Cancer recurrence and mortality in women using hormone replacement therapy after breast cancer: Meta-analysis

LINDA N. MEURER, MD, MPH; AND SARAH LENA
Milwaukee, Wisconsin

KEY POINTS FOR CLINICIANS

- This meta-analysis of observational studies found no increased risk of breast cancer recurrence and a statistically significant reduction in mortality for breast cancer survivors who take hormone replacement therapy compared with those who do not.
- Because of biases inherent in the designs of these studies, randomized controlled trials are warranted.
- There is no compelling evidence to support universal withholding of estrogen from well-informed women who have survived low-stage breast cancer and who suffer from symptomatic menopause.

■ OBJECTIVES We compared the risk of cancer recurrence and all-cause mortality among users and nonusers of estrogen replacement therapy (ERT) after the diagnosis of breast cancer.

■ STUDY DESIGN This was a systematic review of original research. Eligible studies were reviewed by 2 investigators who independently extracted data from each study according to a predetermined form and assessed each study for validity on standard characteristics. Meta-analyses were performed with Review Manager 4.1 to provide a summary of relative risks of cancer recurrence and mortality.

■ POPULATION Studies included 717 subjects who used hormone replacement therapy (HRT) at some time after their diagnosis of breast cancer, as well as 2545 subjects who did not use HRT.

■ OUTCOMES MEASURED Outcomes included breast cancer recurrence and all-cause mortality.

■ RESULTS Nine independent cohort studies and one 6-month pilot randomized controlled trial were identified. Studies were of variable quality. Breast cancer survivors using ERT experienced no increase in the risk of recurrence compared with controls (relative risk, 0.72; 95% confidence interval, 0.47–1.10) and had significantly fewer deaths (3.0%) than did the nonusers (11.4%) over the combined study periods (relative risk, 0.18; 95% confidence interval, 0.10–0.31). All tests for heterogeneity were nonsignificant.

■ CONCLUSIONS Although limited by observational design, existing research does not support the universal withholding of ERT from well-informed women with a previous diagnosis of low-stage breast cancer. Long-term randomized controlled trials are needed.

■ KEY WORDS Estrogen replacement therapy, hormone replacement therapy, breast cancer, survivors, meta-analysis. *(J Fam Pract 2002; 51: 1056–1062)*

Estrogen-containing hormone replacement therapy (ERT) after menopause has been implicated as a causal factor in the development of primary breast cancer.[1,2] Fearing cancer recurrence, most physicians do not offer ERT to postmenopausal women with a history of breast cancer. However, estrogen deficiency, which is especially common in women after chemotherapy, can be associated with severe symptoms, reduced quality of life, and increased risk of osteoporosis and possibly coronary artery disease. Although there are theoretical justifications to discourage the use of ERT by women at high risk for breast cancer, there is little objective evidence that hormone replacement increases the likelihood of breast cancer recurrence or of mortality among survivors of primary breast cancer. It is difficult for clinicians and patients to make rational decisions regarding ERT in these patients, given the paucity of studies and the difficulty of interpreting the few studies available.

Several observational studies have been published on the use of estrogen and/or combined estrogen–progesterone hormone replacement therapy in women who have had breast cancer. Many of these studies have reported single-institution

From the Department of Family and Community Medicine, Medical College of Wisconsin, Milwaukee, WI. This paper was presented in part at the Society of Teachers of Family Medicine Annual Spring Meeting; April 2001; Denver, CO. The project was funded in part by a training grant from the National Cancer Institute. The authors report no competing interests. Address reprint requests to Linda N. Meurer, MD, MPH, Associate Professor, Department of Family and Community Medicine, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226. E-mail: lmeurer@mcw.edu.

series of outcomes among survivors who opted to take ERT for their menopausal symptoms. These studies tend to demonstrate rather unimpressive incidences of recurrence and mortality events. However, it is possible that such studies underestimate the risks because patients who are given ERT may represent a subgroup with a better prognosis than other patients (bias by indication). A smaller number of studies has used comparison groups and attempted to control for disease severity and other factors associated with recurrence.

We conducted a meta-analysis of studies comparing women who used ERT after the diagnosis of breast cancer with a control group of non-ERT users to determine whether ERT is associated with an increased risk of cancer recurrence or all-cause mortality among breast cancer survivors.

METHODS

Search strategy

We identified relevant studies through independent literature searches of Medline (from 1966 to August 2001) and Cancerlit (from 1986 to August 2001) with the use of OVID software and the following search terms: estrogen replacement therapy, hormone replacement therapy, breast neoplasms, neoplasm recurrence, survivors. No language restriction was imposed. A careful review of titles and abstracts was done to identify relevant articles, and for these, the full articles were retrieved for review. Bibliographies of identified studies and review articles were examined for additional citations. Medline and Cancerlit databases were also searched by the names of authors of relevant studies to identify any missed articles. The authors of large studies and experts from our institution were asked to review the reference list for completeness and to suggest sources of unpublished data.

Inclusion criteria

Studies were considered for inclusion into the meta-analysis if they met the following criteria: (1) the population studied was women with a previous diagnosis of breast cancer, (2) the risk factor considered was the use of systemic estrogen or any combination hormone replacement therapy that included estrogen, (3) the outcome measured included the recurrence of breast cancer (whether a new or recurring primary cancer) and/or mortality, and (4) the study design was a randomized controlled trial or cohort study comparing women who used ERT after their breast cancer diagnosis with a concurrent, historical, or population-based control group of women who did not. Single-arm cohort studies were retrieved and summarized qualitatively but not included in the statistical analysis. If more than 1 publication was identified which reported the same data, the study with the most recent or complete data was selected for the analysis. We independently reviewed all studies for inclusion, and any differences were resolved through consensus.

Validity assessment

All included studies were assessed for validity by 2 independent reviewers, blinded to study results, for the following characteristics: (1) prospective data collection, (2) clear subject inclusion criteria, (3) reliability of exposure, (4) similarity between exposed and unexposed groups, (5) loss to follow-up, and (6) reliability of outcome assessment. When threats to study validity were identified, attempts were made to determine whether these threats were likely to significantly influence the results of the study and to estimate the direction of the influence of these threats on the resulting data. Because baseline differences between the study groups are such an important threat to the validity of these studies, the studies were graded as higher quality and lower quality based on whether significant differences in known prognostic factors existed.

Data management and analysis

A data extraction form was created to aid consistent recording of data from all studies, and both investigators extracted data independently. Any discrepancies in data interpretation or abstraction were resolved through consensus. Study characteristics and results for single-arm cohort studies were presented descriptively. For controlled studies, data were entered as dichotomous variables into Review Manager 4.1 software, as distributed by the Cochrane Collaboration. Summary relative risk (RR) estimates were calculated by using a fixed effects model (Mantel-Haenszel method) unless the results were found to be statistically heterogeneous ($P < .1$) through the use of a Q statistic, in which case the more conservative random effects model (DerSimonian-Laird method) was used. A subanalysis was performed based on the quality ratings, with a lower rating given to studies in which the exposed and unexposed groups differed significantly on important prognostic factors such as age, tumor stage, and time since diagnosis. Funnel plots were constructed to identify possible publication bias.

RESULTS

Description of studies

The original search yielded 24 relevant reports, including 1 unpublished report (Bluming AZ, personal communication, 2000) with 2 separate studies. One of these and 12 published single-arm cohort studies[4–14] were excluded because they lacked a control group, but a summary of these studies can be found online (Table W1, available on the JFP Web site: www.jfponline.com). Twelve reports[15–25] met the inclusion criteria and provided

TABLE

Characteristics of included studies

Study	Design (matched variables, when applicable)	ERT/ controls, no.	Disease, stage included	Median DFI, mo*	Median ERT use, mo*	Median follow-up for users/ controls, mo*	Groups similar at baseline†	Recurrence	Death
Beckmann et al[25]	Cohort study; local controls	64/121	0–III	NR	33 (3–60)	37 (3–60)/ 42 (3–60)	No	Yes	Yes
Bluming et al (personal communication)	Cohort study; local controls	95/64	T1N0	60 (NR)	46 (1–88)	107 (3–400)/ 206 (17–251)	No	Yes	0
Dew et al[15]	Cohort study; local controls	167/1305	Any	36 (0–312)	19 (3–264)	NR	No	No	Yes
DiSaia et al[16]	Matched cohort; population controls (age, stage, year of diagnosis)	41/82	0–III	NR	NR	NR NR (6–114)	Yes	Yes	Yes
DiSaia et al[17]	Matched cohort; population controls (age, stage, year of diagnosis)	125/362	0–IV	46 (0–401)*	22 (NR)*	NR	Yes	No	Yes
Eden et al[18]	Matched cohort; local controls (age, year of diagnosis, DFI, nodes, tumor size)	90/180	0–IV	60 (0–300)	18 (4–144)	84 (4–360)/ 72 (4–348)	Yes	Yes	Yes
Habel et al[23]	Retrospective cohort; population sample; exposure identified through mailed survey	64/222	DCIS only	NR	24 (NR)	NR	No	Yes	No
Marsden et al[19]	RCT	51/49	0–II	40 (2–215)	6 (6)	6 (6)	Yes	Yes	0
Natrajan et al[26]	Cohort study; local controls	50/18	I–II	NR	65 (6–384)*	83 (6–384)/ 50 (6–120)*	No	Yes	Yes
Ursic-Vrscaj and Bebar[24]	Matched cohort; local controls (age, year of diagnosis, DFI, nodes, tumor size)	21/42	I–III	62 (1–180)	28 (3–72)	100 (18–234)/ 100 (18–230)	Yes	Yes	Yes
Vassilopoulou-Sellin et al[21]	Prospective cohort study; local controls	39/280	I–II	114 (24–234)	NR	40 (24–99)	Yes	Yes	0

*Values presented as mean (range).
†Based on matching or demonstrated similarity in age at diagnosis, disease stage, and DFI. Estrogen receptor status not available for most subjects, and race was not reported in any study.
0, no deaths occurred; DCIS, ductal carcinoma in situ; DFI, disease-free interval, or number of months between the diagnosis of breast cancer and the initiation of ERT; ERT, estrogen replacement therapy; NR, not reported; RCT, randomized controlled trial.

data comparing the rates of recurrence or mortality among patients who used ERT after the diagnosis of breast cancer and users vs controls. Among these studies were 8 independent cohort studies from the published literature,[15–17,20,21,24–25] one set of unpublished data from Bluming et al, and one 6-month pilot randomized controlled trial.[19] One matched cohort study[18] presented recurrence data for 90 patients and 180 controls who were later included in a larger, non-matched study reporting recurrence and mortality.[15] Another small study[22] reported only deaths from breast cancer from a data set included at least in part in another report[16] and was therefore excluded. Overall, the included studies accounted for 717 subjects who used hormone replacement therapy at some time after their diagnosis of breast cancer compared with 2545 nonusers. Characteristics of included studies are summarized in the Table.

Methodologic quality

The quality of the studies was variable. The only randomized controlled trial[19] was a 6-month pilot study, after which the allocation code was broken and patients were free to choose whether to be on treatment. Of the cohort studies, only 1 trial[21] began with an inception cohort that combined data from 62 patients who elected to be part of a randomized controlled trial with that from another 257 who declined to be randomized but chose on their own whether to take ERT.[21] One study was clearly retrospective[23]; patients with ductal carcinoma in situ were identified through a cancer registry, and their exposures and recurrences were determined through a mailed questionnaire. The remaining studies used clinic records to identify patients who had been prescribed ERT and compared those recurrence and mortality rates with those of a control group comprising the remaining clinic patients[15,18,20,24,25] or matched subjects selected from a regional cancer surveillance database.[15,16] Although the matching process controlled for some important prognostic factors (age, stage, and time since diagnosis), post-diagnosis ERT use was not recorded in the surveillance database, so these control groups may have contained patients who took ERT at some time, thereby diluting any differences that might be observed. Conversely, none of the cohort studies reported means confirming that those for whom HRT had been prescribed actually took it regularly.

Across all studies, the studied interventions included a systemic estrogen, usually in combination with progesterone unless the subject had had a hysterectomy. The mean age at diagnosis of cancer varied among studies, from 42 to 65 years. There was also wide variability among subjects between and within the studies with regard to disease-free interval (the time between diagnosis of cancer and initiating ERT), duration of ERT use, and length of follow-up (Table). A few studies matched controls to ERT users based on these variables[16–18,21] or demonstrated that the groups were comparable.[19–21] In no study were subjects matched on type of treatment, race, estrogen receptor status, smoking, or other potentially important prognostic factors. Estrogen receptor status was unavailable for a large number of patients in these studies and could not be used for comparison.

Several studies contained methodologic flaws that resulted in important differences between comparison groups. Bluming and colleagues provided an unpublished analysis of recurrences in a sample of ERT users with previous T1N0 (stage I) cancers compared with a separate data set of similar patients who did not use ERT. In that study, tumor size was not known for 62% of the control group and 36% of the ERT group. Median follow-up was shorter in the ERT group, the tumors were smaller, the diagnoses were later, and patients were more likely to have received chemotherapy. Natrajan et al[20] compared 50 ERT users with 18 nonusers who left their clinic and were followed elsewhere. ERT users were younger than the nonusers and had longer follow-up. Little information was given regarding the cancer stages of the nonusers, and this was the only study primarily using hormone pellets and combining estrogen with testosterone in most patients. Habel et al[23] included only patients with ductal carcinoma in situ in a retrospective cohort study in which exposure was ascertained by mailed survey. Only 67% responded to the survey, and no baseline data comparing the ERT users with nonusers on important prognostic factors were provided. In a study by Beckman et al,[25] users were younger and less likely than nonusers to have grade 3 cancer (16% vs 30%), although this difference was reported to be nonsignificant. Median duration of follow-up was also longer in nonusers than in users (42 vs 37 months). In an unmatched study[15] of ERT users and nonusers from the same practices in Australia, significant differences were found between groups in age, stage, and type of treatment rendered.

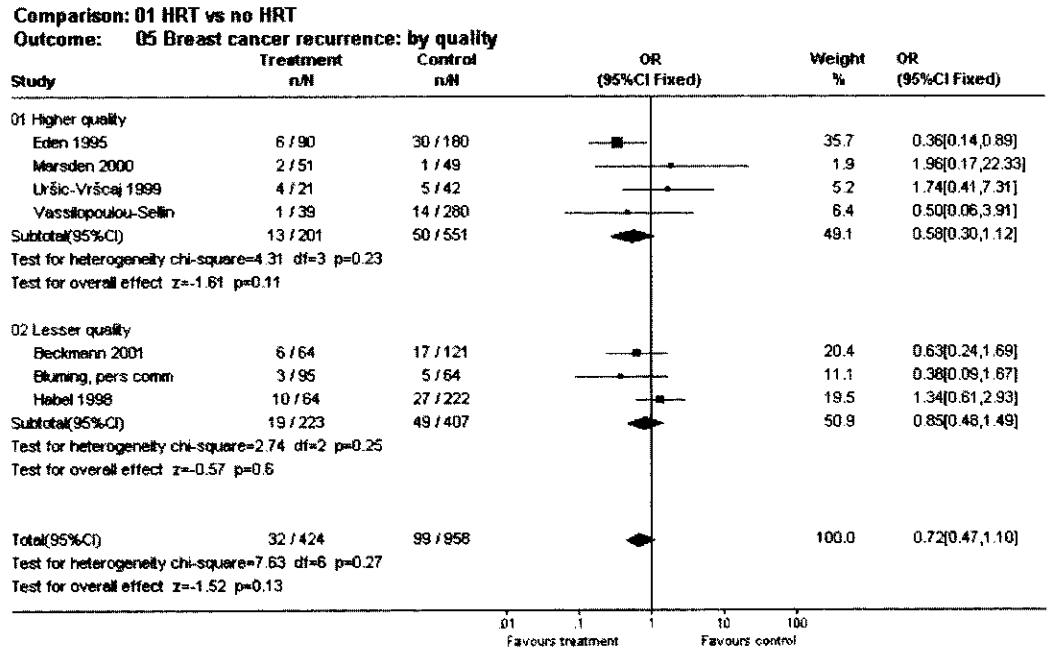
Because of the strong potential for bias due to baseline differences in risk of breast cancer recurrence, subanalyses included only those studies for which differences in important prognostic factors were not apparent.[16–19,21,24] In the case of the Australian study, a subset of the data, matched 2:1 on age, node status, tumor diameter, disease-free interval, and year of diagnosis, was found in an earlier report[18] and used in the subanalysis.

Meta-analysis results

Overall, 8 studies reported the recurrence of breast cancer as an outcome. A meta-analysis of these studies showed that breast cancer survivors using ERT experienced no increase in the risk of recurrence compared with nonusers (8.2% vs 10.2%; RR,

FIGURE 1

Graphic summary of studies on recurrence of breast cancer in ERT users vs nonusers



CI, confidence interval; ERT, estrogen replacement therapy; HRT, hormone replacement therapy; OR, odds ratio.

0.72, 95% confidence interval [CI], 0.47–1.10). Because no statistical heterogeneity was demonstrated, a fixed effects model was used. Studies were analyzed separately depending on whether patients were matched or reportedly similar on factors such as age at diagnosis, tumor stage, and disease-free interval. Results were similar (Figure 1).

Six studies were included in a combined analysis of overall mortality (Figure 2). The ERT users in these studies experienced significantly fewer deaths (3.0%) than the nonusers (11.4%) over the combined study periods (RR, 0.18; 95% CI, 0.10–0.31; numbers needed to treat = 12). Subanalyses of those studies in which groups were comparable showed similar results (RR, 0.21; 95% CI, 0.10–0.46).

Despite the variability in study designs and subjects, all tests for heterogeneity were nonsignificant. In addition, funnel plots showed no evidence of publication bias (Figure W1, available on the JFP Web site: www.jfponline.com).

All studies, controlled or not, that reported data on control of menopausal symptoms reported significant benefit with ERT.[2,7–9,11,19,25]

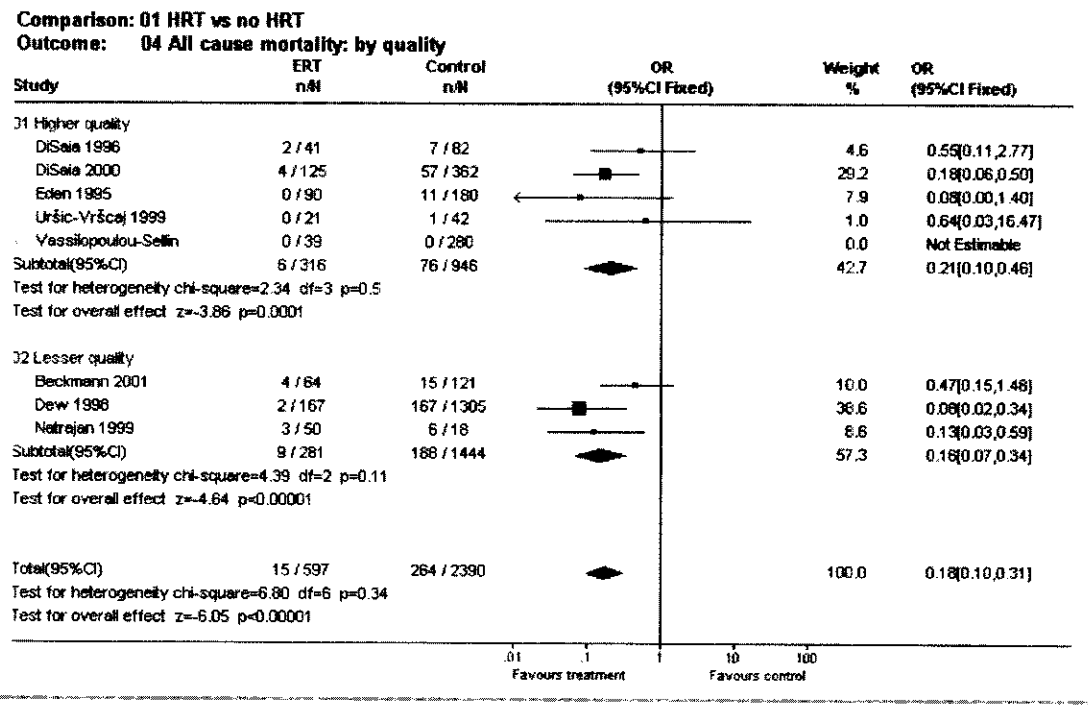
DISCUSSION

This meta-analysis of observational studies in breast cancer survivors refutes the hypothesis that ERT increases the risk of breast cancer recurrence and suggests that it may in fact reduce all-cause mortality. However, conclusions drawn from observational studies can be seriously limited by potential sources of bias. For example, the studies likely had a bias by indication. That is, patients with more aggressive prognostic factors may not have been prescribed ERT, thereby making the treatment group likely to have represented a subgroup with a lower risk of recurrence than the general population used for comparison. However, several studies matched controls on important prognostic factors, and elimination of the unmatched study did not significantly affect study results. Similarly, in the absence of randomization, unmeasured confounders may have played a role. The treatment and control groups might have differed on other predictors of mortality that were not considered, such as in a healthy user effect in which subjects on ERT may have been more informed of its benefits and followed other, more healthy lifestyle behaviors than the comparison groups. They also may have been followed more closely by their physicians than the average breast cancer survivor.

In general, the subjects of the included studies over-represented patients with lower severity of

FIGURE 2

Graphic summary of studies of total mortality among users vs nonusers of estrogen replacement therapy



Subjects in Eden et al[16] represent a matched subset of those in Dew et al.[15]CI, confidence interval; HRT, hormone replacement therapy; OR, odds ratio.

disease than the general population of breast cancer survivors. Few studies included any subjects with a history of stage IV cancer (1 case with distant metastases), and several included patients with stage II or lower. Therefore, the results of this systematic review may be best generalized only to patients with lower stage disease. In addition, although subjects used ERT for as long as 32 years, the average duration of ERT use was shorter than 4 years in all but 1 study; longer follow-up is needed to truly assess the long-term effects of ERT in these high-risk patients. Available published studies also do not provide the detail needed to explore the potential contributions of estrogen receptor status or concomitant tamoxifen use.

Our finding of no significant difference in cancer recurrence associated with ERT use among patients with breast cancer is consistent with that of another recent meta-analysis.[26] Those researchers constructed expected control groups by using the average disease free interval before starting ERT, and known nodal status distribution from several single-arm cohort studies to calculate relative risks of recurrence for these studies. This method introduces additional bias and several assumptions that may not be warranted. For instance, risk of recurrence is much higher in the first few years after treatment for primary breast cancer. Therefore, the remarkable variability in the disease-free intervals and duration of follow-up among subjects within each of these studies make it very difficult to estimate expected recurrence rates without the detailed individual data from the original studies. Despite the "within-study" and "between-study" variabilities, the results of the individual studies are quite similar.

Observational studies, although limited, do not hold the ethical problems inherent to randomized controlled trials and are especially appropriate with a treatment as controversial as estrogen in breast cancer survivors. Available studies have produced findings contrary to conventional belief and to the theory that likens ERT to "fuel on the fire" in breast cancer. Such a theory has, until recently, made it seem unethical to justify a randomized controlled trial of ERT in these patients. However, data from some of these individual studies have provided enough support that enrollment for such trials have begun.[27] Previous studies of breast cancer risk with estrogen use have suggested that more than 10 years of treatment are required to see an increase in primary breast cancer,[28] so we may

not have definitive evidence for some time. Meanwhile, there is no compelling evidence to support universal withholding of estrogen from well-informed women with symptomatic menopause, particularly among survivors of low-stage breast cancer.

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