Estrogen Replacement Therapy for Menopausal Women with a History of Breast Carcinoma

Results of a 5-Year, Prospective Study

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BACKGROUND. Women with a history of breast carcinoma generally have been advised to avoid estrogen replacement therapy (ERT). The validity of this approach has been scrutinized and debated in recent years, and reassessment through appropriate clinical trials has been suggested.

METHODS. The authors conducted a prospective clinical trial to assess the safety and efficacy of prolonged ERT in a group of menopausal women with localized (Stage I or Stage II) breast carcinoma and a minimum disease free interval of 2 years if estrogen receptor (ER) was negative or 10 years if ER status was unknown. For 5 years, the authors followed 77 trial participants and 222 other women with clinical and prognostic characteristics comparable to those of the trial participants. Overall, 56 women were on ERT, and 243 women were not on ERT. The association of ERT with skeletal and lipid changes was assessed in the randomized trial participants. The effect of ERT on the development of recurrent or new breast carcinoma and other carcinomas was analyzed both in the trial participants and in the overall group.

RESULTS. Patient and disease characteristics, such as tumor size, number of lymph nodes involved, ER status, menopausal status, and disease free interval were comparable for women who were on ERT and women who were not on ERT. These same parameters also were comparable for women who joined the trial and women who did not. ERT use was associated with modest lipid and skeletal benefits. The introduction of ERT did not compromise disease free survival. Two of 56 women on ERT (3.6%) developed a contralateral, new breast carcinoma. In the group that was not on ERT, 33 of 243 women (13.5%) developed new or recurrent breast carcinoma. There were no differences in the development of other carcinomas with respect to ERT.

CONCLUSIONS. ERT did not compromise disease free survival in select patients who were treated previously for localized breast carcinoma. Larger scale randomized trials are needed to confirm these findings. ***Cancer* 2002;95:1817–26.**

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Estrogen replacement therapy (ERT) is important for some women after menopause.[1–3] The skeletal, cardiovascular, and neurocognitive benefits and limitations of ERT are discussed vigorously in the literature.[4–6] Concerns that ERT increases the risk for breast carcinoma persist,[7–9] tempering enthusiasm for ERT in many postmenopausal women; prior breast carcinoma, especially, constitutes a generally accepted contraindication.[10] Most women already are menopausal at diagnosis or develop ovarian failure after chemother-

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apy; thus, the potential benefit of ERT is relevant for many women with breast carcinoma.

Information regarding the effect of ERT on breast carcinoma recurrence is encouraging but is limited to a few retrospective reviews,[11–20] prospective single-arm studies,[21–23] or randomized pilot studies.[24] Our recent prospective data[25] and published analyses by O'Meara et al.[26] and Col et al.[27] also offer optimism. The need for large, prospective, randomized studies has been emphasized,[28–39] but information is lacking. It is apparent that large trials[40] may not be launched until more safety data become available. The Boar's Head Consensus Conference statement that, even if studies suggest that estrogen is relatively safe, only a fraction of breast carcinoma survivors would accept its use[35] underscores the problem. The difficulty of enrolling large numbers of women in such randomized trials has been highlighted by the pronounced reluctance that potential participants express when they are asked to join ERT studies.[41]

We have had the opportunity to conduct a randomized, prospective clinical trial to evaluate the efficacy and safety of ERT in select patients with breast carcinoma[42] and now can report on their outcome after a minimum follow-up of 5 years. We also report the outcome of an additional cohort of women who were eligible for the trial, had comparable clinical and prognostic characteristics, but declined randomization on a clinical trial. Our findings suggest that ERT does not compromise disease free survival in these patients.

MATERIALS AND METHODS

Patient Selection

Eligibility criteria for participation in the prospective, randomized trial[42] included Stage I or Stage II breast carcinoma, a minimum disease free interval (DFI) of 2 years if estrogen receptor (ER) was negative or 10 years if ER status was unknown, diagnosis between 1974 and 1994, established menopause (amenorrhea $>$ 6 months, elevated gonadotropins, or surgical ablation), and follow-up for at least 60 months (or until disease occurrence). Patients with ER positive tumors were excluded. The primary objective was to assess the potential association of prolonged ERT with the development of recurrent or new breast carcinoma. The Institutional Review Board for the Protection of Human Subjects approved the study in 1990.

Eligible women with a history of breast carcinoma were asked to participate in the study. In keeping with the recognized risk aversion of patients with breast carcinoma regarding ERT,[41] accrual was slower than anticipated; accordingly, we stopped new patient enrollment after 100 women had joined the trial. Currently, we have completed 5 years of follow-up and have collected data for 77 women (because the controversy related to ERT safety refers to prolonged ERT exposure, participants with $<$ 5 years of follow-up or incomplete oncologic data were excluded). Another 222 eligible women who did not wish to participate in the randomized trial were followed similarly. Among trial participants, 34 women were on ERT, and 43 women were not on ERT; among nonparticipants, 22 women took ERT, as prescribed by their physicians, and 200 women did not. Overall, 56 women were on ERT, and 243 women were not on ERT. Most women were patients at The M. D. Anderson Cancer Center and were seen initially during the period 1992–1994. Among the ERT users, 30 women took ERT for $>$5 years, 20 women took ERT for 2–5 years, and 6 women took ERT for $<$ 2 years.

We monitored these patients prospectively for at least 5 years regarding the development of new or recurrent disease. Disease events within 6 months of entry (three patients with recurrent breast carcinoma in the no-ERT group) were considered preexisting conditions and were excluded. To minimize potential selection bias, we compared trial participants with nonparticipants and ERT users with the no-ERT group regarding known prognostic factors for breast carcinoma outcome (tumor size, number of lymph nodes, ER status, menopause at diagnosis, and DFI at the beginning of the observation period).

Surveillance and Evaluation of Randomized Trial Participants

After discussing the study, eligible women signed informed consent and were randomized to no treatment (no-ERT group) or to conjugated estrogen treatment (Premarin 0.625 mg; Wyeth-Ayerst Pharmaceuticals, Philadelphia, PA) on Days 1–25 of each month (ERT group). Progesterone was omitted because it may have an independent influence on the development of certain carcinomas or on the recurrence of breast carcinoma. Annual gynecologic assessment was done by the patients' gynecologic health teams. Randomization was stratified by age at the time of diagnosis (age $<$ 50 years vs. age $>$ 50 years) and ER status (negative vs. unknown). Participants were seen every 3 months for 2 years and every 6 months for an additional 3 years (the study duration was 5 years) with clinical and laboratory assessment (family history, follicle-stimulating hormone, estradiol, and lipid profile) during each visit. Bone mineral density (BMD) was measured at baseline and annually for 5 years (by dual [100/140 kVp] X-ray absorptiometry on a Hologic 4500 QDR-Elite). The patients' primary breast oncology health teams monitored breast carcinoma outcomes. Additional information on the association of ERT and qual-

TABLE 1
Comparison of Prognostic Characteristics of Randomized and Nonrandomized Participants

Characteristic	Randomized group (n = 77 participants)	Nonrandomized group (n = 222 participants)	Overall (%)	P value[a]
Tumor size (cm)				
< 1	15	33	48 (16.2)	0.31
1–2	36	127	163 (54.9)	—
2.1–5.0	24	59	83 (28.2)	—
ER status				
Negative	54	147	201 (67.2)	0.53
Unknown	23	75	98 (32.8)	—
Lymph nodes involved				
0	46	123	169 (58.3)	0.32
1–3	18	64	82 (28.3)	—
4–7	3	21	24 (8.3)	—
8–11	3	4	7 (2.4)	—
> 11	3	5	8 (2.8)	—
Menopause at diagnosis				
Premenopause	46	124	169 (56.9)	0.64
Menopause	31	97	128 (43.1)	—

ER: estrogen receptor.
[a] Chi-square test of the null hypothesis (no difference between groups).

ity of life was obtained, but this issue was beyond the scope of the current report.

Statistical Analysis

Sample size for the randomized trial was determined assuming a disease free survival (DFS) rate of 90% at 1 year for patients who were not on ERT, exponential distribution of DFS, and monthly accrual of 4 patients (total size, 160 patients who were randomized equally between the ERT group and the no-ERT group to provide 90% power to detect a decrease in DFS to 80% at 1 year for women on ERT at a one-sided significance level of 0.1). Three interim safety analyses were planned. Secondary trial objectives were changes in BMD (surrogate for skeletal benefit) and lipid profile (surrogate for cardiovascular benefit) in the ERT group compared with the no-ERT group. Each patient served as her own control. The association of ERT with these parameters was evaluated with a multivariate analysis of variance (MANOVA) and a repeated-measures analysis of variance (ANOVA).

DFS was measured from the date of randomization to the date of breast carcinoma event or last contact. For nonrandomized patients, DFS was from date of initial contact. DFS probabilities and corresponding 95% confidence intervals (95%CIs) were estimated by using the product-limit (Kaplan–Meier) method,[43] and the null hypothesis was tested using the log-rank test.[44] Estimated hazard ratios and 95%CIs were calculated using the Cox proportional hazards regression model.[45] All P values are based on two-sided tests. Statistical analyses were carried out using S-Plus 2000 software (MathSoft, Inc., Seattle, WA).

RESULTS

Patient Population

At baseline, the median age of all 299 women was 56 years (range, 38–81 years). The median age was 56 years (range, 39–74 years) for women in the ERT group and 53 years (range, 36–82) for women in the no-ERT group. The minimum DFI since diagnosis was 24 months by study design, with a median of 108 months (range, 24–283 months). The minimum duration of observation was 60 months by study design, with a median of 71 months (range, 61–128 months). All women were postmenopausal at baseline. All patients had undergone surgery with additional medical therapy or radiotherapy that varied according to clinical indications and practice standards over time. All participants were disease free after initial treatment (also by study design). There have been 35 events of new or recurrent breast carcinoma and 15 events of other malignancies during the observation period.

Clinical and Prognostic Characteristics of Patient Groups

Table 1 compares the prognostic characteristics of randomized and nonrandomized patients: There were no statistically significant differences. Table 2 compares prognostic characteristics of patients in the ERT group with the no-ERT group, regardless of randomization; again, there were no statistically significant differences (a few data points were missing in the different categories). Also, DFI at the start of the ob-

TABLE 2
Comparison of Prognostic Characteristics of Participants in the Estrogen Replacement Therapy Group and the No Estrogen Replacement Therapy Group

Characteristic	ERT group (n = 56 participants)	No ERT group (n = 243 participants)	Overall (%)	P value[a]
Tumor size (cm)				
< 1	9	38	47 (16)	0.99
1.0–2.5	30	134	164 (55)	—
> 2.5	15	67	82 (27)	—
ER status				
Negative	37	164	201 (67)	0.84
Unknown	19	79	98 (33)	—
Lymph nodes involved				
0	35	133	168 (56)	0.71
1–3	13	70	83 (28)	—
> 3	6	33	39 (13)	—
NA	2	7	9 (3)	—
Menopause at diagnosis				
Premenopause	30	143	173 (58)	0.47
Postmenopause	26	100	123 (42)	—

ERT: estrogen replacement therapy; ER: estrogen receptor; NA: not available.
[a] Chi-square test of the null hypothesis (no difference between groups).

TABLE 3
Association of Estrogen Replacement Therapy and Time to Recurrence of Breast and Other Carcinomas for Randomized Study Participants

Group	Total no.	Breast CA	Other CA	Breast CA DFS proportion		Log-rank P value	Other CA DFS proportion	
				Two years	Five years		Two years	Five years
All								
No ERT	43	4	0	1.00	0.948	0.44	1.00	1.00
Yes ERT	34	2	2	1.00	0.941	—	1.00	1.00
ER negative								
No ERT	29	3	0	1.00	0.92	0.61	1.00	1.00
Yes ERT	25	2	1	1.00	0.92	—	1.00	1.00

CA: carcinoma; DFS: disease free survival; ERT: estrogen replacement therapy; ER: estrogen receptor.

servation period was comparable for women in the ERT group (mean ± standard deviation: 8.8 ± 5.5 years) compared with women in the no-ERT group (8.3 ± 5.0 years). Accordingly, we combined clinical outcome data for the overall group of 299 patients, allowing an increase of sample size without compromising validity. The primary analysis includes carcinoma and metabolic data from the randomized trial participants.

Association of ERT and Time to Recurrence of Breast Carcinoma and Other Malignancies: Analysis for the Randomized Group Only

In the randomized group, tumor size, the number of lymph nodes, ER status, and menopausal status were not of prognostic value regarding DFS (data not shown). Table 3 summarizes the association of ERT and DFS: No differences were noted for the whole group (P = 0.44) or for patients with ER negative tumors (P = 0.61). No differences were noted for DFS from other malignancies. A Cox proportional hazards model was fit to breast carcinoma events, yielding a hazard ratio of 1.94 for the no-ERT group compared with the ERT group (not significantly different from 1.00; 95%CI, 0.35–10.63; P = 0.45). For patients with other malignancies, there were not enough events to formulate a conclusion. Figure 1 shows the Kaplan–Meier estimated survival curves for the ERT group compared with the no-ERT group: These curves indicate that there was no significant difference.

Association of ERT and Time to Recurrence of Breast Carcinoma and Other Malignancies: Analysis for the Entire Group Combined

A similar analysis was carried out for the overall group of 299 women. Again, in the overall group, tumor size,

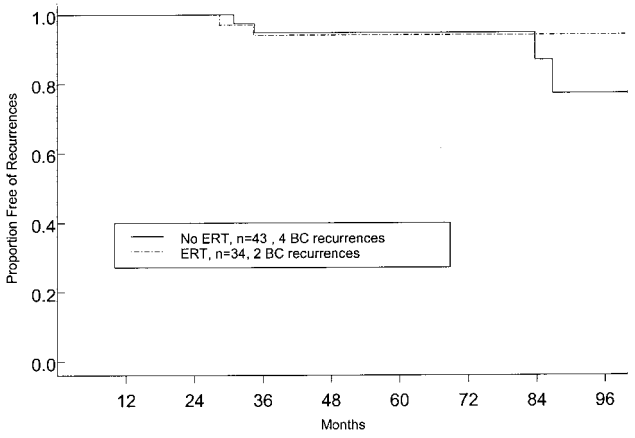

FIGURE 1. Estimated Kaplan–Meier survival curves showing the time to recurrence of breast carcinoma (BC) for the randomized group only. ERT: estrogen replacement therapy.

the number of lymph nodes, ER status, and menopausal status were not associated with DFS for patients with breast carcinoma (data not shown). Table 4 summarizes the association of ERT and DFS; ERT users were more likely to enjoy DFS ($P = 0.04$). The advantage of ERT was not significant when we analyzed the patients with ER negative tumors separately from the patients with tumors of unknown ER status. No significant association was noted for DFS from other malignancies. A Cox proportional hazards model was fit to breast carcinoma events, yielding a marginally significant hazard ratio of 4.08 for the no-ERT group compared with the ERT group (95%CI, 0.98–17.01; $P = 0.053$), indicating that women who did not receive ERT were slightly more likely to develop recurrent disease sooner than women who received ERT. For DFS from other malignancies, this odds ratio was 1.87 (95%CI, 0.41–8.47; $P = 0.42$). Figure 2 shows the Kaplan–Meier estimated survival curves for patients with breast carcinoma in the ERT group compared with the no-ERT group; again, these curves indicate that there was no significant difference.

Breast Carcinoma Events during the Observation Period

New or recurrent breast carcinoma developed in 33 patients (13.5%) in the no-ERT group. Ten women developed new breast carcinoma, 3 women developed regional disease recurrence, and 10 women developed distant metastases (1 patient died from the disease, and 2 patients were seen last with widespread, progressive disease). Two women had atypical hyperplasia, and eight women had ductal carcinoma in situ.

New breast carcinoma developed in 2 patients (3.6%) in the ERT group; both women discontinued ERT. One patient with an ER negative ductal carcinoma developed contralateral ER/progesterone receptor (PR) positive lobular carcinoma 72 months after her initial diagnosis and 27 months after starting ERT. She remains disease free 54 months after the second carcinoma. Another patient who had medullary carcinoma developed contralateral ER/PR negative ductal carcinoma 87 months after her initial diagnosis and 34 months after starting ERT. She remains disease free 36 months after the second carcinoma. There were no patients who developed recurrent breast carcinoma and no deaths from breast carcinoma.

Other malignancies developed in 12 patients who were not on ERT: Three women developed colon carcinoma; 4 women developed lung carcinoma; and 1 woman each developed leiomyosarcoma, mesothelioma, melanoma, ovarian carcinoma, and bladder carcinoma. Among women who were on ERT, three patients developed other malignancies (one woman each developed carcinoma of the colon, thyroid, and lung). One patient in each group died of cardiac or vascular complications.

The Association of ERT and Skeletal Health

The association of ERT and skeletal health was assessed by BMD measurement. BMD at the lumbar spine, femoral neck, and total hip after 2 years and 5 years was compared with BMD at baseline for the two groups (Table 5). At baseline, BMD was comparable in the two groups. When multivariate analysis was done with a one-way MANOVA testing for the effect of ERT on BMD of the spine, femoral neck, and total hip at the three time intervals, no significant effect was found. To test the effect of ERT on BMD, a repeated-measures ANOVA was done at baseline, at 2 years, and at 5 years. At 5 years, there was a significant beneficial effect of ERT in the hip ($P = 0.0001$). A benefit also was found in the no-ERT group ($P = 0.03$), perhaps reflecting supplementation with calcium or other antiresorptive agents to prevent bone loss.

Association of ERT and Lipid Profile

The impact of ERT on lipids was assessed as an intermediate end point of ERT cardiovascular benefit. Serum levels of high-density lipoprotein (HDL) and low-density lipoprotein (LDL) after 2 years and 5 years were compared with levels at baseline for the two groups (Table 6). At baseline, HDL and LDL levels were comparable. When multivariate analysis was done with one-way MANOVA testing for the effect of ERT on HDL and LDL at the three time intervals, no significant effect was found. Relative to the baseline LDL level, there was no significant change after 5 years for either group (101% $\pm$ 5% of baseline for the ERT group and 99% $\pm$ 8% of baseline for the no-ERT group). A modest improvement was noted for HDL

TABLE 4
Association of Estrogen Replacement Therapy and Time to Recurrence of Breast and Other Carcinomas for the Entire Group Combined

Group	Total no.	Breast CA	Other CA	Breast CA DFS proportion		Log-rank *P* value	Other CA DFS proportion		Log-rank *P* value
				Two years	Five years		Two years	Five years	
All									
No ERT	243	33	13	0.97	0.90	0.04	0.99	0.97	0.41
Yes ERT	56	2	2	1.00	0.96	—	1.00	1.00	—
ER negative									
No ERT	164	25	6	0.97	0.90	0.08	0.99	0.97	0.51
Yes ERT	37	2	1	1.00	0.94	—	1.00	1.00	—
ER unknown									
No ERT	79	8	7	0.99	0.95	0.17	0.98	0.96	0.60
Yes ERT	19	0	1	1.00	1.00	—	1.00	1.00	—

CA: carcinoma; DFS: disease free survival; ERT: estrogen replacement therapy; ER: estrogen receptor.

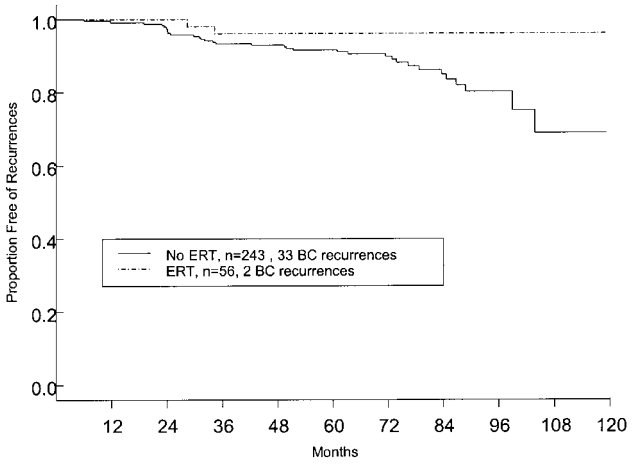

FIGURE 2. Estimated Kaplan–Meier survival curves showing the time to recurrence of breast carcinoma (BC) for the combined groups. ERT: estrogen replacement therapy.

TABLE 5
Association of Estrogen Replacement Therapy and Bone Mineral Density in Randomized Study Participants

Location	BMD		
	Baseline	Two years	Five years
Lumbar spine			
ERT[a]	−1.48 ± 1.93[b]	−1.39 ± 1.74	−1.73 ± 1.39
No ERT	−1.71 ± 1.18	−1.78 ± 1.18	−1.64 ± 1.54
Femoral neck			
ERT	−1.75 ± 1.35	−1.59 ± 1.21	−1.59 ± 0.89
No ERT	−1.84 ± 1.15	−1.89 ± 1.01	−1.31 ± 1.09
Total hip			
ERT	−1.32 ± 1.22	−1.11 ± 1.26	−1.13 ± 1.07
No ERT	−1.39 ± 1.05	−1.43 ± 1.11	−0.63 ± 1.10

BMD: bone mineral density; ERT: estrogen replacement therapy.
[a] Data from women on ERT at the time of the measurement.
[b] BMD is expressed as a T-score, which represents the number of standard deviations from the normal, young adult, mean bone density values.

(132% ± 12% of baseline for the ERT group compared with 100% ± 7% of baseline for the no-ERT group; $P = 0.027$). To test for the effect of ERT on HDL and LDL levels, a repeated-measures ANOVA also was performed at baseline, at 2 years, and at 5 years. At 5 years, HDL was significantly higher from baseline in the ERT group ($P = 0.03$). No significant lipid changes occurred in the no-ERT group.

DISCUSSION

In the current study, we address once more the challenging topic of ERT after breast carcinoma and whether ERT compromises the clinical outcome of women with a history of breast carcinoma. Our findings concur in principle with previous reports on the topic and provide a comprehensive analysis with prolonged follow-up based on our prospective, randomized clinical trial.[42]

The notion that menopause is a hormone deficiency disease that is curable and is totally preventable (with ERT)[46] is a naïve, oversimplified assumption that has been critiqued over time.[47–51] The efficacy of ERT in ameliorating menopausal symptoms and genitourinary atrophy are the clearest motives for most women who decide to begin ERT. In addition to cardiovascular and skeletal benefits, ERT may provide benefits with regard to cognitive function[6] and colorectal carcinoma.[52] Whereas alternative interventions are available for patients with different sequelae of estrogen deficiency, ERT remains the most effective remedy for menopausal symptoms and an option that can provide comprehensive benefit for women with menopausal concerns.

For women with a history of breast carcinoma, however, ERT is generally unavailable at this time based on long-standing clinical practice standards.

TABLE 6
Association of Estrogen Replacement Therapy and Lipid Profile Randomized Study Participants

	Mean ± SD		
Profile	**Baseline**	**Two years**	**Five years**
HDL levels (mg/dL)			
ERT[a]	54.9 ± 12.4	59.8 ± 13.5	65.1 ± 16.5
No ERT	58.1 ± 13.3	58.3 ± 15.1	57.0 ± 20.5
LDL levels (mg/dL)			
ERT	129.6 ± 34.1	118.8 ± 32.2	121.1 ± 30.6
No ERT	139.2 ± 38.4	43.5 ± 43.5	140.2 ± 52.4

SD: standard deviation; HDL: high-density lipoprotein; ERT: estrogen replacement therapy; LDL: low-density lipoprotein.
[a] Data from women on ERT at the time of the measurement ($P = 0.03$ for HDL at 5 years compared with baseline in the ERT group).

Increasingly, however, early detection and comprehensive therapies are improving DFS and overall survival. These women, however, experience frequent and longer estrogen deficiency: Adjuvant chemotherapy accelerates menopause, and women with prior surgical menopause are advised to stop ERT at the time they are diagnosed with breast carcinoma. Thus, a large group of relatively young women who are breast carcinoma survivors with an excellent prognosis are exposed to prolonged estrogen deficiency with its potential adverse health effects and undesirable symptoms.

The recommendation to avoid ERT derives from deep-seated concerns that ERT may reactivate occult, dormant breast carcinoma cells. The correlation between ERT and breast carcinoma has been analyzed amply in the literature and is beyond the scope of the current discussion. Direct data relating ERT with breast carcinoma recurrence, however, still are lacking. A number of recent studies suggest that ERT does not adversely affect the clinical outcome of breast carcinoma survivors (Table 7). These reports summarize information on approximately 800 patients who are largely self-selected with mixed prognostic characteristics; in these cohorts, the frequency of new or recurrent breast carcinoma varies between 0% and 19%, with an average rate of 5%. In addition, there appears to be no adverse survival impact of ERT.[17,23] O'Meara et al.[26] noted a significantly decreased total mortality in women who used ERT after breast carcinoma, including a subgroup of women who took systemic ERT for more than 1 year. Similarly, a reanalysis of published data by Col et al.[27] also found no effect of ERT on breast carcinoma recurrence. The variety of potential selection biases constitutes an inherent limitation of those reports.

Systematic, prospective data are being collected in European trials, but no results are available. The current report provides prospective results of ERT effects after a prolonged observation period (at least 5 years). Among 77 women with breast carcinoma who participated in the randomized, prospective trial, ERT had no effect on DFS. Combining the randomized group with the additional 222 women who had similar follow-up and prognostic characteristics, again, ERT had no adverse effect on DFS. If anything, a Cox proportional hazards model analysis showed a marginal benefit of ERT. ERT did not adversely affect patients with other malignancies, including patients with endometrial carcinoma.

In the ERT group, two patients (3.6%) developed new, localized lesions and were treated curatively. In the no-ERT group, breast carcinoma became a clinical problem in 13.5% of women, including the development of distant metastases. We can speculate that ERT may temper favorably the biology of breast carcinoma, consistent with evidence that women who develop breast carcinoma on ERT have better outcomes.[53–56]

Cognizant of theoretical reservations about combining data from randomized and nonrandomized cohorts, we feel that it is appropriate and important to provide all available information from the entire group of women. The randomized study participants compared with nonparticipants and women in the ERT group compared with the no-ERT group were well matched regarding known clinical prognostic factors; accordingly, the expected disease events also should be comparable. This approach permits reporting on an increased number of patients; this, coupled with the prolonged follow-up of the group, make a quantitative estimate of risk or safety possible and relevant biologically.

Nevertheless, a few important caveats are in order. The available literature indicates that the expected DFS for women with localized disease ranges between 70% and 90% within the first 10 years after diagnosis.[56–59] However, our patients in both the ERT group and the no-ERT group had fewer disease events, perhaps suggesting that they represent a cohort with a particularly good prognosis. The 1-year recurrence rate of 10% proved an overestimate of risk for the no-ERT group; assuming an observed DFS rate of 99%, the accrued sample would lack the power to detect the risk (hazard ratio, 2.1) for which the trial was designed. Thus, failure to detect a DFS difference between the ERT group and the no-ERT group may reflect limitations of statistical power rather than the biologic impact of ERT.

Reconsideration of current ERT practice standards is reflected in recent editorials and reviews,[28–39] which continue to call for large, prospective, random-

TABLE 7
Hormone Replacement Therapy after Breast Carcinoma

Study	No. of patients	ERT (months)		Overall follow-up (mos)[a]	Breast CA (new/recurring)	
		DFI	Duration		No.	%
Powles et al.[11]	35	31	15	43	2	6
Eden et al.[12]	90	60	18	84	7	8
Di Saia et al.[13]	77	24	27	59	7	9
Vassilopoulou-Sellin et al.[14]	43	84	31	144	1	2
Peters and Jones[15]	67	NA	37	94	0	0
Decker et al.[16]	61	44	26	NA	6	10
Gorins et al.[21]	28	NA	33	NA	1	4
Bluming et al.[22]	146	61	28	NA	4	3
Marsden and Sacks[24]	50	NA	6	< 6	0	0
Beckman et al.[19]	64	0	15	32	6	9
Ursic-Vrscaj and Bebar[18]	21	62	28	28	4	19
Espie et al.[20]	107	96	29	29	5	5
Total	789	51	24	58	43	5

ERT: estrogen replacement therapy; CA: carcinoma; DFI: disease free interval (since diagnosis at the time of hormone replacement initiation); NA; not available.
[a] Median or mean duration in months.

ized trials with appropriate power to address ERT safety after patients have been treated for breast carcinoma. However, both patients and physicians[35,60] continue to voice reluctance about ERT and the conduct of large clinical trials. The discussion continues, and nonestrogenic remedies are emphasized for the management of women with menopausal symptoms and the diverse sequelae of estrogen deficiency.[30,37,61–64]

The current report, albeit another small study, provides prospective data with much longer follow-up than previous series and reinforces the notion that ERT does not compromise DFS in patients with curatively treated breast carcinoma. Accordingly, our results extend previously published observations and provide additional reassurance. Larger prospective, randomized trials with appropriate statistical power clearly are very important to define the safety of ERT in this setting and, perhaps, to modify current standards of care for women with a history of treated primary breast carcinoma.

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