamoxifen, high-dose diethylstilbestrol, and placebo that demonstrates an equal advantage for both the tamoxifen and diethylstilbestrol groups over the placebo group.[37]

The laboratory evidence supporting the stimulatory effect of estrogen on breast cancer cell lines or xenografts is incontrovertible. However, the therapeutic use of estrogens in postmenopausal women is not without supporting laboratory data. The breast cancer cell line E8CASS, derived from MCF-7 grown in estrogen-free medium, responds to high-dose 17β-estradiol.[38] This suggests that patients who are postmenopausal and develop breast cancers in an environment of estrogen deficiency will have tumors that may respond to estrogen. Thymidine uptake is decreased in the MCF-7 cell line when exposed to high doses of diethylstilbestrol.[32] Serially transplanted MCF-7 ER-positive tumors in athymic mice seem to develop supersensitivity to estradiol. After tamoxifen therapy in these mice, dramatic regressions of cancer with physiologic doses of estradiol are observed, suggesting that physiologic doses of estradiol in patients previously treated with adjuvant tamoxifen may improve disease control.[39]

ERT should be considered a therapeutic option for the relief of uncontrolled EDS in postmenopausal breast cancer survivors who accept the known benefits and risks. ERT did not increase the risk of an ipsilateral

new primary/recurrence, contralateral breast recurrence, or metastases in this series. CEE and MPA in larger studies with longer follow-up may increase the risk of an ipsilateral new primary/recurrence or contralateral breast recurrence in breast cancer survivors, as observed in the Women's Health Initiative study. It cannot be concluded that ERT stimulates occult metastatic breast cancer from this or other series. Breast cancer survivors wishing to consider ERT to control EDS need to be informed of both the possible benefits of ERT – decreasing the risk of osteoporotic fractures and decreasing the risk of colon cancer – as well as the possible risks – increasing vascular events and increasing the risk of a new breast cancer in remaining breast tissue.

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