Estrogen Replacement Therapy After Localized Breast Cancer: Clinical Outcome of 319 Women Followed Prospectively

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Purpose: **To determine whether estrogen replacement therapy (ERT) alters the development of new or recurrent breast cancer in women previously treated for localized breast cancer.**

Patients and Methods: **Potential participants (n = 319) in a trial of ERT after breast cancer were observed prospectively for at least 2 years whether they enrolled onto the randomized trial or not. Of 319 women, 39 were given estrogen and 280 were not given hormones. Tumor size, number of lymph nodes, estrogen receptors, menopausal status at diagnosis, and disease-free interval at the initiation of the observation period were comparable for the trial participants (n = 62) versus nonparticipants (n = 257) and for women on ERT (n = 39) versus controls (n = 280). Cancer events were ascertained for both groups.**

Results: **Patient and disease characteristics were comparable for the trial participants versus nonparticipants, as well as for the women on ERT versus the controls. One patient in the ERT group developed a new lobular estrogen receptor–positive breast cancer 72 months after the diagnosis of a ductal estrogen receptor–negative breast cancer and 27 months after initiation of ERT. In the control group, there were 20 cancer events: 14 patients developed new or recurrent breast cancer at a median time of 139.5 months after diagnosis and six patients developed other cancers at a median time of 122 months.**

Conclusion: **ERT does not seem to increase breast cancer events in this subset of patients previously treated for localized breast cancer. Results of randomized trials are needed before any changes in current standards of care can be proposed.**

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BASED ON CONCERNS that estrogen replacement therapy (ERT) may reactivate the disease, ERT is generally not recommended for women who reach menopause after successful treatment of breast cancer. However, this long-standing accepted practice is increasingly being scrutinized because, thanks to early detection and improved therapies, more young breast cancer survivors with excellent survival prognoses reach menopause and face several decades of estrogen deficiency.

The need for appropriately designed prospective, randomized studies of ERT in this patient population has been proposed in numerous editorials and commentaries.[1-8] Such trials are now beginning or are underway (HABITS trial, L. Holberg, personal communication, December 1998; ECOG trial, M. Cobleigh, personal communication, July 1997; Tibolone trial, I.S. Fentiman, personal communication, September 1997) but results will not be available for several years. Meanwhile, there is mounting pressure to obtain some information regarding the role of ERT in breast cancer survivors. To address the problem, information is usually sought from experiential observations gained through retrospective reviews,[9-14] prospective single-arm studies,[15,16] or randomized pilot studies.[17]

In addition to the lack of data, it is becoming apparent that earlier calls for large randomized prospective trials[18] may not be feasible without sufficient preliminary data that address ERT safety. In a recently convened consensus conference, it became apparent that ''only a small fraction of breast cancer survivors would accept the use of estrogen even if studies suggested relative safety.''[8] The difficulty of enrolling a large number of women onto randomized trials has been highlighted by the pronounced reluctance that potential participants express when asked to join hormone replacement therapy studies.[19]

To optimize knowledge from the women who take estrogen after treatment for breast cancer, we consecutively identified a group of women who were potential participants onto our randomized, prospective clinical ERT trial[19] and observed them prospectively whether they chose to enroll or

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not. The women were comparable with respect to several breast cancer prognostic factors. This article describes the clinical outcome of these patients with respect to the development of new or recurrent breast cancer in those who were administered ERT compared with women who were not given hormones. Our findings suggest that ERT does not increase cancer events in this subgroup of former breast cancer patients.

PATIENTS AND METHODS

Within the context of enrolling participants onto our prospective, randomized study of ERT after the diagnosis of breast cancer,[20] we identified postmenopausal women who were potential study participants and who, although eligible for the ERT program, may or may not have chosen to participate in a randomized trial. After initial contact (entry), we observed their clinical outcome prospectively for a minimum of 24 months. Most of the women were receiving treatment for their breast cancer at M.D. Anderson Cancer Center, Houston, TX, at the time of initial contact and during the follow-up period. The observation period was from 1991 to 1995, with most participants initially seen between 1992 and 1994.

Subject Selection

The criteria that were required for inclusion in the present study were identical to the eligibility criteria for participation in the randomized trial (which is ongoing)[21]: (a) stage I or II breast cancer; (b) $\geq$ 2-year disease-free interval (DFI), if initial breast cancer was estrogen receptor (ER)–negative, or $\geq$ 10 years if ER status was unknown; (c) breast cancer diagnosis during a defined 20-year period (January 1, 1974, through December 31, 1993); (d) established menopause (amenorrhea for at least 6 months, elevated gonadotropin levels, or surgical ablation); and (e) available follow-up for at least 24 months (or until cancer event occurrence).

Patient Population

Among 331 potentially eligible women, complete data were lacking for 12 who were subsequently excluded from the study. Accordingly, we identified 319 women with the inclusion characteristics and observed them prospectively. Among these, 62 women elected to participate in the prospective, randomized trial (participants) and were assigned to ERT or to no treatment. The other 257 chose not to participate (nonparticipants); although the majority of the latter group decided against ERT, in accordance with current standards of practice, 10 women not participating in the trial were administered estrogen for individualized, clinical considerations (generally related to severe climacteric symptoms). Therefore, a total of 39 women were administered ERT (ERT group), consisting of conjugated estrogens (0.625 mg on days 1 to 25 of each month) without progesterone. The other 280 women (control group) did not take hormones.

Methods

We observed these two patient cohorts (ERT group *v* control group) prospectively for a minimum of 2 years and monitored their clinical outcome with respect to the development of new or recurrent cancer. Cancer events within 6 months of entry (three cases of recurrent breast cancer in the control group) were considered to represent preexisting conditions and were excluded.

To rule out the possibility that the clinical outcome of the different groups of women was influenced by a selection bias among the women who did not enroll onto the randomized trial or who did not take ERT, we assessed and compared the trial participants versus nonparticipants and the ERT group versus control group with respect to several known prognostic factors of breast cancer outcome. These prognostic factors were tumor size, number of lymph nodes involved, tumor ER status, menopause status at the time of breast cancer diagnosis, and DFI between the diagnosis of breast cancer and study entry. Comparisons between groups were performed using the χ^2 test. Quantitative analysis of cancer events was not attempted because of the small number of cases. In most cases, the breast cancer specialists who treated the patients at M.D. Anderson Cancer Center determined oncologic evaluation of disease status during the observation period.

RESULTS

Patient Population

At the time of breast cancer diagnosis, the median age of the 319 women was 46 years (range, 27 to 76 years; Table 1). Median DFI at entry was 114 months (range, 24 to 234 months), and median observation duration was 40 months (range, 24 to 99 months). Although all women were postmenopausal at the time of study entry, 178 women were premenopausal at the time of initial breast cancer diagnosis, and 141 were already postmenopausal. All patients had undergone surgery; the addition of postoperative, adjuvant medical therapy or radiotherapy varied according to clinical indications and protocol participation. All participants were disease-free after initial treatment (as dictated by study design).

Comparison of Disease Characteristics Between Participants and Nonparticipants

Disease characteristics are listed in Table 2 for the 62 women who chose to participate in the randomized trial as well as the 257 women who did not. The two groups were comparable with respect to number of lymph nodes, tumor size, ER status, menopausal status, and DFI between the diagnosis of breast cancer and the beginning of observation. The median observation period for the participants was 48 months (range, 24 to 71 months), which was comparable to the median observation period of 40 months for the overall group. The similarity of the two groups indicates that their

Table 1. Patient and Disease Characteristics of Study Group (n = 319)

	Eligible for Randomized ERT Study	
	Median	Range
Patient age, years	46	27-76*
DFI at entry, months	114	24-234
Overall follow-up, months	40	24-99
Stage I or II at diagnosis		
DFI at entry	> 2 years (ER-negative primary tumor)	
	> 10 years (ER unknown primary tumor)	
Observation duration	> 2 years	

NOTE. Cancer diagnosis interval: January 1, 1974, to December 31, 1993.
Abbreviations: DFI, disease-free interval (time between breast cancer diagnosis and study entry); ER, estrogen receptor of primary tumor.

Table 2. Comparison of Disease Characteristics of the Participants and Nonparticipant Cohort

	Randomized(n = 62)		Nonrandomized(n = 257)		
	No.	%	No.	%	*P*
Lymph nodes					
0	35	56	142	55	
1-3	17	27	71	27	.641
> 3	6	10	35	14	
NA	4	6	9	4	
Tumor size					
< 1 cm	11	17	34	13	
1-3 cm	35	57	150	58	.928
> 3 cm	15	24	70	28	
Occult	1	2	3	1	
ER status					
Negative	47	75	170	66	.143
Unknown	15	25	87	34	
Menopause					
Before	39	62	139	54	.210
After	23	38	118	46	
DFI at entry*					
24-60 months	21	33	88	34	
61-120 months	16	26	51	20	.550
> 120 months	25	40	118	46	

*DFI at entry, disease-free interval between breast cancer diagnosis and beginning of observation.

risk for new or recurrent cancer was comparable. Although not statistically significant, the participants were more likely to have had ER-negative tumors (75% *v* 66%) and to have been premenopausal at the time of cancer diagnosis (62% *v* 54%).

Comparison of Patient and Disease Characteristics in ERT and Control Groups

Patient characteristics for the ERT and control groups (Table 3) were comparable with respect to several prognostic parameters, such as age at the time of cancer diagnosis (45.3 ± 8.6 *v* 48.5 ± 8.9 years; mean ± SD), DFI at time of entry (108.9 ± 65.1 *v* 109.0 ± 62.1 months) and overall observation period (51.7 ± 15.4 *v* 38.0 ± 12.0 months).

Table 3. Comparison of Patient Characteristics of the ERT and Control Groups

	ERT Group	Control
No. of patients	39	280
Age at diagnosis, years		
Median	45	48
Range	27-65	29-76
DFI at entry,* months		
Median	114	114
Range	25-232	24-235
Observation duration, months		
Median	55	36
Range	24-73	24-72

*DFI at entry, disease-free interval between breast cancer diagnosis and beginning of observation.

Although not significant, the observation period for women in the ERT group was longer than that for women in the control group, allowing, in theory, for more cancer events to occur.

Disease characteristics for the 39 women who were administered ERT and the 280 women in the control group (Table 4) were comparable with respect to number of lymph nodes, tumor size, ER status, and DFI at time of entry. Women in the ERT group were significantly more likely to have been premenopausal at the time of breast cancer diagnosis ($P = .014$). Using the same parameters, we have also found that women on ERT are comparable to controls within the small group of the 62 participants in the randomized trial (data not shown).

Cancer Events During the Observation Period

There were 20 cancer events in the control group and one cancer event in the ERT group. All patients were alive at the time of last contact (Table 5).

New or recurrent breast cancer developed in 14 patients (5%) in the control group after a median interval of 139.5 months (range, 63 to 234 months) from the time of diagnosis and 24 months (range, 11 to 64 months) from the beginning of the observation period. Other malignancies developed in six control patients after a median interval of 122 months (range, 63 to 149 months) after breast cancer diagnosis and 38 months (range, 12 to 47 months) after study entry.

Table 4. Comparison of Disease Characteristics of the ERT and the Control Group

	Control (n = 280)		ERT (n = 39)		
	No.	%	No.	%	*P*
Lymph nodes					
0	156	56	21	54	
1-3	77	27	11	28	.640
> 3	37	13	4	10	
NA	10	4	3	8	
Tumor size					
< 1 cm	37	13	8	20	
1-3 cm	164	59	21	54	.523
> 3 cm	76	27	9	23	
Occult	3 cases		1 case		
ER status					
Unknown	92	33	10	26	.365
Negative	188	67	29	74	
Menopause					
Before	149	53	29	74	.013
After	131	47	10	26	
DFI at entry*					
24-60 months	89	32	13	33	
61-120 months	61	22	7	18	.860
> 120 months	130	46	19	49	

*DFI at entry, disease-free interval between breast cancer diagnosis and beginning of observation.

Table 5. Cancer Events During the Observation Period

Control Group	
New or recurrent breast cancer	14
Interval since diagnosis, months	
Median	139.5
Range	63-234
Contralateral cancer	8 cases
Ipsilateral cancer	4 cases
Distant metastases	2 cases
Other cancers in control group	6
Interval since diagnosis, months	
Median	122
Range	63-149
Histologies of other cancers	
Lung	3
Colon	1
Ovary	1
Mesothelioma	1
ERT Group	
New breast cancer (n = 1) 72 months after cancer diagnosis and 27 months after ERT. Initial tumor infiltrating ductal cancer T2N0, ER(−), second breast cancer predominantly infiltrating lobular ER/PR(+) histology.	

Postoperative radiotherapy had been used for the treatment of the breast cancer in four of these cases. The histology of the other malignancies included lung cancer (three cases), ovarian cancer (one case), colon cancer (one case), and mesothelioma (one case).

Only one cancer event occurred in the ERT group. The patient whose primary cancer was an infiltrating T2N0, ER-negative ductal carcinoma developed a contralateral ER/progesterone–positive predominantly infiltrating lobular breast cancer 72 months after initial cancer diagnosis and 27 months after study entry (and initiation of ERT).

DISCUSSION

Localized breast cancer is being detected more frequently as a result of improved screening practices. Early detection coupled with comprehensive therapies is beginning to yield better DFIs and overall survival for the affected women. This group of former patients, however, is exposed to more frequent and longer estrogen deficiency. Adjuvant chemotherapy, for example, is increasingly used to cure localized breast cancer and accelerates natural menopause. In addition, women whose menopause is brought on by hysterectomy are advised to discontinue ERT after breast cancer diagnosis. As the history of breast cancer recedes into the background of their medical history, however, prolonged estrogen deficiency may promote cardiovascular, skeletal, or genitourinary morbidities for the survivors.

The deep-seated concern that ERT may reactivate breast cancer[4,18] underlies the current treatment approach that women with a history of breast cancer should avoid ERT. This position, however, is increasingly tempered by the appreciation that ERT is effective in the preservation of cardiovascular, skeletal, genitourinary, and possibly cognitive health, resulting in an improved quality of life. The emerging skepticism regarding current standards of ERT practice is reflected in recent editorials and reviews,[1-8] which call for prospective, randomized trials. Such trials are now beginning but will not yield evaluable data for some time. Meanwhile, indirect evidence from available studies has shown that patients in whom breast cancer develops while they are taking ERT have a similar (if not better) clinical outcome than women who are not taking estrogen at the time of breast cancer diagnosis.[21-24]

In addition, a number of retrospective analyses of unselected patients[9-14] as well as prospective single-arm[15,16] or randomized pilot[17] studies have been presented and also indicate that ERT does not seem to have an adverse effect on breast cancer outcome. Currently available data are listed in Table 6. The patients included in this

Table 6. Hormone Replacement Therapy After Breast Cancer

First Author	No. of Patients	Age at Diagnosis (years)	ERT (months)		Overall Follow-Up (months)	Breast Cancer, New/Recurring	
			Start	Duration		No.	%
Powles[9]							
Median	35	51	31	15	43	2	5.7
Range		41-70	0-215	1-238			
Eden[10]							
Median	90	47	60	18	84	7	7.8
Range		24-71	0-300	4-144	4-360		
Di Saia[11]							
Median	77	50	24	27	59	7	9.1
Range		26-80	0-324	1-233	10-425		
Vassilopoulou-Sellin[12]							
Median	43	46	84	31	144	1	2.3
Range		26-67	0-286	24-142	46-342		
Peters[13]							
Median	67	NA	NA	37	94	0	None
Range				2-192	1-454		
Decker[14]							
Median	61	52	44	26	NA	6	9.8
Range		32-77	0-233	3-198			
Gorins[15]							
Median	28	NA	NA	33	NA	1	3.6
Range							
Bluming[16]							
Median	146	NA	61	28	NA	4	2.7
Range			2-392	1-52			
Marsden[17]							
Median	50	NA	NA	6	< 6	0	None
Range							

tabulation largelyrepresent self-selected patients with mostly localized disease and mixed ER status. Overall, information on approximately 600 patients is reported, with breast cancer events varying between 0% and 10% during observation on ERT. In the randomized study by Marsden and Sacks,[17] data have been presented on 100 patients, and the breast cancer events consist of one recurrence in a control patient.

In the present study, there were no excess events among the women taking ERT. One patient (2.6%) in the ERT group developed a new breast cancer whereas 14 patients (5.0%) in the control group developed new or recurrent breast cancer. Given the small number of patients (n = 319) and the small number of all events in both groups (n = 20 in the control group and n = 1 in the ERT group), it is difficult to calculate or even speculate whether the observed frequency of events is different from expected rates. Accordingly, we present a description of observed events without attempting quantitative analysis. A review of available literature on expected new or recurrent cancers indicates that expected disease-free survival for women with localized disease ranges between 70% and 90% within the first 10 years after diagnosis.[24-26] In the report by Saphner et al[27] risk of recurrence was tabulated according to prognostic characteristics similar to those used in our analysis (tumor size, DFI since diagnosis, node status, ER status, and menopausal status). The observed numbers/rates of new or recurrent breast cancers in this study (both ERT and control groups) seem to be lower than those reported by Saphner et al, perhaps suggesting that we are monitoring a cohort with particularly good prognoses.

Although the patients in our report do not represent a randomized, prospectively observed cohort, the study participants and the nonparticipants are well matched with respect to known clinical prognostic factors. Similarly, the women in the ERT group were well matched with those in the control group; accordingly, the expected occurrence of new or recurrent breast cancer should also be comparable. It is important to recognize and reemphasize the inherent limitations of analyses that are not based on prospective, randomized data, such as our ongoing trial.[19] Until such information becomes available, however, we suggest that the prospective evaluation of the consecutively identified women with comparable disease characteristics and prognostic factors, reported here, contributes to the currently limited prospective data regarding this important issue. Our results provide additional evidence that ERT may not increase the risk of new or recurrent breast cancer in carefully selected women with a history of breast cancer. Nevertheless, the completion of prospective, randomized trials is needed before changes in current standards of care can be proposed.

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REFERENCES

1. Stoll BA, Parbhoo S: Treatment of menopausal symptoms in breast cancer patients. Lancet 1:1278-1279, 1988

2. Creasman WT: Estrogen replacement therapy: Is previously treated cancer a contraindication? Obstet Gynecol 77:309-312, 1991

3. Theriault RL, Vassilopoulou-Sellin R: A clinical dilemma: Estrogen replacement therapy in postmenopausal women with a background of primary breast cancer. Ann Oncol 2:709-717, 1991

4. Spicer DV, Pike MC: Hormone replacement after breast cancer. Lancet 342:183-184, 1993

5. Vassilopoulou-Sellin R: Estrogen replacement therapy in women at increased risk for breast cancer. Breast Cancer Res Treat 28:167-177, 1993

6. National Cancer Institute: Breast cancer in younger women. Monographs of the National Cancer Institute, No. 16. Bethesda, MD, National Cancer Institute, 1994

7. National Cancer Institute: Clinical Trials of Hormone Replacement Therapy in Patients with a History of Breast Cancer. Bethesda, MD, Division of Cancer Prevention and Control, National Cancer Institute, 1993

8. The Hormone Foundation, Canadian Breast Cancer Research Initiative, National Cancer Institute of Canada, et al: Treatment of estrogen deficiency symptoms in women surviving breast cancer. J Clin Endocrinol Metab 83:1993-2000, 1998

9. Powles TJ, Hickish T, Casey S, et al: Hormone replacement after breast cancer. Lancet 342:60-61, 1993

10. Eden JA, Bush T, Nand S, et al: A case-control study of combined continuous estrogen-progestin replacement therapy among women with a personal history of breast cancer. Menopause 2:67-72, 1995

11. DiSaia PJ, Odicino F, Grosen EA, et al: Hormone replacement therapy in breast cancer. Lancet 342:1232, 1993

12. Vassilopoulou-Sellin R, Theriault R, Klein MJ: Estrogen replacement therapy in women with prior diagnosis and treatment for breast cancer. Gynecol Oncol 65:89-93, 1997

13. Peters GN, Jones SE: Estrogen replacement therapy in breast cancer patients: A time for change? Proc Am Soc Clin Oncol 15:121a, 1996 (abstr)

14. Decker D, Cox T, Burdakin I, et al: Hormone replacement therapy (HRT) in breast cancer survivors. Proc Am Soc Clin Oncol 15:136a, 1996 (abstr)

15. Gorins A, Cremieu A, Espie M, et al: Traitment hormonal substitutif de ménopause chez les femmes ayant un antécédent personnel de cancer du sein. Rev Praticien Gynécol Obstét 3:22-25, 1997

16. Bluming AZ, Waisman JR, Dosik GM, et al: Hormone replacement therapy (HRT) in women with previously treated primary breast cancer: Update III. Proc Am Soc Clin Oncol 16:131a, 1997 (abstr)

17. Marsden J, Sacks NPM: Hormone replacement therapy and breast cancer. Endocr Related Cancer 4:269-279, 1997

18. American College of Gynecology: Estrogen replacement therapy in women with previously treated breast cancer: ACOG Committee Opinion—Committee on Gynecologic Practice, Number 135-April 1994. Int J Gynaecol Obstet 45:184-188, 1994

19. Vassilopoulou-Sellin R, Klein MJ: Estrogen replacement therapy after therapy for localized breast carcinoma: Patient responses and opinions. Cancer 78:1043-1048, 1996

20. Vassilopoulou-Sellin R, Theriault RL: Randomized prospective trial of estrogen-replacement therapy in women with a history of breast cancer. J Natl Cancer Inst Monogr 16:153-159, 1994

21. Bergkvist L, Adami H, Persson I: Prognosis after breast cancer diagnosis in women exposed to estrogen and estrogen-progestogen replacement therapy. Am J Epidemiol 130:221-228, 1989

22. Stoll BA: Hormone replacement therapy in women treated for breast cancer. Eur J Cancer Clin Oncol 25:1909-1913, 1989

23. Bonnier P, Roman S, Giacalone P, et al: Clinical and biologic prognostic factors in breast cancer diagnosed during postmenopausal hormone replacement therapy. Obstet Gynecol 85:11-17, 1995

24. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy: 133 randomized trials involving 31,000recurrences and 24,000 deaths among 750,000 women—Early Breast Trialists' Collaborative Group. Lancet 339:1-15, 71-85, 1992

25. Quiet CA, Ferguson DJ, Weichselbaum RR, et al: Natural history of node-negative breast cancer: A study of 826 patients with long-term follow-up. J Clin Oncol 13:1144-1150, 1995

26. Rosen PP, Groshen S, Kinne DW, et al: Factors influencing prognosis in node-negative breast carcinoma: Analysis of 767 T1N0M0/T2N0M0 patients with long-term follow-up. J Clin Oncol 11:2090-2100, 1993

27. Saphner T, Tormey DC, Gray R: Annual hazard rates of recurrence for breast cancer after primary therapy. J Clin Oncol 14:2738-2746, 1996