Management of Menopausal Symptoms in the Cancer Patient

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In the decades since hormone replacement therapy (HRT) was introduced, there has never been more controversy surrounding it than at present. Physicians and patients are faced with many questions regarding risk and few definitive answers.

Introduction

With the current controversy surrounding hormone replacement therapy (HRT), there is an increased demand by the general population for alternative therapies, particularly for the cancer survivor. The volume of information on HRT to which physicians and patients are exposed is growing exponentially. Nevertheless, there still remain as many questions as answers regarding the risks and benefits of this therapy.

Until the 1970s, women expected to have to suffer through menopausal symptoms as part of their reproductive life. It has since been clearly established that hormones, estrogen in particular, play a significant role in the physical and psychological well-being of women.

The symptoms of estrogen deficiency are often debilitating. The most commonly described are vasomotor symptoms (hot flashes), urinary frequency, mood swings, memory loss, difficulty in concentrating, insomnia, decreased libido, dyspareunia, and vaginal dryness and pruritus. The "silent killers" include heart disease, osteoporosis, and Alzheimer’s disease.

Hormone replacement was initially intended for the short-term treatment of vasomotor symptoms, but data showing a cardioprotective effect and a benefit on bone mineral density support a longer duration of use. The main questions that have arisen include the following:

1. Is HRT safe to use?
2. For how long a period can it be safely used?
3. When should therapy begin?
4. Who should receive HRT?

Because of the possible role that estrogen plays in the pathogenesis of breast and other cancers, its use for postmenopausal therapy has been challenged. As this article will show, HRT is still a safe option for many women, and our goal as clinicians should be to help identify those women who will benefit most from it. This article also will review alternative therapies that have emerged in response to the controversy surrounding hormone replacement. The needs and treatment options for the breast cancer survivor in particular will be addressed.

HRT and Cardiovascular Disease

Cardiovascular disease is the leading cause of noncancer death in postmenopausal women (Figure 1).[1] In Caucasian women 50 to 94 years old, the cumulative risk of death from coronary artery disease is 31%, as compared with a 2.8% risk of death from breast cancer or osteoporosis. These data underscore the need to address cardiovascular and fracture risk in postmenopausal women. Ideally, those at risk should be identified during their reproductive years.

A number of studies have evaluated the role of HRT in the prevention of cardiovascular disease. The cardioprotective mechanism of this therapy is not well elucidated but is postulated to relate to its effects on lipid accumulation in arterial walls, promotion of blood flow, and modulation of vascular responsiveness.

The Nurses’ Health Study,[2] conducted by Grodstein et al from 1976 to 1992, examined the association between hormone replacement and the risk of cardiovascular disease, breast cancer,
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Colorectal cancer, and overall mortality.[2-5] The study followed 59,337 women (age, 30 to 55 years at study entry) for 16 years. This study showed a significant decrease in cardiovascular disease risk among current users of HRT (Figure 2), with a relative risk (RR) of 0.60 (95% confidence interval [CI], 0.43 to 0.78); the greatest benefit was seen among users of estrogen alone (RR, 0.39; 95% CI, 0.19 to 0.78).[2] The apparent benefit disappeared within 5 years after discontinuation of therapy (Table 1).

In a subsequent publication, Grodstein et al[3] evaluated the relationship between HRT and mortality. Current hormone use was associated with the lowest risk of death (RR, 0.63; 95% CI, 0.56 to 0.70), and this benefit appeared to diminish after 10 or more years of use. This was attributable primarily to a 43% increase in death due to breast cancer (RR, 1.43; 95% CI, 0.82 to 2.48). Those women with cardiac risk factors had the largest reduction in mortality (RR, 0.51; 95% CI, 0.45 to 0.57).

The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial[6] was designed to compare the effects of placebo, unopposed estrogen, and three combination hormonal regimens on selected cardiac risk factors. All of the active regimens had a positive effect on lipid profiles. Unopposed estrogen was the most effective regimen but carried an unacceptably high risk of endometrial hyperplasia (34%, vs 1% with combination therapy), limiting its use to women without a uterus. Micronized progesterone had the greatest effect on lipids. The overall findings estimated a 40% to 50% reduction in cardiac deaths.

Most recently, the results of a study evaluating the role of estrogens in the secondary prevention of cardiac disease were published.[7] The investigators concluded that, in individuals with already established coronary artery disease, HRT posed an increased risk of thromboembolic disease (RR, 2.89; 95% CI, 1.50 to 5.58) and gallbladder disease (RR, 1.38; 95% CI, 1.00 to 1.92). The hormone-treated group experienced an 11% decrease in low-density lipoprotein cholesterol and a 10% increase in high-density lipoprotein cholesterol. Despite this effect, the hormone-treated patients exhibited a 50% increase in the rate of myocardial infarction during the first year of the trial. This group had a 40% decreased rate of myocardial infarction during the last 2 years of the trial, suggesting that the positive effect of estrogen on cardiovascular disease is delayed even when lipid profiles are improved.

This study had many limitations. The investigators did not follow patients enrolled in the latter part of the study period long enough to show an effect. (Mean follow-up was 4.1 years.) Moreover, no patients were taking unopposed estrogen, and medroxyprogesterone acetate was the only progesterational agent studied. These data underscore the need for other treatments and lifestyle alterations, with or without HRT.

### HRT and Cardiovascular Disease

Hormone replacement therapy also has been shown to be effective in the prevention and treatment of osteoporosis—a condition that is still largely underdiagnosed. The data point to the need to address fracture risk and its attendant morbidity in the postmenopausal patient and, ideally, to identify those who are at risk even during their reproductive years.

The PEPI trial also assessed the effect of hormone replacement on bone mineral density, and concluded that women assigned to placebo had a significantly lower spine and hip bone mineral density than those in the active treatment groups.[8] Medroxyprogesterone acetate was more effective than micronized progesterone in increasing bone mineral density. (Bone mineral density was up to 5% higher in the spine with medroxyprogesterone vs 3.8% with other regimens.) The Rancho Bernardo Study[9] addressed the optimal timing of hormone replacement for maximizing bone mineral density. This study concluded that estrogen therapy instituted at any time is beneficial, but that the greatest benefit occurs when therapy is started at the onset of menopause and continued indefinitely. Women who used estrogen, even for more than 10 years, and discontinued therapy did not maintain their protection. Among current hormone users, there was no significant difference in bone mineral density between women who started taking estrogen at menopause and those who started it after 60 years of age.

### HRT and Alzheimer’s Disease

Alzheimer’s disease is among the most common reasons for nursing home admissions. The disorder affects twice as many women as men, in part because of the longer life expectancy of women. Kawas et al[10] performed the Baltimore Longitudinal Study of Aging, a prospective, multidisciplinary study of normal aging. The sample consisted of 472 postmenopausal or perimenopausal women...
followed for up to 16 years. Current or ever-users of estrogen were considered users. The findings showed that 45% of the women in the cohort had used estrogen replacement therapy. There were 34 incident cases of Alzheimer's disease, 9 of which occurred in estrogen users. The calculated RR for Alzheimer's disease in estrogen users as compared to nonusers was 0.46 (95% CI, 0.209 to 0.997), supporting a protective effect of estrogen.

HRT and Colon Cancer

At least 18 published epidemiologic studies have examined the relationship between HRT and colon cancer.[11] Of these studies, 12 suggested an inverse association between colon cancer risk and hormone use, with an RR usually in the 0.4 to 0.8 range. In a study by Calle et al,[12] the greatest reduction in risk was seen in current estrogen users (RR, 0.55; 95% CI, 0.40 to 0.76) and with longer duration of use (P = .0001). The mechanism by which estrogen protects against colon cancer is thought to be mediated through a decrease in bile acid concentration and effects at the molecular level.

HRT and Vasomotor Symptoms

Hot flashes are experienced by 85% of postmenopausal women in western countries and may begin in the perimenopausal period when gonadotropin levels are fluctuating. The mechanism by which vasomotor flashes occur has not been well elucidated, but they are associated with changes in core temperature and coincide with luteinizing hormone surges. Vasomotor symptoms are usually self-limited, dying out by 2 to 3 years after menopause. In the interim, however, these symptoms can be debilitating. Hormones can relieve vasomotor symptoms in up to 90% of women.

HRT and Breast Cancer

Although hormone replacement appears to have many benefits, there is growing concern that long-term use may be associated with breast cancer development. Current attention by the media has served only to increase this fear. The following findings support an association between estrogens and breast cancer:[13,14]

1. Oophorectomy has been shown to protect against the occurrence of breast cancer and to favorably alter its prognosis.
2. The presence of estrogen receptors affects prognosis.
3. Antiestrogens are used in the treatment of breast cancer
4. In vitro and in vivo studies have shown that estrogens have a mitogenic effect on breast epithelial cells.

Estrogens have been postulated to act as growth factors, through initiation of mutations, and as promoters and cocarcinogens.[15] The Nurses Health Study concluded that the RR of breast cancer was 1.32 (95% CI, 1.14 to 1.54) in the estrogen-only group and 1.41 (95% CI, 1.15 to 1.74) in the combination therapy group.[4] With more than 5 years of use, the RR increased to 1.46 (95% CI, 1.20-1.74; Table 2). Past users or those with less than 5 years of use showed risks similar to never-users, with the exception of women over the age of 55 years (Figure 3).

Stanford et al[16] evaluated breast cancer risk in a population-based case-control study that involved 537 breast cancer patients and 492 controls. Hormone replacement therapy had been used by 57.6% of the breast cancer patients and 61% of controls[4] a negative finding. The Collaborative Group on Hormonal Factors in Breast Cancer[17] provided perhaps the most informative data but was limited by the problems inherent in a meta-analysis. The collaborative group reviewed approximately 90% of the worldwide epidemiologic evidence on the relationship between breast cancer risk and HRT. As shown in Figure 4, this meta-analysis showed that breast cancer risk appears to increase after 15 or more years of use (RR, 1.58). Current users were at greatest risk, and the risk was reversed 5 or more years after discontinuation of therapy. The increase of 2.3% per year of use is comparable to the
2.8% per year increase in risk for each year that menopause is delayed (assumed average onset of menopause is 51 years).

The epidemiologists from the Nurses’ Health Study[18] also performed a meta-analysis of 25 case-control and six cohort studies. They concluded that ever-use of estrogen carried no increased risk, and current use was associated with an increased risk, which was reversed 2 years after discontinuation of therapy.

**Managing the Menopause**

With the benefits and risks outlined above, it is not surprising that the use of HRT, especially in the cancer patient, has been controversial. Although, in the past, it had been widely thought that estrogen should be used freely, currently available data support the need to exercise caution and to involve the patient in the decision-making process.

How do we, as clinicians, protect the heart and bones of postmenopausal women and address their needs for quality of life without adding morbidity? With the increased survival of cancer patients, often due to treatments that are toxic to the ovaries, this question is even more difficult to answer. The young woman who becomes prematurely menopausal after surviving cancer is exposed to decades of estrogen deficiency and its attendant morbidity.

**HRT in Cancer Patients**

Ideally, HRT would be used for all menopausal symptoms, since it successfully treats the majority of patients and the majority of the common menopausal symptoms. For those women experiencing a decreased libido, the combination of an estrogen and a testosterone (eg, Estratest) may prove to be beneficial.

Hormone replacement therapy can be used in the cancer patient, but one must exercise caution when prescribing it to a woman with a history of a hormone-dependent cancer, such as breast or endometrial cancer. Furthermore, when managing a young woman with premature menopause, it may be more prudent to replace hormones through oral contraceptives and switch to HRT once the expected chronologic time for menopause is reached. Anecdotal evidence suggests that this strategy may be more effective in preserving bone mineral density. Psychologically, the young patient may feel more comfortable using oral contraceptives like her peers rather than hormone replacement like her mother.

**Breast Cancer Survivors**

Breast cancer survivors pose a greater dilemma. Many investigators have been offering HRT to breast cancer survivors.[19-23] Table 3 summarizes the findings of some of the published studies.[24] This table represents the outcomes of about 275 women treated with hormone replacement, most of whom had localized disease and were of comparable mean age at diagnosis. On average, these women started HRT 3.7 years after the diagnosis of breast cancer (range, 24 to 84 months), but some had never discontinued HRT even at diagnosis. Hormone replacement was continued for an average of 2 years (range, 15 to 35 months). Patients’ nodal status and receptor status differed. Recurrence rates varied from 2% to 9%.

Using a combination of estrogen and tamoxifen (Nolvadex), Powles et al.[22] relieved menopausal symptoms in about two-thirds of patients. This may prove to be a valid approach for the relief of menopausal symptoms. DiSaia et al.[19] found no differences in recurrence or disease-free interval between the study group and the control group. Wile et al.[23] concluded that while the sample size was too small to prove the safety of estrogen replacement, it did not show an adverse effect either. Eden et al.[21] performed a case-control study of 90 women with a previous history of breast cancer who were taking HRT. Among the estrogen users, there were no deaths and 7% developed a recurrence. Interestingly, the nonusers had a 10% mortality and a 17% recurrence rate. The flaw in this study, as with the others, is that it was not randomized. In addition, the progestin dose was very high, comparable to that used for the treatment of metastatic breast cancer.

At present, our goal should be to design randomized, controlled trials to evaluate the risk of HRT in breast cancer survivors. It is equally important to include the patient who is experiencing the symptoms in the decision-making process. It must be acknowledged that it is not merely the quantity of life but also its quality that is important. Patients have a right to make informed decisions, and there is no definitive evidence of a link at this time.

Vassilopoulou-Sellin[24] recently published a study focusing on the desires of breast cancer survivors with regard to HRT. A random group of 200 breast cancer survivors were asked to anonymously respond to a survey with questions ranging from the presence of menopausal symptoms to the perceived risk of hormone replacement. Of these survivors, 78% reported being concerned about cancer recurrence, but 70% also feared osteoporosis and heart disease. Overall, 44% of menopausal
women and 59% of premenopausal women were willing to consider HRT. Subsequently, Vassilopoulou-Sellin and Klein surveyed patients with localized breast cancer about their views on HRT.[25] Among 418 women eligible for hormone replacement, 33% were not interested due to trial demands or age, 33% declined due to concerns about recurrence, and 33% were interested in therapy. Of note, 13% were already taking estrogen or were trying to start therapy.

**Endometrial Cancer Survivors** A number of studies have retrospectively evaluated the safety of HRT after therapy for endometrial cancer.[26,27] All of these studies were limited by their design. Creasman et al[26] studied the effects of HRT in 47 patients with stage IA (N = 30) or stage IB (N = 17) endometrial cancer. Hormone replacement was initiated a median of 15 months after cancer therapy, and there were no recurrences during follow-up of up to 12.5 years. An American College of Obstetricians and Gynecologists (ACOG) committee concluded that there are no definitive data to support specific recommendations regarding estrogen use after endometrial cancer.[28]

### Alternatives to HRT for Menopausal Symptoms

The alternatives to traditional HRT have varying degrees of effectiveness. Unfortunately, no single agent can replace estrogen. Therefore, a number of therapies must be combined to achieve a similar response.

#### Vasomotor Symptoms

Antidepressants have been increasingly used for the treatment of vasomotor symptoms. Venlafaxine hydrochloride (Effexor), in a dose of 12.5 mg orally twice daily, has been shown to decrease the frequency and severity of hot flashes by more than 50% during a 4-week study.[29] Fluoxetine (Prozac), sertraline (Zoloft), and trazodone have also shown efficacy. Megestrol (Megace), a progestational agent, has been used effectively at a dose of 20 to 40 mg/d.[30] It has not been shown to prevent cardiac disease or osteoporosis but may improve hot flashes in up to 70% of patients. Megestrol has also been used for the treatment of metastatic breast cancer. Other progestins that can be used to manage vasomotor symptoms include medroxyprogesterone acetate, administered either intramuscularly (150 mg monthly) or orally (10 mg/d).[31]

Side effects of the progestins include increased appetite and weight gain. Uterine bleeding may occur with progestin withdrawal.[30] Neither megestrol nor medroxyprogesterone appears to have adverse effects on the lipid profile.[32] Although the progestins have been associated with depression and worsening of vaginal atrophy, they remain an excellent option for vasomotor symptoms in the breast cancer patient.

Clonidine hydrochloride, an alpha-adrenergic agonist used in the treatment of hypertension, is also effective in decreasing hot flashes.[33] It is available in patch (Catapres-TTS) and oral formulations. The 0.1-mg patch should be changed weekly. Alternatively, 0.1 mg of the oral form twice daily can be used. Side effects of clonidine include hypotension, lethargy, irritability, vomiting, and diminished reflexes.

Physical approaches, such as massage, acupuncture, exercise, and decreasing intake of caffeine, alcohol, and spicy foods, have also been tried, with varying results.

#### Osteoporosis

The alternatives to hormone replacement available for the management of osteoporosis are more effective and palatable than the options for vasomotor and genitourinary symptoms. Raloxifene hydrochloride (Evista) was approved by the FDA for the prevention of osteoporosis in December 1997. It improves the lipid profile and has no effect on the endometrium.[34] Hot flashes, however, appear to be increased in raloxifene-treated patients.

All patients should take 1,000 to 1,500 mg of calcium and 400 to 800 IU of vitamin D. Weight-bearing exercise for 30 minutes at least three times weekly is also effective in maintaining or increasing bone mass.

#### Phytoestrogens

The phytoestrogens are naturally occurring compounds found in over 300 plants that are functionally similar to 17-beta-estradiol. Although phytoestrogens bind to estrogen receptors, they are not steroidal estrogens.

Interest in the phytoestrogens stems from the quest to find a safer alternative to HRT. The belief that phytoestrogens may be this ideal alternative comes from indirect evidence obtained in Asian populations documenting a lower incidence of heart disease, as well as breast, uterine, and prostate
cancer, associated with high soy intake; the soybean is particularly rich in phytoestrogens.[35] The relative potency of the phytoestrogens is 2% that of estradiol,[36] and the precursors of the biologically active compounds can be found in soybean products (isoflavoenoids) and whole-grain cereals, seeds, and nuts (ligans).

Phytoestrogens act as estrogens and antiestrogens, depending on their concentration, the presence of endogenous estrogens, and patient gender and menopausal status. Their antiestrogenic activity is thought to be mediated by competitive inhibition with 17-beta-estradiol for the estrogen receptor. Some of the benefits of the phytoestrogens may be due to metabolic properties independent of their effects on the estrogen receptor. Currently, their benefits on the heart, for example, are thought to be mediated, in part, by the protein fiber moiety of the phytoestrogen, which affects lipid metabolism. Through their effects on bile acids, phytoestrogens may also decrease the risk of colon cancer. The intestinal flora plays a role in the concentration of phytoestrogens available, since the precursor compounds found in high-fiber foods are converted to phytoestrogens, which then exert their estrogenic or antiestrogenic effects.

Currently, the FDA is reviewing phytoestrogens for use only as cholesterol-lowering agents. Although the evidence is sparse, there is growing epidemiologic data to suggest that phytoestrogens may play a role in altering or preventing certain diseases. Specific therapies and doses have not yet been determined.

At the 1998 North American Menopause Society meeting, Brzezinski et al[37] presented the results of a study evaluating the effects of isoflavones in postmenopausal women. They found that soy capsules (20 mg/d) alleviated menopausal symptoms (P = .005), and improved the lipoprotein profile. Phytoestrogens may also protect against bone loss. There is growing evidence that phytoestrogens do not exert estrogenic activity on either the breast or endometrium. They are, in fact, antagonistic at these sites, preventing the usual proliferative changes induced by estradiol.[38,39]

More studies evaluating the effects of phytoestrogens on vasomotor symptoms, as well as on other parameters, need to be performed before conclusions regarding their safety and efficacy can be drawn.

Natural Remedies
Natural remedies have become increasingly popular in the treatment of menopausal symptoms. These alternatives have not been proven effective in any trials. Their dosage, efficacy, and safety remain uncertain.

Anecdotal evidence supports the use of vitamins B, C, and (particularly) E in the treatment of vasomotor symptoms.[40] Black cohosh, blue cohosh, chasteberry, Dong Quai, ginseng, licorice, and wild yam have all been used in the treatment of vasomotor symptoms, with varying efficacy. Ginseng is a root that contains plant estrogens. It can be taken as a capsule, tea, powder, or syrup. Extensive use may lead to hypertension, vaginal bleeding, insomnia, diarrhea, and irritability.[41] It should be noted that a search of the English literature reveals no placebo-controlled trials that support claims of the efficacy of herbal remedies in the treatment of menopausal symptoms. The results of a double-blind, placebo-controlled trial evaluating the efficacy of Dong Quai in a population of women with vasomotor symptoms showed no difference in the two groups for the following outcomes: endometrial thickness, vaginal maturation index, number of hot flashes (determined by Kuperman index or patient diaries), and serum estrone, estradiol, and steroid hormone-binding globulin levels.[42]

Genitourinary Symptoms
The effects of vaginal atrophy on a woman’s physical and psychological well-being can be as debilitating as the impact of vasomotor symptoms. No agent improves the vaginal mucosa and decreases the urinary symptoms of estrogen deficiency as effectively as does estrogen. Conjugated estrogen cream (Premarin), applied twice-weekly, is usually sufficient to maintain vaginal health. However, there is some systemic absorption of estrogen with the cream, particularly during the early phase of treatment when vaginal atrophy is worst; this poses a problem for women who are trying to avoid estrogens.

A new format for estrogen delivery, the vaginal estrogen ring (17-beta-estradiol [Estring]), is now available. The ring is thought to result in minimal systemic absorption, estimated at 7.5 mg/24 h.[43] The ring is inserted for a 3-month period and then replaced. We have used the vaginal estrogen ring in breast cancer survivors with good subjective response. Excluding the first 24 hours, the plasma estradiol levels remain in the untreated postmenopausal range, and there is no endometrial stimulation.

Vitamin E capsules also can be inserted into the vagina after making a small puncture and allowing
the contents to lubricate the vaginal mucosa. Other lubricants, such as Astroglide, K-Y Jelly, Vagisil, and Replens, can also be used. These methods, if effective, may take up to 3 months to relieve symptoms.

**Conclusions**

It is clear that more research on the management of menopausal symptoms must be done to maximize the physical and psychological well-being of postmenopausal women with and without cancer. It is equally important to keep in mind that no conclusive data support a causal relationship between HRT and breast cancer. There is clear evidence, however, showing the health benefits of estrogen, particularly in protecting against cardiovascular disease and osteoporosis. The facts must be put into perspective: A postmenopausal woman is far more likely to develop coronary artery disease than breast cancer. In the breast cancer patient, the greatest risk is the recurrence of cancer, and this must be weighed against the detrimental effects of estrogen deficiency and the possible causal relationship between hormones and breast cancer. Breast cancer survivors do not take the issue of hormone replacement lightly. If they choose to start HRT, it is a decision that requires great time and thought. If hormone replacement is to be prescribed in a breast cancer survivor, ideally it should be done in the context of a controlled trial so that the findings may finally help put to rest the question of safety. The Women’s Health Initiative, a prospective, randomized, controlled trial due for publication in 2005, may answer some of these questions. In the interim, we must be aware of the alternative treatments available and help our patients make individualized decisions based on their needs and desires.

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