Hormonal replacement therapy in breast cancer

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Introduction

Hormone replacement therapy with either estrogen (ERT) or estrogen and progesterone (HRT) is often recommended to healthy women at menopause, for relief of menopausal symptoms, particularly ‘hot flashes’, based on its documented long-term effect on osteoporosis and perceived effect in reducing the risk of coronary artery disease (CAD).

ERT/HRT has, however, long been considered contraindicated in women with a prior diagnosis of breast cancer. Basic biology suggests that estrogen contributes to the development of breast cancer and may contribute to recurrence after primary therapy for early disease. There are also data suggesting that progesterone may increase the risk of developing breast cancer and of disease recurrence.

ERT/HRT in healthy women

Menopausal physiology

Menopause occurs when ovaries stop secreting estradiol. Without that positive feedback, serum follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels increase. Hot flashes, vaginal dryness and urinary symptoms then occur, resulting in decreased quality of life [1]. 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 cohort [3], women who underwent bilateral oophorectomy without ERT had a significant increase in cardiovascular disease. Other changes are often attributed to menopause including skin and hair changes, mood changes and reduction in cognitive function.

ERT/HRT in treatment of menopausal symptoms

Estrogen is known to be effective in controlling hot flashes [1]. Oral medroxyprogesterone (MPA) 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 [5]. Thus, symptom relief can be achieved with estrogen with or without a progestational. Progesterone alone may have some of the same benefits. There have been no direct comparisons of progestationals to estrogen in terms of vasomotor symptom control or overall quality of life.

Long-term effects of ERT/HRT

Osteoporosis

Estrogen is now approved in many countries for osteoporosis prevention and has been shown to maintain or increase bone density and prevent fracture whether given transdermally or orally, immediately after menopause or later [6, 7].

Cardiovascular disease

The role of estrogen in cardiovascular disease is less clear, since 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]. Estrogen also has direct effects on vessel walls, on the myocardium [10] and on platelets and coagulation factors. The randomized Postmenopausal Estrogen/Progestin Interventions (PEPI) trial has shown an effect of estrogen with or without progestationals in increasing HDL and reducing LDL compared with placebo. This trial was not powered for cardiovascular endpoints, however [11].

Investigators have inferred reductions in coronary artery disease (CAD) of about 40% from observational studies of HRT users compared with non-users [12]. In such studies, however, the more healthy women may also be the ones who receive ERT. A recent meta-analysis of CAD endpoints in 22 randomized trials, designed primarily to study other outcomes in 4124 postmenopausal women, found no effect of HRT on CAD [odds ratio (OR) = 1.39; 95% confidence intervals (CI) 0.48 to 3.95] [13]. The only published randomized trial of ERT/HRT with CAD as a primary endpoint, the Heart and Estrogen/Progesterone Replacement Study (HERS), a randomized trial of HRT for secondary prevention of CAD in postmenopausal women, showed that women started on HRT shortly after a cardiac event were more likely to suffer a second cardiac event over the next year. They were less likely to suffer a second cardiac event in years four and five of follow-up, however, so that overall, there was no significant difference in cardiac morbidity [14]. Since this randomized trial showed early results opposite to those from observational data, there has been re-examination of the assumption that the results of observational studies will be duplicated in randomized trials. The Women’s Health Initiative (WHI), a study...
comparing ERT/HRT to placebo in over 25,000 postmenopausal women is continuing accrual and will provide the first evidence from a randomized trial of primary cardiovascular (CVD) endpoints and overall mortality [15].

**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. The recently published Alzheimer’s Disease Cooperative Study of Mulnard and co-workers, 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 showed no such effect, however [17], but these results relate to only the specific group of women already 75 years of age and already having Alzheimer’s. It is still possible that estrogen may improve cognition in women in mid-life or in older women without Alzheimer’s disease. The influence of ERT/HRT on memory and mental function is currently undergoing prospective evaluation in the Women’s Health Initiative Memory Study (WHI-MS), a randomized trial in postmenopausal women aged from 65 to 79 years [15].

**Colon cancer**

A series of observational studies have demonstrated that the risk of colon cancer is lower in association with ERT/HRT (RR = 0.5) [18]. Colon cancer incidence will also be measured in the WHI study.

**Breast cancer**

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, it seems that there is a relative risk of 1.3 or 1.4 associated with ERT/HRT use, particularly if long term. The most recent collaborative analysis of data from 51 epidemiological 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 [19].

<table>
<thead>
<tr>
<th>Author [reference]</th>
<th>Design</th>
<th>Increased risk of breast cancer/year of use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nurse’s Cohort Study [23]</td>
<td>Cohort</td>
<td>Estrogen alone: 3.3%</td>
</tr>
<tr>
<td>Swedish [24]</td>
<td>Cohort</td>
<td>Estrogen alone: 0%</td>
</tr>
<tr>
<td>Schairer et al. [25]</td>
<td>Cohort</td>
<td>Estrogen alone: 1%</td>
</tr>
<tr>
<td>Ross et al. [26]</td>
<td>Case–control</td>
<td>Estrogen alone: 1%</td>
</tr>
</tbody>
</table>

There has been considerable uncertainty about the effect of progesterone added to estrogen on breast cancer risk [20, 21]. Reliable data on the long-term use of combination therapy have only recently become available [22]. These newer studies suggest that the risk is increased by the addition of a progestin [19, 23–26] (Table 1). In the collaborative analysis of epidemiological 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 [19]. All of these studies are subject to the risks of bias associated with observational designs. Until the results of randomized studies such as WHI are available, however, one must continue to assume that healthy women receiving ERT/HRT are at a small increased risk of developing breast cancer, and that the length of ERT and the addition of progestationals appear to increase this risk.

**Thromboembolic events**

Using case–control and cohort designs, a 200–300% increase in thromboembolic events associated with ERT/HRT has been identified [27, 28]. The HERS randomized trial has confirmed a comparable increased thromboembolic risk for HRT [29]. Transdermal or vaginal HRT which avoids an estrogenic first pass effect may avoid this risk.

**The use of ERT/HRT in women with a previous diagnosis of breast cancer**

There are many animal and in vitro models in which the development of breast cancer is estrogen dependent, but such data concerning progestin is less conclusive. There are some models in which progestin has a breast differentiating effect, while in others it supports cancer growth. Some have suggested that estrogen and progesterone may have a greater effect in the development of breast cancer than on its recurrence or in metastasis [30]. The Oxford meta-analysis, however, shows that adjuvant ovarian ablation results in a significant reduction in recurrence and death, presumably by the removal of estrogen [31]. Furthermore, the enhanced effects of adjuvant chemotherapy in premenopausal women may relate in part to ovarian ablation by cytotoxic drugs.

On the other hand, a large number of women now completing adjuvant breast cancer chemotherapy will live for a long time, and could therefore be candidates for prevention of complications of menopause with ERT/HRT, should such therapy be shown to be safe. Patient acceptance of such a strategy is
uncertain. In 224 randomly selected women with breast cancer, Vassilopoulou-Sellin and Zolinski [32] found that 8% of those who were postmenopausal had taken ERT at some point following cancer diagnosis. Seventy-eight per cent feared that ERT might precipitate cancer recurrence, but many also feared osteoporosis (70%) and heart disease (72%). Forty-four per cent indicated that they would consider taking ERT under medical supervision. A survey of a similar population by Couzi et al. [33] reported that 31% would take ERT under medical supervision.

There is little clinical data describing the use of ERT/HRT after a diagnosis of breast cancer. Women who develop breast cancer during pregnancy or become pregnant within 1–2 years of breast cancer diagnosis have a worse outlook than might otherwise be expected [34]. Women who become pregnant more than 1 or 2 years following a diagnosis of breast cancer, do not have any obvious increase in risk of recurrence of their disease, but such women are clearly a highly selected group, who may have chosen or been advised to consider pregnancy because of favourable prognostic factors.

At least six case series of women with breast cancer who have received ERT/HRT for relief of menopausal symptoms have been published [35–40]. None of these small series showed any obvious increase in risk of recurrence but such highly selected cases without controls provide little useful data.

Powles et al. [41] and Marsden et al. [42] recently published reports in which ERT was given together with tamoxifen for the relief of hot flashes in women with breast cancer. This approach appeared to ameliorate hot flashes. At present, it is unknown, however, whether the addition of tamoxifen to ERT for women with a history of breast cancer offers protection from any ERT-induced increased risk of breast cancer recurrence.

Three case–control studies have also been conducted. Wile et al. [43] matched 25 women with a history of breast cancer who subsequently took HRT to 50 controls by stage, age and duration of observation. During the mean duration of observation on HRT of 2 years, one patient and two controls had cancer-related deaths. The authors concluded that no adverse effect of HRT upon outcome could be detected. Eden [44] studied 1072 breast cancer patients, 67 of whom used estrogen for menopausal symptoms. A case–control study from this cohort suggested a reduced risk of recurrence in the HRT cohort, a result which may be subject to bias from physician and patient selection of HRT. Most recently, O’Meara et al. [45] identified 174 women who took HRT from 2755 women with breast cancer enrolled in a Health Maintenance Organization (HMO). Each HRT user was matched to four non-users. Rates of breast cancer recurrence and mortality were statistically significantly lower in HRT users compared with non-users (Table 2).

These reports illustrate that data regarding ERT/HRT in women with breast cancer are scarce, that patients given ERT/HRT are probably highly selected, and that 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 900) compared with the much greater number who apparently received ERT based on the survey of Vassilopoulou-Sellin and Zolinski [32]. Thus publication bias may be present. In addition, the mean follow-up time of published cases is

<table>
<thead>
<tr>
<th>Author [reference]</th>
<th>No. of women/controls</th>
<th>ERT/HRT [length of therapy (months)]</th>
<th>Follow-up (months) range (mean)</th>
<th>Recurrences ERT/controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stoll [35]</td>
<td>65/0</td>
<td>Conjugated equine estrogen/norgestrel (3–6 months)</td>
<td>≥24</td>
<td>0</td>
</tr>
<tr>
<td>Wile et al. [43]</td>
<td>25/0</td>
<td>ERT 0.625–1.25 mg ± progesterone (same as FU)</td>
<td>24–82 (35.2)</td>
<td>2</td>
</tr>
<tr>
<td>Decker et al. [37]</td>
<td>66/0</td>
<td>HRT</td>
<td>4.8–192 (28)</td>
<td>2</td>
</tr>
<tr>
<td>Blumming et al. [38]</td>
<td>146/0</td>
<td>HRT</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>Gorins [39]</td>
<td>99/0</td>
<td>HRT (concurrent 88%) (sequential 12%)</td>
<td>4.0–120 (3)</td>
<td>3</td>
</tr>
<tr>
<td>Powles et al. [41]</td>
<td>35/0</td>
<td>ERT 0.625–1.25 mg plus tamoxifen (mean of 14.6 months)</td>
<td>1–238 (43)</td>
<td>2</td>
</tr>
<tr>
<td>DiSaia et al. [36]</td>
<td>41/82</td>
<td>ERT/HRT (conjugated estrogen 0.625 mg ± progesterone)</td>
<td>27</td>
<td>6/7</td>
</tr>
<tr>
<td>Marsden et al. [42]</td>
<td>50/50</td>
<td>HRT (30 also on tamoxifen)</td>
<td>≥48</td>
<td>1/1</td>
</tr>
<tr>
<td>Vassilopoulou-Sellin et al. [40]</td>
<td>39/280</td>
<td>ERT alone</td>
<td>24–99 (40)</td>
<td>1/14</td>
</tr>
<tr>
<td>Eden [44]</td>
<td>90/180</td>
<td>ERT/HRT (4–144) (mean = 18)</td>
<td>4–3060 (78)</td>
<td>6/30</td>
</tr>
<tr>
<td>O’Meara et al. [45]</td>
<td>174/696</td>
<td>HRT</td>
<td>44 (rec) 55 (mortality)</td>
<td>16/101</td>
</tr>
</tbody>
</table>

ERT, estrogen; HRT, estrogen and progesterone.
relatively short, given the fact that an increased risk of breast cancer in healthy women is mainly associated with longer durations of ERT.

Interestingly, a number of somewhat paradoxical observations have been made regarding the behaviour of breast cancer which presents for diagnosis in women receiving ERT/HRT. Dhodapkar et al. [46], Powles and Hickish [47] and Booser [48] have all described response to HRT withdrawal as the sole intervention in women who developed breast cancer while receiving HRT. In addition, several observational studies have reported a favourable prognosis for women diagnosed with breast cancer while on HRT [49, 50]. Recently Melody Cobleigh and others found a marked increase in the incidence of high S-phase in women with ER positive tumours who were receiving HRT at diagnosis, compared with women with ER positive tumours who had never used HRT [51]. Just as HRT may stimulate the growth of receptor positive cancers, so its withdrawal may be therapeutic, thus explaining the improved prognosis reported in such patients. This observation may also relate to better health care access among HRT users.

Goodwin [52] performed a decision analysis of ERT/HRT in women made prematurely menopausal by adjuvant chemotherapy. Based on available data regarding risk of recurrence, risk of death from other causes and menopausal symptoms, she suggested that the use of ERT/HRT might be reasonable for women with node-negative breast cancer and substantial menopausal symptoms. A decision analysis by Perlman et al. [53], however, suggested that in women with previous breast cancer, because of the greatly increased relative risk of death from breast cancer in comparison to other causes, it would be difficult to gain any overall mortality benefit. Thus, the use of ERT/HRT for short-term symptom relief may be a more appropriate subject for investigation. If short-term use were to prove safe in well designed randomized trials, exploration of the long-term use of ERT/HRT in women at very low risk of recurrence, such as those with ductal carcinoma in situ or very favourable 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 breast cancer will accept considerable anti-cancer treatment for very small benefits [54], women with breast cancer are averse to accepting much increased risk of recurrence in order to take HRT [55, 56]. Thus, very large trials will be required in order to rule out the very small increases in risk that women would like to avoid. Three large studies, each randomizing women to ERT/HRT or not for 2 years, after a diagnosis of breast cancer, are now underway. A smaller randomized trial by Vassilopoulou-Sellin and Theriault [57], which will rule out a ≥10% difference in recurrence rate, has been ongoing for >8 years. 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 from ERT/HRT in this setting. If, for example, 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 as high as any gain from adjuvant systemic therapy. This would clearly be unacceptable. In addition, there is concern associated with the use of HRT in breast cancer patients receiving breast sparing procedures, since ERT/HRT increases breast density [58, 59], making the diagnosis of recurrence or of a new breast cancer more difficult.

**Alternatives to the use of ERT/HRT**

**Genito-urinary symptoms**

KY jelly and Replens can significantly reduce vaginal dryness and other local genito-urinary symptoms [60, 61], as can vaginal estrogen creams and Estring [62]. Estrogen creams are associated with vaginal absorption of estrogen to levels which may, in some cases, be comparable with those achieved with oral use [63], but Estring tends to provide more consistent local effects with lower systemic absorption [62].

**Osteoporosis**

Osteoporosis can now be prevented and treated with approaches that do not involve ERT/HRT. In addition to recommendations for diet, exercise and calcium supplementation [64, 65], a wide array of bisphosphonates including didronel, alendronate [66], clodronate [67], pamidronate and resorionate [68] are now known to inhibit bone absorption and normalize bone turnover. In addition, clodronate [69] and pamidronate [70] have significantly reduced skeletal complications and perhaps the development of bone metastases in breast cancer patients [69, 71].

Tamoxifen also improves bone mass and reduces fractures in postmenopausal women [72, 73], as do other selective estrogen receptor modulators (SERMs). Tamoxifen also improves lipid profiles but is known to cause hot flashes and a small but significant increase in endometrial cancer and in deep vein thrombosis (DVT). Raloxifene, one of the newer SERMs, has recently been approved for the treatment and prevention of osteoporosis. Like tamoxifen, it is associated with hot flashes and increased DVT. It does, however, also favourably influence lipid profiles [74] in a fashion similar to 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 [75, 76]. Preclinical data strongly suggests that raloxifene is not as likely as tamoxifen to cause endometrial cancer, but there is 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 Adjuvant Breast and Bowel Project, Study of Tamoxifen and Raloxifene) is ongoing.
Cardiovascular disease

Similarly CVD can be affected by a variety of other approaches including diet [77], tamoxifen or other SERMS, exercise, hypertension, smoking cessation and the statins which may improve lipid levels and significantly reduce CVD events [78, 79].

Colon cancer

Other drugs such as aspirin and non-steroidal anti-inflammatory drugs (NSAIDs), which are without reported adverse risk of breast cancer, have also been suggested to prevent colon cancer [80].

Alzheimer’s disease

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

Vasomotor symptoms

The Mayo Clinic and North Central Cancer Treatment Group (NCCTG) have conducted a series of short clinical trials of alternatives for alleviating hot flashes. In these trials [81–84] the placebo is associated with a relatively consistent 20–25 per cent reduction in hot flashes over a 4-week period. This documented placebo effect should be taken into account when studying new agents and evaluating anecdotal experiences.

The first NCCTG placebo-controlled trial demonstrated that clonidine could reduce hot flashes by about 15% more than placebo [81]. Clonidine was, however, associated with statistically significantly more toxicity and patients did not prefer it to placebo at study end.

The second NCCTG trial evaluated a low dose of megestrol acetate compared with placebo [82]. This trial demonstrated a hot flash reduction of about 80% with megestrol acetate. The therapy was well tolerated, and women significantly preferred megestrol acetate. Subsequent investigation suggested that megestrol acetate continues to control hot flashes for up to 3 years of therapy [85]. Most women were able to achieve effective control of hot flashes with <20 mg/day.

The NCCTG subsequently completed a placebo-controlled trial of vitamin E 800 IU/day [83]. This clinical trial did demonstrate a statistically significant decrease in hot flashes for vitamin E over placebo. Although vitamin E was well tolerated, this hot flash reduction amounted to only one hot flash per person per day.

The NCCTG also recently completed a placebo-controlled trial of a soy phytoestrogen preparation. Over 180 patients were entered on this clinical trial in 2 months. Unfortunately soy protein did not significantly reduce the severity or frequency of hot flashes, nor was it preferred by patients [86].

A pilot trial conducted at the Mayo Clinic initially suggested that a very low and easily tolerated dose (37.5 mg daily) of the antidepressant venlafaxine (Effexor) decreased hot flashes by about 50% [84]. A placebo-controlled dose-finding clinical trial comparing venlafaxine 37.5 mg, 75 mg and 150 mg daily to placebo has now shown that 75 mg daily is the most effective dose [86]. The 75 mg dose does cause a mild increase in dry mouth, anorexia and nausea in comparison to 37.5 mg but is still well tolerated. Anecdotal information has suggested that other selective serotonin reuptake inhibitors (SSRIs) also can decrease hot flashes. Further trials are ongoing.

Other compounds such as black cohosh and Bellergal® have been utilized, but have not undergone placebo-controlled trials designed to clarify benefits and toxicities.

Alcohol and other forms of intake are without reported adverse effects in breast cancer since they carry a so much higher risk of dying of breast cancer. Any factor which increases this risk by even a very small amount would be problematic.

Summary

In counselling women with a previous diagnosis of breast cancer, as suggested in a recent review article by Chlebowski [87], the following points should be made clear:

- Women with previous breast cancer have a substantial risk of cancer recurrence which persists for as long as 20–30 years following diagnosis and results in a greater risk of death from breast cancer than from any other cause.
- Long-term use of ERT/HRT is associated with an increased risk of breast cancer development in observational studies.
- Estrogen reduction via oophorectomy in premenopausal women significantly reduces the risk of breast cancer recurrence or death from breast cancer.
- We do not know how the use of ERT/HRT in women with previous breast cancer will affect the risk of breast cancer recurrence, but it is quite possible that there may be an increased risk similar to that seen in etiology.
- ERT/HRT is known to cause other undesirable effects, such as an increased risk of thromboembolism, and an increase in breast density, resulting in reduction in mammographic sensitivity and specificity.
- The effects of ERT/HRT on mortality in the general population are not extrapolable to women with previous breast cancer since they carry a so much higher risk of dying of breast cancer. Any factor which increases this risk by even a very small amount would be problematic.
- There are alternatives for the management of vasomotor estrogen deficiency symptoms, including vitamin E,
clonidine and venlafaxine. Other alternatives are being explored.

- There are alternatives for the management of osteoporosis including calcium supplements, bisphosphonates, tamoxifen, other SERMS, exercise and diet.
- There are alternatives for the prevention of cardiovascular disease including diet, exercise, smoking cessation, statins and/or SERMS.

Clearly a multidisciplinary approach, in which the combined input of the medical oncologist, gynecologist, family doctor and/or primary care internist is considered together with patient preferences will provide optimal information for management of women in this situation.

References


