**Hormone Replacement in Women with a History of Breast Cancer**

Kathleen I. Pritchard

*The Oncologist* 2001, 6:353-362.
doi: 10.1634/theoncologist.6-4-353

# Hormone Replacement in Women with a History of Breast Cancer

**KATHLEEN I. PRITCHARD**

Toronto-Sunnybrook Regional Cancer Centre and The University of Toronto, Toronto, Ontario, Canada

**Key Words.** *Breast cancer · Hormone replacement therapy · Estrogen · Progesterone*

## ABSTRACT

**Estrogen used alone (estrogen replacement therapy [ERT]) or with the addition of progesterone (hormone replacement therapy [HRT]) is known to be effective in reducing menopausal symptoms including hot flashes, vaginal dryness and urinary symptoms. It has been traditionally contraindicated, however, in women with a previous diagnosis of breast cancer because of fear that it may increase the risk of recurrence. There are considerable basic scientific data but little methodologically strong observational data and none from randomized studies concerning the use of ERT in women with a prior diagnosis of breast cancer. From our knowledge of the physiology of breast cancer, however, estrogen and/or progestational agents should be used with caution in women with a previous diagnosis of breast cancer. There are currently many alternatives to ERT/HRT in the prevention of menopausal symptoms such as vitamin E, clonidine and selective serotonin reuptake inhibitor antidepressants such as venlafaxine. There are also a variety of other approaches to the prevention of osteoporosis and cardiovascular disease including bisphosphonates, diet, and exercise; and diet, exercise, and statins, respectively. Other suggested beneficial effects of estrogen such as colon cancer prevention can be approached by the use of aspirin or the non-steroidals. Several trials of ERT/HRT used for 2 years versus no therapy in menopausal women with a previous diagnosis of breast cancer are ongoing in Europe and Britain, and should give us stronger data as to the role of HRT in this setting.** ***The Oncologist*** *2001;6:353-362*

## INTRODUCTION

In evaluating the use of estrogen/hormone replacement therapy (ERT/HRT) in women with a prior diagnosis of breast cancer, it is important to consider: A) the aims of ERT/HRT in general; B) the alternatives by which the goals of ERT/HRT might be achieved, and C) the safety of ERT/HRT in healthy women and women with a previous diagnosis of breast cancer.

## MENOPAUSAL PHYSIOLOGY

Menopause occurs when ovaries stop secreting estradiol. Estradiol is replaced by estrone, a less active estrogen produced by conversion from androstenedione. Serum follicle-stimulating hormone and luteinizing hormone levels increase without the usual positive feedback of estradiol production. Hot flashes, vaginal dryness, and urinary symptoms occur in most women and result in a measurable decrease in quality of life [1]. With decreased levels of estrogen, bone turnover increases and the balance of bone resorption to formation tips [2]. Menopause is also linked to cardiovascular health. In the Nurses Health Study [3], women who underwent bilateral oophorectomy without ERT had a significant increase in cardiovascular disease (CVD). Other changes including skin and hair changes, mood changes and reduction in cognitive function are often attributed to menopause but may be less clearly associated.

## ERT/HRT IN TREATMENT OF MENOPAUSAL SYMPTOMS

ERT is known to be effective for control of hot flashes [1]. Oral medroxyprogesterone is also superior to placebo in controlling vasomotor symptoms [4]. Transdermal estradiol and norethisterone acetate have been shown to improve quality of life in postmenopausal women after 3 months of treatment [5]. Thus, symptom relief can be achieved by estrogen with or without a progestational agent. Progesterone alone may have some of the same benefits. There have been no

*Correspondence: Kathleen I. Pritchard, M.D., Toronto-Sunnybrook Regional Cancer Centre, 2075 Bayview Avenue, Toronto, Ontario M4V 1H6 Canada. Telephone: 416-480-4616; Fax: 416-480-6002; e-mail: kathy.pritchard@tsrcc.on.ca* *Received November 2, 2000; accepted for publication May 10, 2001.* 

direct comparisons of progesterone to estrogen in terms of vasomotor symptom control or overall quality of life.

## Long-Term Positive Effects of ERT/HRT

### Osteoporosis

ERT is now approved in a variety of countries for osteoporosis prevention and has been clearly shown to be effective in maintaining or increasing bone density and preventing fracture whether given transdermally or orally, immediately after menopause or later [6, 7].

### Cardiovascular

The role of estrogen in CVD is less clear because most studies are observational rather than interventional. It is known that estrogen with or without progesterone increases high density lipoprotein (HDL) cholesterol and decreases low density lipoprotein (LDL) cholesterol [8, 9], but this is believed to represent only part of its action. Estrogen also has other effects on the cardiovascular system including direct action on vessel walls, specific effects on the myocardium [10] and effects on platelets and other coagulation factors. One randomized trial has shown an effect of estrogen alone or with a variety of progestationals in increasing HDL and reducing LDL in women over a 3-year period compared to a placebo control. This trial was not powered to examine cardiovascular end points, however [11].

Investigators have commonly inferred reductions in CVD events of the order of 40% from case-control and cohort study results [12] for HRT users compared to nonusers. Because these are observational studies, however, patient and physician selection factors may result in more healthy women being the women who receive ERT. A recent meta-analysis of coronary heart disease (CHD) end points in 22 available randomized trials which were primarily designed to study other outcomes in 4,124 postmenopausal women found no effect of HRT on CHD events (odds radio = 1.39; 95% confidence intervals = 0.48 to 3.95) [13]. The only published randomized trial of ERT/HRT with CHD events as a primary end point, the Heart and Estrogen/Progesterone Replacement Study (HERS), a randomized trial of estrogen plus progestin for secondary prevention of CHD in postmenopausal women, showed that women started on such HRT shortly after a cardiac event were more likely to suffer a second cardiac event over the next year. As these patients were followed further, however, those randomized to receive HRT were less likely to suffer a second cardiac event in years 4 and 5 of follow-up, so that there was overall no significant difference in cardiac morbidity in those randomized to HRT or placebo [14]. Since this randomized trial showed early results that are opposite to those expected based on observational data, there has been some reexamination of the assumption that the results of observational studies in this area will be duplicated in randomized trials. The Women's Health Initiative (WHI) Study comparing ERT/HRT to placebo in over 25,000 postmenopausal women is only part way through its accrual [15]. This trial will provide the first randomized evidence of ERT/HRT influence on primary CVD end points and overall mortality.

### Alzheimer's Disease and Cognitive Function

Several observational studies have suggested a relationship between ERT/HRT and improved cognitive function or reduced risk of Alzheimer's disease [16]. These studies may also be subject to selection bias. However, the recently published Alzheimer's Disease Cooperative Study of *Mulnard* and coworkers, which randomized 97 women with mild to moderate Alzheimer's disease to low-dose (0.625 mg) or high-dose (1.25 mg) estrogen or placebo daily clearly showed no such effect. After 1 year the average score on the 7-point Clinical Global Impression of Change scale for women receiving estrogen was 5.1 compared with 5.0 for women taking placebo. There was no significant difference between the groups in measures of mood, memory, attention, language skills, motor function, or activities of daily living [17]. The authors feel that although these results are clearly negative, they relate to only the specific group of women already 75 years of age and having Alzheimer's. It is still possible that estrogen can improve cognition in women in mid-life or in older women without Alzheimer's disease. Currently the influence of ERT/HRT on memory and mental function is undergoing prospective evaluation in a randomized trial in postmenopausal women aged 65-79 in the WHI Memory Study [15]. Once again however, results will not be available for 5 or 6 years.

### Colon Cancer

It has also been demonstrated, in a series of observational studies, that the risk of colon cancer is considerably lower in association with the use of ERT/HRT. A relative risk of as low as 0.5 in these studies would seem to suggest a real association [18]. Colon cancer incidence will be one of the outcomes measured in the WHI study.

## Alternatives

It is important to understand that there are alternatives to the use of ERT/HRT.

### Estrogen Deficiency Symptoms

Estrogen deficiency symptoms can be managed by a variety of alternatives [19, 20]. KY Jelly and Replens can significantly reduce vaginal dryness and local menopausal symptoms [21, 22]. Other approaches for persistant local

symptoms include vaginal estrogen creams and Estring [23], which are, however, known to be associated with vaginal absorption of estrogen to levels which may, in some cases, be comparable to those achieved with oral use [24]. Estring tends to provide more consistent local effects with lower systemic absorption than the use of creams. Hot flashes can be treated with a variety of nonhormonal therapies.

Because of the perceived unacceptability of ERT/HRT in women with a previous diagnosis of breast cancer, the Mayo Clinic and North Central Cancer Treatment Group (NCCTG) have conducted a series of clinical trials involving over 650 cancer survivors to look at various methods for alleviating hot flashes. In this series of clinical trials [25-28], the effect of a placebo on hot flashes is well illustrated, demonstrating that it causes a relatively consistent 20%-25% reduction in hot flashes over a 4-week period. It is not clear how much of this is actual placebo effect versus the natural history of hot flashes to diminish with time. This placebo effect needs to be taken into consideration, however, when evaluating new agents and understanding anecdotal experiences.

The NCCTG recently completed a placebo-controlled trial looking at a soy phytoestrogen preparation. The magnitude of interest in this compound for this symptom is illustrated by noting that 180 patients were entered on this clinical trial over a 2-month time period. Unfortunately there was no suggestion that soy protein significantly reduced the severity or frequency of hot flashes in comparison to placebo. At study completion, patients preferred the soy product 33% of the time, the placebo 31% of the time, and neither substance 31% of the time [29].

The NCCTG also recently completed a placebo-controlled trial of vitamin E 800 I.U. per day [27]. This clinical trial did demonstrate that vitamin E was able to statistically significantly decrease hot flashes over placebo. However, this hot flash reduction amounted to one hot flash per person per day. The vitamin E was well tolerated in this clinical trial.

Another NCCTG placebo-controlled hot flash trial demonstrated that clonidine could reduce hot flashes by approximately 15% more than placebo [25]. Nonetheless, in this clinical trial, clonidine was associated with statistically significantly more toxicity and patients did not prefer it over placebo at study end.

The further NCCTG hot flash trial evaluated a low-dose of megestrol acetate compared to a placebo [26]. This trial demonstrated a hot flash reduction of approximately 80% with megestrol acetate. The therapy was well tolerated in this short-term double-blind, crossover clinical trial and women preferred megestrol acetate significantly more than placebo. A subsequent investigation suggested that megestrol acetate continues to control hot flashes for up to 3 years of therapy [30]. Most women who continued to use megestrol acetate were able to utilize a dose of ≤20 mg per day with effective control of hot flashes.

A pilot trial also conducted at the Mayo Clinic suggested that a very low dose of the relatively new antidepressant, venlafaxine (Effexor), was able to decrease hot flashes by approximately 50% [28]. This low dose of venlafaxine appeared to be relatively well tolerated overall. Anecdotal information has suggested that other selective serotonin reuptake inhibitors (SSRIs) also can decrease hot flashes, leading to a number of other ongoing clinical trials. A placebo-controlled dose-finding clinical trial is in development in the NCCTG to more definitively determine the efficacy and potential toxicity of venlafaxine for hot flashes in breast cancer survivors.

Thus, depending on hot flash severity, patient preferences, patient willingness to undertake theoretical risk, and physician prejudices, there are a number of options. Vitamin E can be utilized, as it statistically significantly decreases hot flashes. This medication is inexpensive, nontoxic, and readily available. It would allow a patient to get the well-described placebo effect and maybe a bit more. Nonetheless, vitamin E has limited efficacy. Clonidine is an option that some physicians utilize given the information that it can decrease hot flashes. The demonstrated increase in toxicity, however, needs to be factored into the decision as to whether to utilize this in clinical practice. Given the promising preliminary information described above, low doses of venlafaxine are reasonable to try, pending results from randomized placebo-controlled clinical trials. A daily dose of 37.5 mg in a sustained release preparation appears appropriate. Doubling of this dose may provide additional benefit (anecdotal information). The role of a variety of other SSRIs is still being explored. Other compounds such as black cohash and Bellergal®, have been utilized, but these have not undergone placebo-controlled trials to illustrate benefit and toxicities.

Lastly, the use of megestrol acetate for controlling hot flashes can be considered. Megestrol acetate appears to decrease hot flashes as well as does estrogen, at least judged by cross-study comparisons. Many physicians and patients, however, perceive a real risk from using low doses of progesterone in both inducing primary breast cancer in well women and inducing recurrence in breast cancer survivors, since many animal and in vitro models show that progestationals may increase or accelerate breast cancer development and/or progression, and since progesterone is clearly linked with breast cancer etiology in women. As for estrogen, there are no good data to date to demonstrate whether low doses of megestrol acetate used in women with a previous diagnosis of breast cancer increase or decrease the risk of recurrence, or have no effect. Once again, large randomized trials would

be required to clarify the safety of this approach. Thus progestationals should probably be regarded with the same degree of caution as estrogen in the setting of a previous diagnosis of breast cancer.

### Osteoporosis

Osteoporosis can now be prevented and treated with a number of approaches that do not involve estrogen or progesterone. In addition to recommendations for diet, exercise and calcium supplementation, a wide array of bisphosphonates including didronel, alendronate, clodronate, pamidronate, and residronate are now known to inhibit bone absorption and normalize bone turnover. Alendronate has been studied in large randomized trials and found to improve bone density and reduce fractures [31] in women without breast cancer. Clodronate reduces chemotherapy-induced bone loss in patients with primary breast cancer [32], while residronate also prevents cortical and trabecular bone loss in women with breast cancer who have gone through chemotherapy-induced menopause [33]. In addition, clodronate [34] and pamidronate [35] have significantly reduced skeletal complications and perhaps the development of bone metastases [34, 36] in breast cancer patients. Thus, bisphosphonates clearly provide an alternative for osteoporosis prevention in well women as well as in those with a previous diagnosis of breast cancer.

Tamoxifen also preserves bone density and reduces fractures in postmenopausal women [37, 38], as do a variety of newer selective estrogen receptor modulators (SERMs). Tamoxifen is, however, known to cause a small but significant increase in endometrial cancer and in the risk of deep vein thrombosis (DVT). Raloxifene is one of the newer SERMs which has been recently approved for the treatment and prevention of osteoporosis. It provides somewhat less beneficial effect on bone density than HRT, however, and does not relieve menopausal symptoms [39]. In fact it produces hot flashes, with an incidence similar to that seen with tamoxifen. It does, however, favorably influence total and HDL lipid profiles [40] in a fashion similar to that seen with tamoxifen. Recent follow-up from over 12,000 postmenopausal women randomized to raloxifene versus placebo has also suggested a significantly lower risk of breast cancer in raloxifene users [41, 42]. These data must be interpreted with caution, however, since it was gained from studies in which incidence of breast cancer was not a primary end point. Raloxifene is associated with an increased incidence of DVT similar to that seen with tamoxifen. Preclinical data strongly suggest that raloxifene is not as likely as tamoxifen to cause endometrial cancer, but there are as yet insufficient clinical data to draw a certain conclusion in this regard. A large randomized trial of raloxifene versus tamoxifen as prevention for breast cancer (the National Surgical Breast and Bowel Project STAR trial) is ongoing and will provide considerable additional information on all of these outcomes. It should also be remembered that diet and exercise, and appropriate calcium intake are important factors in the prevention of osteoporosis [43, 44].

### Cardiovascular Disease

Similarly CVD can be affected by a variety of other approaches including diet [45], tamoxifen or other SERMS, exercise, hypertension, smoking cessation, and the statins which may reduce total and LDL cholesterol and significantly reduce CVD events [46, 47].

### Colon Cancer

Other drugs such as acetylsalicylic acid and nonsteroidal anti-inflammatory drugs, which are without any adverse risk in terms of breast cancer, have also been suggested to prevent colon cancer [48].

### Alzheimer's Disease

Drugs or strategies to prevent Alzheimer's and cognitive deterioration are still being sought.

## Long-Term Negative Effects of ERT/HRT

### Breast Cancer

In healthy women, these positive effects associated with ERT/HRT may, to some extent, be balanced by what is now a fairly well-documented increase in the risk of development of breast cancer in women receiving ERT/HRT. More than 50 case-control and cohort studies of this subject have been carried out. Initially, the results seemed conflicting, but with longer use of ERT/HRT, and the use of meta-analysis to examine these results, it has become clear that there is probably a relative risk of 1.3 or 1.4 associated with ERT/HRT use, particularly if the use is long-term. The most recent collaborative analysis of data from 51 epidemiologic studies of 52,000 women with breast cancer and 108,000 women without breast cancer reported a 1.31 relative risk for long-term HRT users [49].

There has been considerable uncertainty about the role of the addition of progesterone to estrogen in breast cancer risk. Two early studies suggested that the addition of progesterone might reduce breast cancer risk [50, 51], but these studies were small and did not adequately control for confounding. Reliable data on the effects of long-term use of combination therapy have only recently become available [52]. These newer studies provide firm evidence that the addition of progestin to estrogen does not reduce the risk of breast cancer and suggest that the risk is actually increased [49, 53-59]. In the collaborative analysis of epidemiologic studies described above, among current or recent hormone

users, the risk of breast cancer was 53% higher for combination therapy and 34% higher for estrogen alone compared with no hormone use [49]. Since the publication of that meta-analysis, at least four subsequent studies have further explained this matter. These important trials are summarized in Table 1. Once again, all of these studies are observational and subject to the associated risks of bias. Until the results of randomized studies such as WHI are available, however, one must continue to assume that well women receiving ERT/HRT have a small increased risk of developing breast cancer, and that progesterone appears to increase this risk.

### Thromboembolic Events

The use of HRT and the development of DVT and pulmonary embolism are clearly related. Using case-control and cohort study designs, a 200%-300% increase in thromboembolic events in populations receiving ERT/HRT has been identified [57, 58]. The recent HERS prospective randomized trial described above has confirmed a comparable magnitude of increased thromboembolic risk for HRT [59]. Transdermal or vaginal HRT which avoids an estrogenic first-pass effect may avoid this risk.

## Effects on Mammographic Screening

In addition, there is concern associated with the use of HRT in healthy women and breast cancer patients receiving breast-sparing procedures, since there are increasing data showing that ERT/HRT increases breast density [60, 61], making the diagnosis of recurrence or new breast cancer more difficult.

## Use of ERT/HRT in Women with a Previous Diagnosis of Breast Cancer

The use of ERT/HRT has long been considered contraindicated in women with a previous diagnosis of breast cancer. Our understanding of the basic biology of breast cancer would suggest that estrogen contributes to its development, and may contribute to recurrence after primary therapy for early disease. There are also considerable data to suggest that progesterone may further increase the risk of developing breast cancer and/or the risk of disease recurrence.

There are many animal and in vitro models in which the development of breast cancer is estrogen-dependent. Virtually every mouse mammary tumor model and mouse xenograft model, as well as many in vitro cell lines, are dependent on estrogen for their growth and spread. Animal and in vitro data concerning progesterone are less conclusive. There are some models in which progesterone has a disease-differentiating effect, while in others it supports breast cancer growth. Some investigators have suggested that estrogen and progesterone may have more of an effect in the development of breast cancer than in its recurrence or metastases [62]. It is well known, however, from the recent Oxford meta-analysis of ovarian ablation in premenopausal women with breast cancer, that ovarian ablation in women with breast cancer results in a significant reduction in recurrence and death [63]. Furthermore, it is felt that the enhanced effects of adjuvant chemotherapy in premenopausal women may in part relate to the induction of ovarian ablation by the cytotoxic drugs involved. There are also, as outlined above, considerable observational data in women suggesting that estrogen and probably progesterone are real contributors to an increased risk of the development of breast cancer.

On the other hand, a large number of lower risk women who are now completing chemotherapy will live for a long time, and are therefore potential candidates for prevention of both long and short-term complications of menopause with ERT/HRT. Patient acceptance of such a strategy is uncertain. In a survey of patient attitudes, *Vassilopoulou-Sellin* and *Zolinski* [64] randomly selected 224 women with breast cancer to respond to questions concerning menopause, symptoms related to estrogen deficiency, concerns about osteoporosis or heart disease, and attitudes and perception about ERT. At the time of completion of the survey, 77% were postmenopausal. Of those, 8% had taken ERT at some point subsequent to their cancer diagnosis. Seventy-eight percent were afraid that ERT might precipitate a cancer recurrence, but many were also concerned about the risks of osteoporosis (70%) and heart disease (72%). Forty-four percent of menopausal women indicated

**Table 1.** Recent observational studies of the use of estrogen with or without progesterone in healthy menopausal women

| Author | Design | Increased risk of breast cancer/year of use | |
|---|---|---|---|
| | | Estrogen alone | Estrogen plus progesterone |
| Nurse's cohort study [53] | Cohort | 3.3% | 9.0% |
| Swedish [66] | Cohort | 0.0% | 11.7% |
| *Schairer* [55] | Cohort | 1.0% | 8.0% |
| *Ross* [56] | Case/control | 1.0% | 4.0% |

**Table 2.** Case series and case-control studies of women treated with ERT/HRT following a diagnosis of breast cancer

| Author | *n* of women/controls | ERT/HRT (length of therapy) in months | FU (months) range (mean) | Recurrences ERT/controls |
|---|---|---|---|---|
| *Stoll* [84] | 65/0 | conjugated equine estrogen/norgestrel (3-6 months) | ≥24 | 0 |
| *Wile* [69] | 25/0 | ERT .625-1.25 mg ± progesterone (same as FU) | 24-82 mos (mean = 35.2 mos) | 2 |
| *Decker* [86] | 66/0 | HRT | 4.8-192 (28) | 2 |
| *Bluming* [87] | 146/0 | HRT | | 2 |
| *Gorins* [88] | 99/0 | HRT (concurrent 88%) (sequential 12%) | 4.0-120 15 | 3 |
| *Powles* [67] | 35/0 | ERT .625-1.25 mg plus tamoxifen (mean of 14.6 months) | 1-238 (43) | 2 |
| *DiSaia* [85] | 41/82 | ERT/HRT (conjugated estrogen .625 mg/± progesterone) | 27 | 6/7 |
| *Marsden* [68] | 50/50 | HRT (30 also on Tam) | ≥48 | 1/1 |
| *Sellin* [89] | 39/280 | ERT alone | 24-99 (40) | 1/14 |
| *Eden* [70] | 90/180 | ERT/HRT (4-144) (mean = 18 months) | 4-3,060 (78) | 6/30 |

that they would consider taking ERT under medical supervision. A survey of a similar population by *Couzi et al*. [65] reported that 31% would take ERT under medical supervision. These results suggest that the use of ERT/HRT following breast cancer is of interest and concern to women with breast cancer, and that at least some women would consider its use.

There are few clinical data describing the results of ERT/HRT in women with a prior diagnosis of breast cancer. From the observational literature, it has been observed that women who develop breast cancer during pregnancy or have a pregnancy within 1 to 2 years of breast cancer diagnosis, have a poorer outlook than might otherwise be expected [66]. Such studies have also shown that women who become pregnant more than 1 or 2 years following a diagnosis of breast cancer have no obvious increase in recurrence of their disease. It is clear, however, that women who become pregnant following a diagnosis of breast cancer are a highly selected group who may have chosen to become pregnant and/or been advised to consider pregnancy because of a variety of favorable prognostic factors.

At least eight case series of women with breast cancer who have received ERT/HRT for the relief of menopausal symptoms have been published. These are summarized in Table 2.

These reports illustrate that data regarding ERT/HRT in women with breast cancer are scarce, patients given ERT/HRT are probably highly selected, and these observations must be viewed as preliminary and uncontrolled. The total number of women with breast cancer who received ERT/HRT represented in these published reports is small (about 600) compared with the much greater number of women with breast cancer who have apparently received ERT based on the survey reported by *Vassilopoulou-Sellin* and *Zolinski* [64]. Thus, publication bias may also be present. In addition, the mean follow-up time of published cases is relatively short, given the fact that an increased risk of breast cancer in healthy women may be associated with mainly longer durations of ERT.

Interestingly, a number of somewhat paradoxical observations have been made regarding the behavior of breast cancer that presents for diagnosis in women currently receiving ERT/HRT. *Dhodapkar et al*. [71] reported on four women who developed metastatic breast cancer while taking ERT. In each case, withdrawal of ERT alone resulted in regression of metastatic disease. Whether the ERT sped or

slowed the development of the metastases was impossible to determine, but the investigators suggested that this maneuver is appropriate as initial treatment for metastatic disease that develops on ERT. *Powles* and *Hickish* [72] reported on a single similar case, in which withdrawal of HRT resulted in complete clinical resolution of a primary breast cancer in a patient who deferred primary surgery for 3 months after initial biopsy. However, at surgery, a residual pathologic cancer was present. *Booser* has also described response to HRT withdrawal as the sole intervention in three of eight similar breast cancer patients [73].

In addition, and also somewhat paradoxically, several observational studies have reported a favorable prognosis for women diagnosed with breast cancer while on HRT [74, 75]. This may relate to the better health care access of HRT users. Recently *Melody Cobleigh* and others explored the relationship between ERT/HRT and prognostic factors in a cohort of 349 breast cancer patients [76]. A marked increase in the incidence of high S phase was found in women with estrogen receptor $(ER)^+$ tumors who were using HRT at the time of diagnosis, compared to women who had never used HRT and had $ER^+$ tumors. Thus, as HRT may stimulate the growth of receptor-positive cancers, its withdrawal could prove therapeutic, and may explain the improved prognosis reported in some series of such patients.

*Goodwin* [77] performed a decision analysis of ERT/HRT in women made prematurely menopausal by adjuvant chemotherapy. Based on the available data regarding risk of recurrence, risk of death from other causes, and menopausal symptoms, it appeared that for women with node-negative breast cancer who have substantial menopausal symptoms, the use of ERT/HRT might be reasonable. A decision analysis by *Perlman et al*. [78], however, suggested that in women with a previous diagnosis of breast cancer, because of the greatly increased relative risk of death from breast cancer in comparison to the risk of death from CVD, osteoporosis or other causes, it would be virtually impossible for such women to gain any overall mortality benefit from the use of ERT/HRT, even if ERT/HRT caused only a very small increase in risk of breast cancer recurrence and death. Thus, it seems that in women with a previous diagnosis of breast cancer, the use of ERT/HRT for short-term symptom relief may be a more appropriate subject for investigation than its use long-term. If short-term use were to prove safe, in well-designed and conducted randomized trials, exploration of the long-term use of ERT/HRT in women at very low risk of recurrence (i.e., ductal carcinoma in situ, very small favorable characteristic invasive disease) might then seem appropriate.

In considering trials of even short-term use, however, it is important to recognize that, just as women with a diagnosis of breast cancer will accept a considerable amount of treatment for very small benefits [79], women with a previous diagnosis of breast cancer are averse to accepting much increased risk of recurrence in order to take HRT [80, 81]. Thus, it is probable that a very large trial would have to be done in order to rule out the very small increases in risk that women would like to avoid. With this in mind, three large studies, the HABITS study (opened in 1996), a second Swedish study (opened in 1998), and a British study (opened in 2000), each randomizing women to ERT/HRT or not for 2 years, after a diagnosis of breast cancer, are now under way. The results of these trials will be greeted with considerable interest. In addition, the smaller randomized trial by *Vassilpoulou-Sellin*, which will rule out a 10% or greater difference in recurrence rate has been ongoing for more than 8 years [82]. Accrual is not yet complete, however, reflecting the difficulty of carrying out studies in this area.

Until results from these randomized trials are available, it would seem foolhardy to believe that there is no increased risk related to ERT/HRT in this setting. If even the 1.3 to 1.4 relative risk seen in the etiology literature applied to the risk of recurrence, one could see increases in recurrence that would be as high as any gain obtained by giving adjuvant chemo or hormonal therapy. This would clearly be unacceptable.

## Summary

It seems that in counseling women who have had a previous diagnosis of breast cancer, as recently suggested in a recent review article by Chlebowski [83], it should be made clear that: A) women with diagnosed breast cancer have a substantial risk of cancer recurrence which persists for as long as 20-30 years following diagnosis and results in a much greater risk of death from breast cancer than from any other cause; B) long-term use of ERT/HRT is associated with an increased risk of breast cancer development in observational studies. HRT may be associated with a higher risk than ERT alone; C) as breast cancer adjuvant therapy, estrogen reduction via oophorectomy in premenopausal women significantly reduces the risk of breast cancer recurrence or death from breast cancer; D) we do not know what the use of ERT/HRT in women with a previous diagnosis of breast cancer will do to the risk of breast cancer recurrence, but it is quite possible that there may be a risk similar to that seen in etiology; E) ERT/HRT is known to cause some other negative effects such as an increase in the risk of thromboembolic events and an increase in breast density resulting in a reduction in mammographic sensitivity and specificity; F) the data on the effects of ERT/HRT on all causing mortality in the general population cannot be extrapolated to women with a previous diagnosis of breast cancer since they carry so much higher a risk of dying of

breast cancer. Any factor that increases this risk by even a very small amount would be worrisome; G) there are alternatives for the management of vasomotor estrogen deficiency symptoms, including vitamin E, clonidine, and venlafaxine, although they may not be as effective as estrogen or progesterone. Better alternatives are currently being explored, and H) there are alternatives for the management of osteoporosis including calcium supplements, bisphosphonates, tamoxifen, other SERMS, exercise, and diet. There are alternative strategies for the prevention of cardiovascular disease including diet, exercise, smoking cessation, statins, and/or SERMS.

## REFERENCES


1 Daly E, Gray A, Barlow D et al. Measuring the impact of menopausal symptoms in quality of life. Br Med J 1993;307:836-840.

2 Riggs BL, Melton LJ. The prevention and treatment of osteoporosis. N Engl J Med 1992;327:620-627.

3 Colditz GA, Willett WC, Stampfer MJ et al. Menopause and the risk of coronary heart disease in women. N Engl J Med 1987;316:1105-1110.

4 Schiff I, Tulchinsky D, Cramer D et al. Oral medroxyprogesterone in the treatment of postmenopausal symptoms. JAMA 1980;224:1443-1445.

5 Wiklund I, Berg G, Hammar M et al. Long-term effect of transdermal hormonal therapy on aspects of quality of life in postmenopausal women. Maturitas 1992;14:225-236.

6 Cauley JA, Seeley DG, Ensrud K et al. Estrogen replacement therapy and fractures in older women. Ann Intern Med 1995;122:9-16.

7 Lufkin EG, Wahner HW, O'Fallon WM et al. Treatment of postmenopausal osteoporosis with transdermal estrogen. Ann Intern Med 1992;117:1-9.

8 Lobo BA. Effects of hormonal replacement on lipids and lipoproteins in postmenopausal women. J Clin Endocrinol Metab 1991;73:925-931.

9 Bush TL, Miller VT. Effects of pharmacologic agents used during menopause: impact on lipids and lipoproteins. In: Mishell DR, ed. Menopause: Physiology and Pharmacology. Chicago: Year Book Medical Publishers, 1987:187-208.

10 McGill HC. Sex steroid hormone receptors in the cardiovascular system. Postgrad Med 1989;85:64-68.

11 The PEPI Trial. Effects of estrogen or estrogen/progestin regimes on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial. JAMA 1995;273:199-208.

12 Grodstein F, Stampfer MJ, Colditz GA et al. Postmenopausal hormone therapy and mortality. N Engl J Med 1997;336:1769-1775.

13 Hemminiki E, McPherson K. Impact of postmenopausal hormone therapy on cardiovascular events and cancer: pooled data from clinical trials. Br Med J 1997;315:149-153.

14 Hulley S, Grady D, Bush T et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. For the Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA 1998;280:605-613.

15 The Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. Control Clin Trials 1998;19:61-109.

16 Paganini-Hill A, Henderson VW. Estrogen deficiency and risk of Alzheimer's disease in women. Am J Epidemiol 1997;140:256-261.

17 Mulnard RA, Cotman CW, Kawas C et al. Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease. A randomized controlled trial. JAMA 2000;283:1007-1015.

18 Calle EE. Estrogen replacement therapy and risk of fatal colon cancer in a prospective cohort of postmenopausal women. JNCI 1995;87:517-523.

19 Loprinzi CL. Management of menopausal symptoms in breast cancer survivors. Am Soc Clin Oncol Educ 1996;190-192.

20 Kessel B. Alternatives to estrogen for menopausal women. Proc Soc Exp Biol Med 1998;217:38-44.

21 Love SM, Lindsey K. Making informed choices about menopause. In: Addison Wesley, ed. Dr. Susan Love's Hormone Book. New York: Random House, 1997:159-189.

22 Law M, Loprinzi CL, Kugler J et al. Double-blind crossover trial of Replens versus KY Jelly for treating vaginal dryness and dyspareunia in breast cancer survivors. Proc Am Soc Clin Oncol 1996;15:241a

23 Henriksson L, Stjernquist M, Boquist L et al. A one year multicenter study of efficacy and safety of a continuous, low dose estradiol-releasing vaginal ring (Estring) in postmenopausal women with symptoms and signs of urogenital aging. Am J Obstet Gynecol 1996;174:85-92.

24 Sitruk-Ware R. Estrogen therapy during menopause. Practical treatment recommendations. Drugs 1990;39:203-217.

25 Goldberg RM, Loprinzi CL, O'Fallon JR et al. Transdermal clonidine for ameliorating tamoxifen-induced hot flashes. J Clin Oncol 1994;12:155-158.

26 Loprinzi CL, Michalak JC, Quella SK et al. Megestrol acetate for the prevention of hot flashes. N Engl J Med 1994;331:347-352.

27 Barton D, Loprinzi CL, Quella SK et al. Prospective evaluation of vitamin E for hot flashes in breast cancer survivors. J Clin Oncol 1998;16:495-500.

28 Loprinzi CL, Pisansky T, Fonseca R et al. Pilot evaluation of Venlafaxine hydrochloride for the therapy of hot flashes in cancer survivors. J Clin Oncol 1998;16:2377-2381.

29 Quella SK, Loprinzi CL, Barton D et al. Evaluation of soy phytoestrogens for the treatment of hot flashes in breast cancer survivors: a North Central Cancer Treatment Group Trial. J Clin Oncol 2000;18:1068-1074.

30 Quella SK, Loprinzi CL, Sloan JA et al. Long term use of megestrol acetate for treatment of hot flashes in cancer survivors. Cancer 1998;82:1784-1788.

31 Liberman UA, Weiss SR, Broll J et al. Effect of oral Alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase II Osteoporosis Treatment Study Group. N Engl J Med 1995;333:1437-1443.

32 Saarto T, Blomqvist C, Valimaki M et al. Chemical castration induced by adjuvant cyclophosphamide, methotrexate and flurouracil chemotherapy causes rapid bone loss that is reduced by clodronate: a randomized study in premenopausal breast cancer patients. J Clin Oncol 1997;15:1341-1347.

33 Delmas PD, Balena R, Carfraveus E et al. Bisphosphonate risedronate prevents bone loss in women with artificial menopause due to chemotherapy of breast cancer: a double-blind placebo-controlled study. J Clin Oncol 1997;15:955-963.

34 Paterson AHG, McCloskey EV, Ashley S et al. Reduction of skeletal morbidity and prevention of bone metastases with oral clodronate in women with recurrent breast cancer in the absence of skeletal metastases. Proc Am Soc Clin Oncol 1996;15:81a

35 Hortobagyi GN, Theriault R, Porter L et al. Efficacy of Pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. N Engl J Med 1996;335:1785-1791.

36 Diel IJ, Solomayer EF, Goerner R et al. Adjuvant treatment of breast cancer patients with the bisphosphonate clodronate reduces incidence and number of bone and non-bone metastases. Proc Amer Soc Clin Oncol 1997;16:461a.

37 Fornander T, Rutqvist LE, Sjoberg HE. Long-term adjuvant tamoxifen in early breast cancer: effect on bone mineral density in postmenopausal women. J Clin Oncol 1990;8:1019-1024.

38 Love RR, Barden HS, Mazess RB et al. Effect of tamoxifen on lumbar spine bone mineral density in postmenopausal women after 5 years. Arch Intern Med 1994;154:2585-2588.

39 Delmas PD, Bjarnason NH, Mitlak BH et al. Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. N Engl J Med 1997;337:1641-1647.

40 Walsh BW, Kuller LH, Wild RA et al. Effects of raloxifene on serum lipids and coagulation factors in healthy postmenopausal women. JAMA 1998;279:1445-1485.

41 Cummings SR, Norton L, Eckert S et al. Raloxifene reduces the risk of breast cancer and may decrease the risk of endometrial cancer in postmenopausal women. Two-year findings from the multiple outcomes of raloxifene evaluation (MORE) trial. Proc Am Soc Clin Oncol 1998;17:2a

42 Jordan VC, Glusman JE, Eckert S et al. Incident primary breast cancers are reduced by raloxifene: integrated data from multicenter, double-blind, randomized trials in ~12,000 postmenopausal women. Proc Am Soc Clin Oncol 1998;17:122a.

43 Nordin BEC. Calcium and osteoporosis. Nutrition 1997;13:664-686.

44 Prior JC, Barr SI, Chow R et al. Physical activity as therapy for osteoporosis. Can Med Assoc J 1996;55:940-944.

45 Eagles CJ, Gulait R, Martin U. Non-pharmacological modification of cardiac risk factors. J Clin Pharma Ther 1996;21:289-296.

46 Hebert PR, Gaziano JM, Chan KS et al. Cholesterol lowering with statin drugs, risks of stroke, and total mortality. JAMA 1997;278:313-321.

47 Vaughan CJ, Murphy MB, Buckley BM. Statins do more than just lower cholesterol. Lancet 1996;348:1079-1082.

48 Thun MJ. NSAID use and decreased risk of gastrointestinal cancers. Gastroenterol Clin North Am 1996;25:333-348.

49 Early Breast Cancer Trialists' Collaborative Group. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Lancet 1997;350:1047-1059.

50 Nachtigall LE, Nachtigall RH, Nachtigall RD et al. Estrogen replacement therapy II: a prospective study in the relationship to carcinoma and cardiovascular and metabolic problems. Obstet Gynecol 1979;54:74-79.

51 Gambrell DR, Maier RC, Sanders BI. Decreased incidence of breast cancer in postmenopausal estrogen-progestogen users. Obstet Gynecol 1983;62:435-443.

52 Willett CG, Colditz GA, Stampfer MJ. Postmenopausal estrogens—opposed, unopposed, or none of the above. JAMA 2000;283:534-535.

53 Colditz GA, Rosner B, Nurses' Health Study Research Group. Use of estrogen plus progestin is associated with greater increase in breast cancer risk than estrogen alone. Am J Epidemiol 1998;147:645.

54 Persson I, Weiderpass E, Bergkvist L et al. Risks of breast and endometrial cancer after estrogen and progestin replacement. Cancer Causes Control 1999;10:253-260.

55 Schairer C, Lubin J, Troisi R et al. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. JAMA 2000;283:485-491.

56 Ross RK, Paganini-Hill A, Wan PC et al. Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. J Natl Cancer Inst 2000;92:328-332.

57 Grodstein F, Stampfer MJ, Goldhaber SZ et al. Prospective study of exogenous hormones and risk of pulmonary embolism in women. Lancet 1996;348:983-987.

58 Daly E, Vessey MP, Hawkins MM et al. Risk of venous thromboembolism in users of hormone replacement therapy. Lancet 1996;348:977-980.

59 Grady D, Hulley SB, Furberg C. Venous thromboembolic events associated with hormone replacement therapy. JAMA 1997;278:477.

60 Laya MB, Larson EB, Taplin SH et al. Effect of estrogen replacement therapy on the specificity and sensitivity of screening mammography. J Natl Cancer Inst 1996;88:643-649.

61 McNicholas MM, Henegan JP, Milner MH. Pain and increased mammographic density in women receiving hormone replacement therapy: a prospective study. Am J Roentgenol 1994;163:311-315.

62 Dickson RB, Thompson EW, Lippman ME. Regulation of proliferation, invasion and growth factor synthesis in breast cancer by steroids. J Steroid Biochem Mol Biol 1990;37:305-316.

63 Early Breast Cancer Trialists' Collaborative Group. Ovarian ablation in early breast cancer: an overview of the randomized trials. Lancet 1996;348:1189-1196.

64 Vassilopoulou-Sellin R, Zolinski C. Estrogen replacement therapy in women with breast cancer: a survey of patient attitudes. Am J Med Sci 1992;304:145-149.

65 Couzi RJ, Helzlsouer KJ, Fetting JH. Prevalence of menopausal symptoms among women with a history of breast cancer and attitudes toward estrogen replacement therapy. J Clin Oncol 1995;13:2737-2744.

66 Clark RM, Chua T. Breast cancer and pregnancy: the ultimate challenge. Clin Oncol (Royal College of Radiologists) 1989;1:11-18.

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

68 Marsden J, Baum M, Jurkovic D et al. A randomized pilot study of HRT in breast cancer patients: the combined effects of tamoxifen and HRT on the endometrium. Breast 1997;6:238-243.

69 Wile AG, Opfell RW, Magileth DA. Hormone replacement therapy in previously treated breast cancer patients. Am J Surg 1993;165:372-375.

70 Eden JA. A case controlled study of combined continuous estrogen-progestin replacement therapy among women with a personal history of breast cancer. Menopause 1995;2:67-72.

71 Dhodapkar MV, Ingle JN, Ahmann DL. Estrogen replacement therapy withdrawal and regression of metastatic breast cancer. Cancer 1995;75:43-46.

72 Powles TJ, Hickish T. Breast cancer response to hormone replacement therapy withdrawal. Lancet 1995;345:1442.

73 Booser D. Estrogen withdrawal as initial treatment for metastatic breast cancer. Proc Am Soc Clin Oncol 1998;17:130a

74 Bergkvist L, Adami HA, Persson I et al. Prognosis after breast cancer diagnosis in women exposed to estrogen and estrogen-progestogen replacement therapy. Am J Epidemiol 1989;139:221-228.

75 Magnusson C, Holmberg L, Norden T et al. Prognostic characteristics in breast cancers after hormone replacement therapy. Breast Cancer Res Treat 1996;38:325-334.

76 Cobleigh MA, Norlock FE, Do FE et al. Hormone replacement therapy and high S phase in breast cancer. JAMA 1999;281:1528-1530.

77 Goodwin PJ. Decision analysis (DA) of estrogen replacement therapy (ERT) in women made prematurely menopausal during adjuvant chemotherapy (ADJ/CXT) for breast cancer (BC). Breast Cancer Res Treat 1989;14:147a.

78 Perlman JA, Parnes HL, Ford LG. Projections of the longevity effects of tamoxifen (TAM) + progestin (T+P) versus hormone replacement therapy (HRT) in breast cancer survivors requiring hormonal symptom relief. Proc Am Soc Clin Oncol 1997;16:131a.

79 Lindley CM, Vasa SP, Swayer WT et al. Eliciting preferences for adjuvant therapy in patients with early stage breast cancer: tradeoffs between treatment, care, and survival. Proc Am Soc Clin Oncol 1995;14:149.

80 Ganz PA, Greendale GA, Peterson LM et al. Managing menopausal symptoms in breast cancer survivors: results of a randomized controlled trial. J Natl Cancer Inst 2000;92:1054-1064.

81 Pritchard K, Llewellyn-Thomas HA, Lewis J et al. The use of a probability trade-off task (PT-OT) to assess maximal acceptable increment in risk of breast cancer recurrence (MAIRR) in order to estimate sample size for a randomized clinical trial of hormone replacement therapy (HRT) in women with a previous diagnosis of breast cancer. Proc Am Soc Clin Oncol 1996;15:213.

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

83 Chlebowski RT. Elements of informed consent for hormonal replacement therapy in patients with diagnosed breast cancer. J Clin Oncol 1999;17:130-142.

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

85 DiSaia PJ, Grosen EA, Kurosaki T et al. Hormone replacement therapy in breast cancer survivors: a cohort study. Am J Obstet Gynecol 1996;174:1494-1498.

86 Decker D, Cox T, Burdakin J et al. Hormone replacement therapy (HRT) in breast cancer survivors. Proc Am Soc Clin Oncol 1996;15:209a.

87 Bluming AZ, Waisman JR, Dosik GA et al. Hormone replacement therapy (HRT) in women with previously treated primary breast cancer, update IV. Proc Am Soc Clin Oncol 1997;17:496a.

88 Gorins A. Traitment hormonal substitutif de menopause chez la femme ayant des antecedents personnels de mastopathie benigne ou de cancer du sein. Gynecol Oncol 1999;94:25-29.

89 Vassilopoulou-Sellin R, Asmar L, Hortobagyi GN et al. Estrogen replacement therapy after localized breast cancer: clinical outcome of 319 women followed prospectively. J Clin Oncol 1999;17:1482-1487.