A clinical dilemma: Estrogen replacement therapy in postmenopausal women with a background of primary breast cancer

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Summary. It is common practice to forego the prescribing of estrogen replacement therapy (ERT) for patients with a history of breast cancer. The consequences of estrogen deprivation particularly cardiovascular morbidity and osteoporosis are reviewed in the context of the potential risks of ERT in patients with prior breast cancer. The published data regarding breast cancer risks with oral contraceptive use and ERT in healthy women is reviewed. The rationale for a clinical trial of ERT in breast cancer patients, the proposed appropriate patient group and positive end points for assessing benefit of ERT in the population are presented. Lack of reliable clinical data makes ERT in breast cancer patients an unresolved clinical dilemma.

Key words: breast cancer, estrogen replacement therapy, menopause, osteoporosis, cardiovascular disease, chemotherapy effects

Introduction

It has been, and remains, common practice to forego prescribing of hormonal agents, especially estrogen, for women who have had a primary breast cancer. The concern of promoting the growth and/or dissemination of occult malignant cells has been the primary consideration for these patients. The dictum ‘primum non nocere’ has been the guiding principal of hormone use in breast cancer patients. In consideration of recent data regarding breast cancer risk, cardiovascular, cerebrovascular and mortality risks with the use of estrogen replacement therapy, it is time to re-examine the current practice of not prescribing estrogen replacement therapy (ERT) for women with a history of breast cancer. It is time to ask, are we hurting our patients because we don’t know better?

What are the potential risks and benefits of ERT for women with a history of breast cancer? What morbidity and mortality risks need to be weighed.

Background

In 1990, it is estimated that more than 150,000 women in the U.S. will be treated for newly diagnosed breast cancer. The majority of these women will be menopausal, and many premenopausal patients who will receive adjuvant chemotherapy will also become menopausal. While there is some debate about the advisability of administering chemotherapy to patients who do not have lymph node involvement, studies showing improved disease-free survival in these patients have prompted the statement that ‘chemotherapy treatments ... represent credible therapeutic options worthy of careful attention’ [1]. In practice, more and younger patients are being treated with adjuvant chemotherapy.

The benefit of adjuvant chemotherapy in terms of disease control has been greatest in premenopausal patients [2]. Although the report of the Early Breast Cancer Trialist's Collaborative Group has not clearly established benefit for chemotherapy in women greater 50 years of age, benefit from doxorubicin-containing chemotherapy has been reported for postmenopausal patients [3, 4].

As survival and disease-free survival of adjuvantly treated patients improve, the consequences of therapy need to be assessed. Ovarian dysfunction is a common complication of treatment with cytotoxic agents. Ovarian function has been shown to be affected by chemotherapy in a variety of clinical circumstances including neoplastic and non-neoplastic disease states [5–7]. Cyclophosphamide, for example, has produced ovarian failure in breast cancer patients [8]. The effects of chemotherapy on premenopausal ovarian function are reported to be dependent on dose [8, 9].

Amenorrhea and ovarian dysfunction as a result of single or multiagent adjuvant chemotherapy in premenopausal breast cancer patients have also been shown to be age-dependent in a number of studies [9–11]. In reviewing the effects of chemotherapy on gonadal function, Shilsky et al. concluded that ‘alkylating agent chemotherapy accelerates the onset of menopause, particularly in the older patient, while young patients may tolerate higher total doses before amenor-
rhea becomes irreversible' [12]. Patients treated at The University of Texas M.D. Anderson Cancer Center have been shown to develop chemotherapy-induced menopause while treated with FAC (fluorouracil, doxorubicin (Adriamycin), and cyclophosphamide) in both the adjuvant and metastatic disease setting [9, 13].

**Menopause-consequences in persons without breast cancer**

The critical factor in the development of menopause is the loss of production of ovarian estrogen. This loss leads to a secondary rise in pituitary luteinizing hormone and a reversal of the estrogen/estradiol ratio. Most patients develop changes classically associated with menopause, including vasomotor instability, hot flashes, and changes in sleeping pattern. Psychological effects including emotional lability, anxiety, and depression may be seen. Estrogen deprivation leads to vulvovaginal atrophy, which may result in sexual dysfunction and dyspareunia. In addition, masculinization of skin, hair, and body habitus may ensue. The quality of life issues associated with estrogen deficiency are inseparable from the serious morbidity/mortality issues of cardiovascular disease and osteoporosis in menopausal patients.

Cardiovascular disease remains the leading cause of death in women in the United States with approximately 350,000 deaths per year compared with approximately 40,000 deaths per year from breast cancer [14]. The risk of cardiovascular mortality increases 18-fold after menopause and is directly linked to estrogen deficiency [15]. Elevated levels of total cholesterol and low-density lipoprotein (LDL) cholesterol have been causally related to increased risk of cardiovascular disease (CVD). The Expert Panel of the National Cholesterol Education Program has classified persons with total cholesterol level of >240 mg/dl or LDL cholesterol level of >160 mg/dl as being at high risk for the development of CVD [16, 17]. In contrast, lowering LDL cholesterol levels has been reported to be of benefit in reducing morbidity and mortality from CVD. It has been suggested that each 1% reduction in cholesterol level results in approximately a 2% reduction in CVD [20–23]. While most of the data regarding LDL cholesterol levels and coronary heart disease risks derived from studies of men, the Framingham study demonstrates that LDL cholesterol elevation is a risk factor for women also [24]. The overall death rate for women in the U.S. is approximately 2000/100,000 population for myocardial infarction, 100/100,000 for breast cancer and 3/100,000 for endometrial cancer. Clearly cardiovascular disease is the greatest risk for women without a history of breast cancer.

Osteoporosis is the most common metabolic bone disease and estrogen lack is the most significant factor in the development of osteoporosis [25–27]. Oophorectomy in women younger than 45 years of age has been shown to be associated with premature loss of bone from the skeleton [28, 29]. It is estimated that in the United States 1.3 million fractures per year, including approximately 250,000 hip fractures, occur as a result of osteoporosis [30–32]. Twelve percent to 20% of persons having hip fractures die, and 25% require extended or permanent nursing care in rehabilitation facilities. The U.S. overall mortality associated with osteoporosis is projected at greater than 50,000 deaths per year [31, 32]. Studies of the risks of development of osteoporosis as a result of ovarian dysfunction associated with adjuvant chemotherapy are under way.

**Interventions to prevent menopause-associated morbidity/mortality**

Vasomotor and genitourinary symptoms of menopausal women have been treated with a variety of non-hormonal systemic medications without success. Vaginal atrophy and dryness have been treated with the use of topical lubricants and creams. No controlled clinical trials of the treatment of these complications with non-hormonal medications in breast cancer patients have been reported. While clonidine has been reported as ‘effective and safe’ in the treatment of hot flashes in breast cancer patients, many patients so treated have additional drug related symptoms including somnolence, dry mouth and hypotension [33].

Hormone replacement therapy is the most effective and specific treatment for menopausal symptoms [34–37].

In addition to vasomotor and genitourinary symptoms estrogen supplementation has been shown to have a favorable influence on high-density lipoproteins, LDL, and total cholesterol levels [38–40].

Drug treatment for atherosclerosis associated with familial hypercholesterolemia has been shown to cause regression in coronary stenotic lesions in men and women. The change in stenotic lesions is correlated with low-density lipoprotein levels [41].

A number of cohort studies of ERT have shown reduced risk of death from cardiovascular and cerebrovascular events in patients treated with estrogens [42–44].

A recent prospective study of a large number of women showed a 20% reduction in all cause mortality in women with a history of estrogen use, a 40% reduction in overall mortality in current estrogen users, and, importantly, a reduction in death due to cancer [45].

The development of osteoporosis involves loss of trabecular bone. Once destroyed, this cannot be restored. Estrogen supplementation can reduce or prevent trabecular bone loss and the development of osteoporosis [46–48] and can reduce or prevent osteoporosis-associated morbidity and mortality. Other treatment strategies for osteoporosis including calcium supplementation, exercise, and fluoride administration have not been of benefit [49–50]. A recent study suggests that fluoride may increase the fracture risk in persons with osteoporosis [51]. There are no data to
show long-term benefit or decrease in fracture incidence in women with osteoporosis treated with calcitonin [51].

Intermittent cyclical etidronate may improve bone mass and reduce fracture risks in postmenopausal osteoporosis, but has no effect on CHD risk or relief of vasomotor or genitourinary symptoms [52, 53].

Estrogen administration is effective in maintaining bone mass, in slowing loss of bone, and most important, in reducing fracture risk. In one study, only 4% of women given estrogen after oophorectomy showed loss of vertebral body height compared with 38% of control women [54]. Studies consistently show reduced incidence of hip and Colles fractures in women treated with long-term estrogen [55–57]; this is true in postmenopausal and premenopausal women [57].

Estrogen and breast disease

The association between estrogen administration and the development of mammary tumors comes, primarily, from in vitro or animal studies.

Estradiol-17β produced by graafian follicles in response to anterior pituitary secretion of follicle-stimulating hormone and luteinizing hormone, stimulates the growth of normal ductal epithelium. It has been suggested that the mechanism for the development of 'benign breast disease' is hyperestrinism. This is based on the observation that estrogen administration can induce adenosis in rats [58]. High-dose estrogen administration to castrated rats in the formation of breast cysts and epithelial proliferation [59].

In experimentally induced (7, 12-dimethylbenz[a]anthracene) mammary tumors, estrogen administration may stimulate tumor growth while estrogen deprivation from oophorectomy generally results in tumor regression [60]. In the MCF-7 breast cancer cell line, physiologic estradiol administration can stimulate cell proliferation [61]. However, the growth-promoting effects may not be a direct result of estrogen but of estrogen-regulated autocrine and paracrine growth factors [62].

The evidence linking estrogen to the development of breast cancer in humans is inferred from epidemiologic studies showing protective effects of early first pregnancy, early menopause, late menarche, and early oophorectomy and the very low risk of breast cancer in men [63].

Abnormal metabolism of estradiol has been hypothesized to be an initiator of breast cancer. Excess metabolism of endogenous estrogen through the 16α-hydroxylase pathway could lead to excess or prolonged estrogenic stimulation [63–64]. The model for this is an inbred strain of mouse that shows a high incidence of mammary tumors and high 16α-hydroxylase activity.

No long-term prospective studies have demonstrated consistently measurable hormonal changes in breast cancer patients that would distinguish them from controls [63]. The data supporting the contention that any dose of exogenous estrogen initiates the growth of breast cancer in humans or promotes the growth of human breast cancer are limited [65, 66].

Postmenopausal estrogen replacement-risks

Estrogen supplementation has been reported to be absolutely contraindicated in patients with undiagnosed abnormal uterine bleeding, pregnancy, and active thromboembolic disease or known hemostatic abnormalities associated with a hypercoaguable state.

The relative risks of developing osteoporosis with fracture-associated morbidity and mortality is greater by a factor of 3–5 than the risk of developing or dying of endometrial carcinoma as a result of estrogen supplementation [49].

Endometrial cancer

A large prospective cohort study examining the risk of endometrial cancer with estrogen or estrogen/progestin exposure concluded that estrogens alone increased 2 to 3 fold the risk of developing endometrial neoplasia [67]. Over an average follow-up period of >5 years estrogen with progestagens eliminated this risk.

Greater risk of endometrial cancer, up to 15 fold increase has been reported with unopposed prolonged estrogen administration [68]. This risk is obviated in those who have undergone hysterectomy.

The risk of breast cancer development associated with the use of hormonal agents has been a subject of controversy and conflicting literature reports. Most studies of oral contraceptive hormone use show no increased breast cancer risk, while a recent study is inconclusive [69–74]. A reduced risk of breast cancer development in users of oral contraceptives has also been suggested [69]. The majority of case/control studies indicate no change in risk of breast cancer development including treated patients with a history of breast cancer and use of oral contraceptives (OC) before first pregnancy (Table 1).

The data from these 10 studies indicate the following: seven studies showed no change in risk with OC use; 5 studies report no change with increasing duration of use with one reporting decreased breast cancer risk for women >45 years of age and one indicating increase risk for those with duration of use 4–5 years or >10 years. An explanation for the lack of increase risk for duration of use of 1–4 years and 6–9 years is not apparent. Four reports indicate no change in risk relative to age of use of OC while one supports increased breast cancer risk in users 30–34 years of age. A family history of breast cancer and risk of OC use was assessed in 3 studies and no change in breast cancer risk was observed. For those OC users with a history of benign breast disease, 3 studies showed no change in risk, 1 study reported increased risk of breast cancer and one decreased risk [69–78].

In postmenopausal women it has been reported that
Table 1  Oral contraceptive use and breast cancer risk.

<table>
<thead>
<tr>
<th>Author</th>
<th>Ref</th>
<th>Year</th>
<th>Type of Study</th>
<th># Patients/ # controls</th>
<th>Risk change Δ</th>
<th>Risk Δ benign disease</th>
<th>Risk Δ duration of use</th>
<th>Risk Δ family history</th>
<th>Risk Δ by age</th>
<th>Risk Δ use before 1st. pregnancy</th>
<th>Risk Δ by agent used</th>
<th>Risk Δ nulliparous women</th>
<th>Risk Δ by parity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paffenberger et al.</td>
<td>75</td>
<td>1977</td>
<td>Case/control</td>
<td>452/872</td>
<td>+/-</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>+/-</td>
</tr>
<tr>
<td>Kelsey et al.</td>
<td>73</td>
<td>1978</td>
<td>Case/control</td>
<td>99/99</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>NA</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Ory et al.</td>
<td>71</td>
<td>1983</td>
<td>Case/control</td>
<td>689/1077</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Rosenberg et al.</td>
<td>70</td>
<td>1984</td>
<td>Case/control</td>
<td>1191/5026</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Sattin et al.</td>
<td>69</td>
<td>1986</td>
<td>Case/control</td>
<td>471/4676</td>
<td>+/-</td>
<td>NA</td>
<td>+/-</td>
<td>NA</td>
<td>+</td>
<td>(30–34 yr. RR 3.3)</td>
<td>NA</td>
<td>+ (for parity 1)</td>
<td>NA</td>
</tr>
<tr>
<td>Kay et al.</td>
<td>72</td>
<td>1988</td>
<td>Case/control</td>
<td>239</td>
<td>+/-</td>
<td>NA</td>
<td>+</td>
<td>NA</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>+/-</td>
</tr>
<tr>
<td>Chilvers et al.</td>
<td>74</td>
<td>1989</td>
<td>Case/control</td>
<td>755/755</td>
<td>+ &gt; 48 months</td>
<td>+</td>
<td>NA</td>
<td>+</td>
<td>+/-</td>
<td>(‘high estrogen pills’)</td>
<td>- (for progesterone only pills)</td>
<td>NA</td>
<td>+/-</td>
</tr>
<tr>
<td>Vessey et al.</td>
<td>76</td>
<td>1989</td>
<td>Case/control</td>
<td>755/755</td>
<td>+ &gt; 48 months</td>
<td>+</td>
<td>NA</td>
<td>- for women &gt; 45 years</td>
<td>NA</td>
<td>NA</td>
<td>+/-</td>
<td>NA</td>
<td>+/-</td>
</tr>
<tr>
<td>Merik et al.</td>
<td>77</td>
<td>1989</td>
<td>Case/control</td>
<td>422/722</td>
<td>+</td>
<td>NA</td>
<td>+</td>
<td>NA</td>
<td>+</td>
<td>NA</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Murray et al.</td>
<td>78</td>
<td>1989</td>
<td>Case/control</td>
<td>4750/4754</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>NA</td>
<td>+/-</td>
</tr>
</tbody>
</table>

Risk Δ +: increased risk; +/-: no change; -: decreased risk; NA: not available.
ERT is associated with an increased relative risk for the development of breast cancer that is related to the dose and duration of estrogen administration; the risk was seen after natural menopause and in women who developed ‘benign breast disease’ after starting estrogen therapy [79-81]. It has also been reported that there is no increased relative risk from ERT in women with surgical menopause, in women with or without intact ovaries, in women with benign breast disease or family history of breast cancer, or in women treated with conjugated estrogens, and that there is no apparent estrogen dose response or duration of treatment effect indicating any increased relative risk [82-87]. Importantly a meta-analysis has not shown an increased risk of development of breast cancer in women treated with estrogen replacement therapy [82].

A review of twelve case control and prospective studies (Table 2) can be summarized as follows: increased risk of breast cancer, two studies; no change in breast cancer risk, 5 studies; decreased breast cancer risk, one study. One study reported a decreased risk on first analysis but increased risk in patients with surgical oophorectomy [80-85, 87, 88, 90-93]. The meta-analysis suggested there may be a dose related increase in breast cancer risk for women treated with >0.625 mg/day of conjugated estrogens [88].

All of these studies for oral contraceptive use and hormone replacement therapy have reviewed women without an antecedent history of breast cancer. Whether the use of supplemental low-dose ERT affects the risk of recurrence or development of metastases in postmenopausal breast cancer patients is unknown.

The conclusion of a recent special topic conference regarding ERT was that an increased risk of breast cancer associated with postmenopausal estrogen use has not been proved and that previous breast cancer should be considered a relative contraindication to the administration of otherwise indicated estrogen administration [48]. In experiments of nature in which breast cancer patients have become pregnant after surgery with or without radiation therapy or systemic adjuvant chemotherapy, there appears to be no increased risk of recurrence or death from breast cancer [94, 95]. There is no conclusive evidence that pregnancy associated breast cancer has an increased risk of metastases and death [95].

Authors providing ‘cost effective’ analysis of hormone replacement therapy have judged treatment to be ‘cost effective’ [96-98]. A net reduction in mortality suggested by one analysis has been supported by the prospective study of Henderson et al. in which a 40% reduction in overall mortality was observed for ERT [45].
Patient selection for a trial of ERT in patients with a background of primary breast cancer— one perspective

There are no data to show that estrogens are de novo carcinogens in humans, however there is the theoretical possibility of stimulating the growth of extant but subclinical metastases; therefore, patients at higher risk of having occult metastases would seem to have a greater risk of accelerated cancer growth and earlier development of clinically apparent metastases from ERT.

In the metastatic disease setting the level of ER and PR positively correlate with response to endocrine therapy [99, 100].

While a number of studies have shown that primary breast cancers which are ER negative are more likely to have recurrence and metastases, these tumors are less likely to be hormone dependent for growth and/or proliferation [101, 102] and intuitively less likely to have occult metastatic disease stimulated or disseminated by ERT.

Patients with stage I breast cancer are expected to have an approximately 90% disease-free survival rate at 5 years after diagnosis [103]. Recent adjuvant chemotherapy trials for node-negative stage I and II disease have shown a 77–84% disease free survival rate at 4 years’ follow-up [104-106]. Rosen et al. have reported 78–91% freedom from disease at 10 years of follow-up [107]. Patients with stage I breast cancer are, therefore, the lowest risk group to have occult metastases of patients with a background of breast cancer.

Nearly all patients who develop metastasis do so without exogenous estrogen exposure at either physiologic or pharmacologic levels. Some clinical trials in which ovarian ablation has been tried in order to eliminate physiologic estrogen levels in premenopausal women with breast cancer have not shown beneficial effects on survival or recurrence rates [108, 109]. A subsequent overview analysis of pooled data from randomized trials of ovarian ablation is consistent with reduced mortality from breast cancer and decreased recurrence in women less than 50 years of age [110]. Whether physiologic estrogen levels have a deleterious effect on survival or recurrence rate in premenopausal women with a background of primary breast cancer needs further study in randomized clinical trials.

Assessing benefit of ERT in women with a background of breast cancer

Osteoporosis

Measurements of bone mineral density (BMD) can predict fracture risk. The most accurate single technique for measurement of BMD is quantitative digital radiography (QDR) [111]. This technique is similar to dual photon absorptiometry but uses an x-ray source rather than gadolinium. The precision error with QDR is <1% at a radiation exposure of approximately 3 mrad/scan.

Fracture risk correlates with declining bone mass with BMD <0.85 g/cm² considered high risk and >1.0 g/cm² low risk [112]. A reduction of bone mass of 0.1 g/cm² has been reported to increase the non-spine fracture risk 1.5 to 2.2 times [113]. The 8 year probability of any non-spine fracture for a BMD <0.6 g/cm may be as high as 80% [113].

At a BMD of 0.80–0.89 g/cm², the intertrochanteric fracture incidence in women 35 years of age has been reported to be 1.4 per 1,000 person-years and for cervical femoral fractures 2.9 per 1,000 person-years. These incidence figures rise to 16.6 and 8.3 for a BMD of <0.60 g/cm² and decrease to 0.4 and 1.2 for a BMD >0.90 [114].

Sixteen percent of women 35–44 years of age and 30% of women 45–54 years of age may have a BMD of <1.0 g/cm² [114]. Maintaining a BMD of >1.0 g/m² would be a reasonable goal of ERT. The postmenopausal bone loss may be as high as 2–5% per year; therefore, 5 years after menopause, ERT-treated patients may be expected to have a 10–25% greater BMD than untreated patients [115].

Cardiovascular disease

The prevalence of high blood cholesterol (>240 mg/dl) increases with age in white and black women (Table 3) [116].

In addition to direct enumeration of morbid cardiovascular events – acute myocardial infarction, new-onset angina pectoris, congestive heart failure, and cerebrovascular thrombotic infarction-cardiovascular benefit can be assessed by indirect measures.

If more than 90% of women 35–44 years of age and/or more than 70% of women 45–54 years of age treated with ERT maintain total cholesterol levels below 240 mg/dl, the ERT therapy can be considered beneficial.

Lovastatin and probucol, two FDA-approved cholesterol-lowering agents, have been shown to reduce cholesterol 10–27% in treated patients. This is projected to lower CVD morbidity and mortality by up to 60%.

Patients with stage I disease 2 years post diagnosis are least likely, compared to other breast cancer patients, to have occult metastases. Patients with ER negative tumors are least likely to have stimulation of occult disease by estrogen administration. These patients would seem to be lowest risks and potentially to have the greatest benefit from ERT.

<table>
<thead>
<tr>
<th>Table 3. Blood cholesterol increases with age.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>35-44</td>
</tr>
<tr>
<td>45-54</td>
</tr>
<tr>
<td>55-64</td>
</tr>
</tbody>
</table>

Ref. 81.
In addition to assessing fracture incidence and cardiovascular and cerebrovascular events, indirect measures of benefit can be determined as previously mentioned. A number of quality of life assessments are available, and although none have been specifically designed to assess post menopausal symptoms, signs, and quality of life, such assessments are being developed [117].

An early stopping rule based on observed differences in benefit can be used to safeguard patients treated with placebo or ERT.

A clinical trial emphasizing the positive beneficial effects of ERT in patients with a background of primary breast cancer is needed, if not, in ten or fifteen years we will not know if we are helping or hurting our patients by denying them estrogen replacement therapy.

**ERT in women with background of breast cancer**

Tamoxifen, an effective therapy for some breast cancer patients in both the adjuvant and metastatic disease setting, has been reported to have beneficial effect on lipids and bone loss in treated women [118, 119].

Tamoxifen chemo prevention trials have been proposed for women at high risk of breast cancer development [120].

The control arm proposed has been a placebo, however this has been questioned on the basis that ERT may be the best available therapy [121].

No controlled, prospective studies have addressed the risks versus benefits of ERT in women with a background of cancer. Because of the potential for real benefit in terms of quality of life, reduction in cardiovascular morbidity and mortality, and reduction of the morbidity and mortality associated with osteoporosis by postmenopausal administration of estrogen and because of the lack of any available data regarding estrogen use in this setting, a prospective, randomized, controlled trial would help resolve the clinical dilemma of ERT for women with a background of breast cancer.

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