Treatment of Estrogen Deficiency Symptoms in Women Surviving Breast Cancer, Part 2


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There are several million breast cancer survivors worldwide. In the United States, 180,000 women were diagnosed with breast cancer in 1997, and approximately 97,000 of these women have an extremely low chance of suffering a recurrence of their cancer. With an average age at diagnosis of 60 years and a 25-year expected duration of survival, the current number of breast cancer survivors in the United States may approach 2.5 million women. Since breast cancer is now being detected at an earlier stage than previously and since adjuvant chemotherapy may cause ovarian failure, an increasing number of women are becoming postmenopausal at a younger age after breast cancer treatment. This conference was convened in September 1997 to consider how menopausal breast cancer survivors should be treated at the present time and what future studies are needed to develop improved therapeutic strategies. A total of 59 breast cancer experts and patient advocates participated. The proceedings of the conference will be published in six installments in successive issues of oncology. The first part, published last month, defined the problem and explored its magnitude and ramifications for patient management. This second part focuses on the benefits and risks of hormone replacement therapy (HRT) in patients with breast cancer. [ONCOLOGY 13(2):245-267, 1999]

Introduction

Impact of HRT at and Prior to Breast Cancer Diagnosis

Paul Goss, MD: A preliminary analysis of results regarding the effect of receiving hormone replacement therapy (HRT) at and prior to the diagnosis of breast cancer could be of significant interest to clinicians, for several reasons:

1. It may help determine the appropriate adjuvant therapy for breast cancer in this setting.
2. If HRT is an important prognostic factor, it should be stratified for in randomized clinical trials or included in multivariate analyses.
3. It may be appropriate to reanalyze some of the larger published adjuvant therapy trials according to whether or not patients were receiving HRT.

Clinical Studies

Three previous studies relate particularly to these issues. One study, published in 1984,[1] focused on 63 postmenopausal HRT users and 165 nonusers who were diagnosed with breast cancer. In this study, Gambrell found that HRT users were more likely than nonusers to be diagnosed at an earlier stage of presentation and to have negative axillary lymph nodes. Harding and colleagues[2] reported on 108 postmenopausal HRT users (in this study, HRT use was defined as use for more than 3 months within the year prior to breast cancer diagnosis) vs 325 nonusers who also developed breast cancers. The researchers found that tumors in the HRT users were more likely to be well differentiated, or grade 1. The two groups did not differ significantly with respect to tumor size, steroid receptor status, or axillary nodal status. The third study, by Bonnier and colleagues from France,[3] compared HRT users vs nonusers and found fewer locally advanced cancers in the user group. In addition, the HRT users had more well-differentiated (infiltrating lobular and histologic grade 1) tumors. These researchers also found a lower incidence of estrogen receptor (ER) positive and progesterone receptor (PR) positive tumors in women taking HRT. In the study by Bonnier et al, 84% of patients were taking progesterone plus estrogen (ie, opposed estrogen), while 12% were receiving estrogen alone (unopposed estrogen).

Toronto Hospital Analysis

My colleagues and I studied the clinical and pathologic presentation of breast cancer in postmenopausal patients referred to a single institution in Toronto.[4] Because we required a sample...
size of 941 patients to detect a common odds ratio of 1.5 for the main primary end points of ER and PR status and overall nuclear grade of the tumors, we surveyed over 1,700 women. We included postmenopausal women who were amenorrheic for ≥12 months or had undergone a bilateral oophorectomy and who had histologically confirmed breast cancer or breast cancer in situ. We identified three groups: HRT nonusers (ie, those who have never used HRT), past HRT users, and current HRT users (ie, those who were HRT users at the time of clinical detection of breast cancer). From a sample of 985 eligible patients, we found 636 non-HRT users, 165 past users, and 184 current users. Among the current users, 40% were taking estrogen plus progesterone (ie, opposed estrogen) and 53%, unopposed estrogen. The majority of the past HRT users had received unopposed ERT, a few had received opposed estrogen, and a large number could not recall the type of HRT that they had taken.

The duration of HRT use was significantly longer, on average, in current users than in past users. Younger patients were more likely to be HRT users, as were women who had undergone a hysterectomy or had previously used oral contraceptives. Women with a family history of breast cancer were less likely to be HRT users.

Breast cancer was diagnosed by mammography more frequently in HRT users than in nonusers. Users were also more likely to be practicing breast self-examination (BSE) than nonusers and also were more likely to be undergoing regular mammographic surveillance.

Women who used HRT generally had their first mammogram at a younger age, and more commonly underwent needle localization as a method of diagnosis. Surprisingly, however, stage at presentation did not differ between users and nonusers. There was a small difference between past users and nonusers with respect to tumor size, but this was probably clinically irrelevant. There was no difference between users and nonusers with regard to the number of positive lymph nodes. More HRT users than nonusers had grade 1 tumors, however. This was true for both overall grade and nuclear grade. No difference was found in ER and PR status between the user and nonuser groups. However, there was a difference in ER positivity between women who received unopposed vs opposed estrogen: Patients who took opposed estrogen had fewer numbers of ER positive tumors than those who received unopposed therapy. These findings are consistent with progesterone's ability to reduce ER levels.

Our analysis thus confirmed previous clinical findings of more grade 1 and well-differentiated tumors overall among HRT users than nonusers but did not find the expected differences in ER and PR status. We did, however, show reduced ER positivity in women receiving opposed vs unopposed hormone replacement.

Discussion

Melody Cobleigh, MD, asked whether the issue of tumor differentiation was significant in multivariate or univariate analysis. Dr. Goss replied that the results presented were from a univariate analysis and that this analysis had not been completed.

Dr. Elizabeth Barrett-Connor asked how many patients in the study had in situ carcinoma. Dr. Goss answered that there were only 46 women with ductal carcinoma in situ (DCIS).

Trials of Estrogen in Breast Cancer Patients

Kathleen Pritchard, MD: Minimal data exist regarding the effects of estrogen replacement therapy (ERT) in women who have been diagnosed with breast cancer. The data used to counsel patients in this situation are extrapolated largely from those available in healthy women and, therefore, represent the etiologic risk associated with ERT/HRT. Extrapolation of these data is based on the implicit assumption that the increased risk of recurrence for a patient with a diagnosis of breast cancer is proportionately similar to the etiologic risk of developing breast cancer in a well woman taking ERT/HRT. In fact, we do not know whether this assumption is correct.

Observational Data

Currently available data are observational and of several types. First, some studies suggest that women who develop breast cancer during or in close temporal proximity to pregnancy have a worse prognosis. In contrast, Clark and Chua from the Princess Margaret Hospital[5] (as well as other researchers) have published series showing that women who became pregnant more than 1 year after a diagnosis of breast cancer seemed to do as well as matched controls who did not become pregnant. Undoubtedly, however, these series are subject to a “selection bias,” in that women who became pregnant after a diagnosis of breast cancer were self-selected for good prognostic features. Vassilopolou-Sellin and Zolinski[6] surveyed 224 randomly selected women with a previous diagnosis of breast cancer, 77% of whom were postmenopausal, about their attitudes concerning ERT/HRT.
They found that 8% of the women had taken ERT after their cancer diagnosis. The majority (78%) were afraid that they would develop a recurrence if they took ERT, but 70% were concerned about osteoporosis and heart disease. Slightly less than half (44%) of the women said that they would consider taking estrogen replacement under medical supervision.

Dr. Pamela Goodwin has developed a decision-tree model suggesting that, in women with node-negative breast cancer who have substantial menopausal symptoms, the decision to use ERT or HRT may be reasonable. This model assigns a number of risk estimates, however, some of which are quite uncertain.

In 1995, Dhodapkar et al described a small series of four patients who developed metastatic breast cancer while taking ERT/HRT.[7] Three of the women had been diagnosed between 8 and 15 years earlier and had been taking HRT for a protracted period. The fourth patient presented with metastatic disease while taking ERT.

All four women had a partial response of their cancer when the estrogen was withdrawn. This somewhat paradoxical observation shows that, even in women who have been taking estrogen for a prolonged period without breast cancer development or recurrence, once the cancer recurs or progresses, it may shrink in response to estrogen withdrawal.

**Effects of Estrogen on Control of Symptoms**

At least three case series of women with a previous diagnosis of breast cancer who received ERT/HRT have been published. Powles and colleagues[8] described 35 women who received estrogen plus tamoxifen (Nolvadex). They obtained good symptom control with 0.625 mg of conjugated estrogens (Premarin), although a higher dose was required in five women to control symptoms. The women received estrogen for a mean duration of more than 1 year and were followed for close to 43 months. There were only two relapses in the group, no more than might be expected in a group of similar size who were not receiving ERT/HRT.

Stoll[9] described 65 postmenopausal breast cancer patients who received estrogen and progesterone for 3 to 6 months and were followed for 2 years afterward. There were no breast cancer recurrences in this population. Symptom control was achieved.

Disaia[10] also reported on a series of 77 patients who began taking HRT about 24 months after the diagnosis of breast cancer and continued this therapy for more than 2 years. Data from this series, which have been updated several times, revealed only seven recurrences. This rate of recurrence is no greater than might be expected in a similar group of patients not receiving estrogen replacement. A single case-control study conducted by Eden[11] observed approximately 25 women who had taken HRT (cases) and 50 who had not taken HRT (controls) for 2 years. This study found no difference in recurrence rate between the cases and controls.

In a randomized, controlled trial conducted by Loprinzi et al,[12] megestrol acetate, given for 6 weeks, was more effective than placebo in relieving hot flashes in a group of patients with a previous diagnosis of breast cancer. Of course, with this short length of treatment, no data concerning recurrence could be derived.

**Ongoing and Future Research**

Dr. Vassilopoulou-Sellin is carrying out a randomized trial of HRT vs no therapy in women with a previous diagnosis of breast cancer. Another ongoing trial, the Hormonal Replacement Study After Breast Cancer: Is it Safe? (HABITS), is randomizing women with a previous diagnosis of breast cancer and more than four positive axillary nodes at the time of diagnosis who have not had any recurrence and have completed adjuvant systemic therapy, except for tamoxifen.[L. Holmberg, personal communication, 1998] These women will receive either HRT, as it is given in the local center, or no hormone replacement. Women with an intact uterus will be given estrogen plus progesterone, while those who have had a hysterectomy will receive estrogen alone. The study is of sufficient size to detect a difference between the projected recurrence rate in this group of women (20%) and a recurrence rate that would be 4% to 5% higher (ie, 24% to 25%). A total of 1,300 hundred women will be enrolled in this study, which is currently accruing participants in Sweden and other European countries.

Another study of similar design and size has been proposed in Britain but is not yet underway.[J. Haughton, M. Baum, personal communication, 1998]

Later in this conference, Dr. Cobleigh will discuss two pilot studies being conducted in the United States. A recent article written by Dr. Cobleigh and colleagues[13] suggests that prior to beginning randomized trials, we should carry out some preliminary work on outcome measures, including quality-of-life and symptom indices.

My group at Sunnybrook Health Science Center University in Toronto is currently involved in a
longitudinal, descriptive study of a group of women who have been diagnosed with breast cancer and who are about to enter menopause, either natural or chemotherapy-induced. We are administering a series of questionnaires and checking follicle-stimulating hormone (FSH) levels at 3-month intervals. Most interestingly, we are administering a probability trade-off task, an exercise in which risk-benefit information is used to assess a woman’s maximum acceptable increase in risk of recurrence of breast cancer (MAIRR) for the use of HRT. We will be collecting data on the results of this trade-off task as the women enter the study and also 3 months and 1 year after they become menopausal. We will thereby assess the MAIRR these women are willing to accept in order to derive the known and potential benefits of ERT/HRT, and whether their decision-making changes as they develop menopausal symptoms and experience those symptoms over a protracted period.

Discussion
Rena Vassilopoul-Sellin, MD, noted that are other case series of interest: one from Decker et al in Michigan[14] with approximately 100 patients, and one from Bluming et al in California[15] with 155 patients. Eden’s data includes about 160 patients, and Disaia and Brewster will be publishing data on 145 patients. These are all small series, however, and are largely without controls and/or are noninterventional, so that only limited conclusions can be drawn. Barbara Parker asked whether the data from Dhodapkar et al demonstrated the same principles of resistance as those seen when a woman’s breast cancer becomes resistant to tamoxifen after she has taken that agent for a long time. Dr. Pritchard replied that this might be the case. Michael Kleerekoper, MD, observed that surgeons and medical oncologists often give patients very different advice, with surgeons tending to oppose the use of ERT in patients with a prior history of breast cancer. Charles Loprinzi, MD, suggested that the poor prognosis related to pregnancy might actually be an effect of the relatively young age of the patient, and that the data of Dhodapkar et al[7] might indicate that there is a “&ldots; possibility of getting one more hormonal maneuver in these particular patients.” Dr. Pritchard agreed that this was possible. A number of comments related to menopausal symptoms. Jerilynn Prior, MD, expressed the view that it is the change in estrogen levels from high to medium or from medium to low that provokes hot flashes. She observed that around the time of menopause, progesterone levels are lower than normal, and there is a greater imbalance between estrogen and progesterone than at any other time in a woman’s reproductive life. Her own randomized, double-blind study comparing conjugated estrogens with medroxyprogesterone acetate in women who have had a premenopausal oophorectomy found no difference between the two with respect to symptom control.[16]

Properties of Breast Tumors in HRT Recipients

Melody Cobleigh, MD: In a review of the literature, three out of four breast cancer cell lines that were analyzed were ER negative and one was ER positive. In tissue culture, the ER positive lines showed an increase in tritiated thymidine uptake (a measure of DNA synthesis or cell proliferation) when estrogen was added and a reduction in tritiated thymidine uptake when tamoxifen was added.[17] The ER negative cell line did not respond in any way to either tamoxifen or estrogen. Similarly, human tumor xenografts were uniformly estrogen responsive if they were ER positive and estrogen unresponsive if they were ER negative.[18] The counterpart of tritiated thymidine labeling index is the proportion of cells in S-phase. Patients with a high S-phase are believed to have a poor prognosis.

HRT, S-Phase, and Prognosis
Based on the above data, if breast cancer in humans mirrors the animal or cell models, HRT should increase the S-phase measurement in ER positive breast cancer. Accordingly, women taking HRT at the time of breast cancer diagnosis should have an increased S-phase if their tumors were ER or PR positive and an unaffected S-phase if the tumors were ER or PR negative. Data from a manuscript submitted for publication suggest that this theory is correct. In patients with ER negative tumors, HRT did not affect S-phase. The Harvard Nurses’ Health Study[19] showed no difference in ER status between current HRT users and never-users—findings similar to those seen in a number of other studies. In the San Antonio database, tumors containing estrogen and progesterone receptors generally had a low median S-phase, whereas tumors without these hormone receptors had a high median S-phase. Our own data suggest, however, that HRT users whose tumors are ER positive are more likely to develop PR positive cancers and to have a high S-phase. The paradox here is that if a high
S-phase is a poor prognostic factor, it would seem counterintuitive that women using HRT would have a better prognosis when they develop breast cancer, as has been shown to be the case. Perhaps this is because HRT stimulates growth, allowing the cancer to be diagnosed sooner, before additional mutations that might confer resistance to adjuvant treatment or increased metastatic potential can occur. Also, when HRT is subsequently withdrawn, it may have a therapeutic effect. In eight studies in which the mortality of women who never used HRT and those who used hormone therapy was compared, once breast cancer was diagnosed, every study reported a reduced mortality among those receiving HRT at the time of breast cancer diagnosis.

The natural history of ER positive, high S-phase tumors may be less aggressive if patients with those lesions have been taking HRT. In other words, high S-phase in those cancers may be iatrogenic. Another very interesting group to consider are the HRT users with ER positive cancers that have a low S-phase. It is possible that these patients may have nonfunctional ERs and, consequently, may be unresponsive to tamoxifen, as well as to estrogen. This should be tested in prospective, randomized clinical trials.

It may therefore be suggested that trials of HRT in women with a previous diagnosis of breast cancer could be divided into two groups: For the ER positive patient, HRT plus tamoxifen could be compared with placebo. For the ER negative patient, women could be randomized to HRT vs placebo.

**Risk of Recurrence**

A breast cancer survivor who is thinking about taking HRT should understand the likelihood of recurrence over time. Analyzing data from the Eastern Cooperative Oncology Group (ECOG) on the annual hazards of recurrence is instructive in this regard (Figure 1 and Figure 2). [20] For node-positive patients, these data showed a very high risk of recurrence between years 1 and 2, with a gradual drop-off between years 4 to 5. Even up to 9 years, there was a 5% annual risk of recurrence. In the node-negative population, however, the annual risks decreased to approximately 0% to 1% after 5 years. It is in this population that HRT trials may be appropriate. The node-negative patients in this ECOG database have a worse prognosis than might be seen currently, as some of them did not receive adjuvant therapy.

Data amassed by Peter Rosen of Memorial Sloan-Kettering also is very instructive. Of the node-negative patients followed for 20 years in his institution who did not receive adjuvant therapy, 23% died of breast cancer and 6.5% of other cancers (some of these were colon cancers, against which HRT may be protective), whereas 10.4% succumbed to cardiovascular disease and 8% died of other causes. Only 50% of the cohort died. Death from cardiovascular disease is likely to overtake breast cancer as the major cause of death as this group is studied further. These data suggest that if women are at low risk of developing a recurrence of breast cancer, competing causes of mortality will be more important to them.

**Discussion**

Henry Burger, MD, asked whether these data would help clinicians decide whether to recommend HRT for some patients with a prior diagnosis of breast cancer. One participant thought that only randomized trials would answer this question.

Dr. Pritchard asked for clarification of the cut-offs for ER positivity and negativity. This is an important issue, as the current view is that only individuals with truly negative levels (ie, both ER and PR levels of 0) should be tested in trials of ERT vs placebo in which patients are not receiving tamoxifen.

Dr. Cobleigh was asked whether or not the data that she presented discouraged her from conducting a trial of ERT in women with a previous diagnosis of breast cancer. Dr. Cobleigh responded that, in the presence of tamoxifen, estrogen levels may be high, as they are known to be in premenopausal women, and that patients still respond to tamoxifen with tumor shrinkage. Thus, ER positive patients should be randomized to tamoxifen plus HRT vs tamoxifen plus placebo.

Dr. Pritchard observed that even if some of these patients do have a slightly increased risk of recurrence with estrogen, they might still wish to take estrogens. Since clinicians do not know the magnitude of the increased risk, however, they cannot advise these patients. Dr. Cobleigh added that it is important to look at these different prognostic factors as future technology allows analyses to be made of very small amounts of tumor tissue.

Richard Santen, md, commented on the hazard ratios and the fact that women continue to develop recurrences at a low but constant rate in both the node-negative and node-positive groups. Dr. Cobleigh replied that the statistician who presented the ECOG data suggested that there were too few observations after 9 years to be certain of this trend, and that although it looked like the recurrence rates had reached a plateau, it is unclear whether they might actually be decreasing. Other data show that even at 30 years of follow-up, women who have had surgery for breast cancer
continue to die from breast cancer at a higher rate than the general population. This may relate, in part, to the development of contralateral primaries.

Asked about the design of future studies, Dr. Cobleigh suggested that it seemed that a trial assessing ERT vs placebo would be appropriate in an ER negative cohort, while randomization to ERT plus tamoxifen vs tamoxifen plus placebo would be safer in an ER positive cohort. If tamoxifen is only being given for 5 years, however, the duration of ERT might only be 5 years and thus the only outcomes of interest would be those of symptom control.

Dr. Prior commented on the fact that it might be impossible to conduct a blinded trial testing ERT vs placebo because of the symptom control achieved. She added that it might be appropriate to separate premenopausal and perimenopausal women from postmenopausal patients because, for example, tamoxifen may produce bone loss in premenopausal women and perhaps they should not be treated in a trial such as this one. Dr. Prior also suggested that medroxyprogesterone or oral micronized progesterone should be studied. Dr. Cobleigh responded that the ECOG study is being conducted only in postmenopausal women.

### Ongoing Trials of HRT in Women With Breast Cancer

Rena Vasiliopoulou-Sellin, MD: HABITS, a Scandinavian multicenter study, will include approximately 1,300 women who have breast cancer diagnoses ranging from in situ through stage II disease. These women will be stratified by center, HRT before diagnosis, and concomitant tamoxifen use during the study. The intervention will be HRT given for 2 years, according to current practice at the individual centers.

A second ongoing study in Europe is examining the use of tibolone (Livial), a compound that has been designed for menopause management. Tibolone has antiestrogenic effects on the breast and uterus, a positive estrogenic effect on bone, and an androgen component that is designed to improve libido but may have adverse effects on high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol levels.

A pilot study evaluating the effect of this drug on symptoms and its endometrial safety has begun within the past year. The interventions are tamoxifen plus tibolone vs tamoxifen plus placebo. The pilot study will accrue 32 patients to each arm and patients will be treated for 12 months.

Dr. Cobleigh and other ECOG investigators are planning a randomized study in which subjects will be stratified, prior to randomization, by tumor size, history of a hysterectomy, and symptoms. Women with an intact uterus will be randomly assigned to receive tamoxifen plus placebo vs tamoxifen plus progesterone and estrogen, whereas those who do not have a uterus will be randomized to tamoxifen plus placebo vs tamoxifen plus estrogen. Treatment duration will be 6 months. This pilot study will enroll slightly more than 100 patients, and the end point will be symptom relief. The study will open soon, pending successful preparation of a placebo tablet.

Dr. Albain is coordinating a Southwest Oncology Group (SWOG) study in which the intervention will be placebo vs megestrol acetate (20 mg/d, with a possible escalation to 40 mg/d for 9 months) for treatment of menopausal symptoms. Accrual is to begin shortly.

Dr. Vassilopoulou-Sellin and colleagues at M. D. Anderson Cancer Center are conducting a prospective, randomized trial of patients with stage I or II disease who have been free of disease for at least 2 years if their tumor is ER negative or for 10 years if ER status is unknown. Patients are being stratified by age and ER status to receive either conjugated estrogen on days 1 through 25 for 5 years or no treatment. End points are disease recurrence and skeletal health preservation. History, physical, and gynecologic examinations are being performed regularly. Quality-of-life data, lipid measurements, and symptom review data are being collected and will be analyzed but are not statistical end points.

Progesterone was omitted from the study design because of the relatively short duration of intervention and because of its potential adverse effect on breast cancer, insulin resistance, and lipid changes. Placebo was omitted from the trial because of the difficulty in fabricating it without pharmaceutical industry support, and the fact that placebo alone would not influence breast cancer recurrence or bone mineral density. A total of 100 patients have entered the study over the past 5 years, most of whom are in their 50s and 60s. The researchers expect to begin analyzing the data within the next 2 years.

### Discussion

JoAnn Pinkerton, MD, raised the issue of the effects of using conjugated estrogens alone for 5 years. Since atypical endometrial hyperplasia may develop in as many as 25% of patients within 1 year, she argued that these women ought to have ultrasound scans and endometrial biopsies. Dr.
Vasilopoulou-Sellin replied that this was not a focus of her study, but that all of the study participants had independent gynecologic evaluation and intervention as needed. The participants agreed that emphasis should be focused on the fact that patients have different perspectives than physicians, and that the former are often more concerned with immediate symptoms than with long-term cardiovascular and bone disease. A patient’s willingness to trade off an increase in risk of breast cancer recurrence for a reduction in symptoms may vary over time and at different stages of disease. Other patients continue to be concerned about breast cancer recurrence, however, and want a better understanding of the exact risks associated with ERT. Dr. Vasilopoulou-Sellin commented that there are a number of other symptoms that were not considered as end points for treatment 10 or 15 years ago. She added that our views regarding the prevention of osteoporosis have changed in the 1990s and that the cardiovascular effects of HRT are understood much more clearly today. We now know that, in addition to effects on lipid levels, estrogen has very important direct effects on blood vessels and vascular endothelium. The effects of HRT in reducing the risk of developing Alzheimer’s disease may be important as well.

Patricia Ganz, MD, a medical oncologist observed that, although she sees patients with significant menopausal symptoms, the patients are frightened of estrogen and its potential effect on recurrent breast cancer.

The issue of phytoestrogens was also raised. Many herbs sold on the market for relief of menopausal symptoms, for example, alfalfa flowers, ginseng tea, and black cohosh, are clearly estrogens and have been shown to cause endometrial hyperplasia and to lower FSH levels in laboratory rats. Other issues to consider are legitimate concerns about quality control, on the one hand, and prevailing attitudes that herbal therapies are safe because they are “natural,” on the other.

One participant asked why the accrual of patients in Dr. Vasilopoulou-Sellin’s study was slow. She replied that, although she approaches many eligible women, the study remains limited largely to M.D. Anderson patients. The participants are referred from a wide variety of physicians, but significant reluctance to take estrogen still persists. Unfortunately, many potential participants ultimately have chosen not to participate in this clinical trial.

Risk-Benefit Ratios of Estrogen on Health Outcomes

Kathy Helzlsouer, MD: Little information is available to assess the risk of ERT among breast cancer survivors. Most of the information relating ERT to the development of breast cancer, even in well women, comes from observational studies. Patients with a previous diagnosis of breast cancer should be approached in a manner similar to that used for women with a family history of breast cancer or other factors that place women at increased risk. These otherwise healthy women are also worried about the effects of ERT on breast cancer risk because they are at a high risk of developing breast cancer.

The results of meta-analyses show an increased risk of developing breast cancer with long duration of HRT.[21] Prospective cohort studies with long-term follow-up show interesting associations between current and past use of HRT and subsequent breast cancer. Substantial data exist for the use of estrogen alone, but less data regarding estrogen plus progesterone are available. There does not seem to be a significant difference between the use of estrogen alone and estrogen plus progesterone.

In a study of participants of the Breast Cancer Detection and Demonstration Project,[22] an increased risk was found among current HRT users with long duration of use. However, among past users, no association was found, even with³15 years of HRT. Similarly, the Nurses’ Health Study[19] found an increased risk of breast cancer only among current users. In this regard, current HRT use ranging in duration from <2 years to ≥10 years was associated with an increased breast cancer risk. Notably, there was no increased risk for past users who had used HRT for ≥10 years.

A question that arises commonly is whether known risk factors amplify the increased risk imparted by HRT use. The effect of a positive family history for breast cancer is the major focus of this query. In the Nurses’ Health Study, women with a family history of breast cancer did not have a greater increase in risk with HRT use than did women without a family history. In fact, no increased risk associated with HRT use was observed among women with a family history of breast cancer.[19]

Overall Mortality inWomen Receiving HRT

In considering HRT, it is necessary to integrate the sum of all risks and benefits associated with HRT. Ettinger et al[23] compared all-cause mortality in postmenopausal women using estrogen vs matched controls with over 20 years of follow-up. Estrogen users had a better survival than nonusers. Studies that have looked at relative risk and mortality among ERT users also have shown a
reduction in risk of mortality from all causes associated with estrogen use. The fact that this finding is consistent across different populations and different studies is reassuring. It suggests that estrogen use is not only associated with breast cancer development but also with effects that reduce mortality from other causes. We know, however, that women who take estrogen have different health behaviors. Consequently, one must conclude that these findings are associated with reduced mortality but not necessarily causally related.

The Nurses’ Health Study examined the overall mortality issue.[24] The most recent report includes postmenopausal women using HRT up to 1994. This analysis showed a reduction in risk of death from all causes among current HRT users. Specifically, the relative risk of dying from cardiovascular disease and stroke was 0.6.

The beneficial effects of HRT were limited to current users. There was no mortality reduction in past users who had used ERT for < 5 years, 5 to 10 years, or ≥ 10 years. Among current users, there was approximately a 50% reduction in mortality with up to 5 years of use. The magnitude of this reduction decreased somewhat with longer use, however. It seems that there was a higher risk of breast cancer death in long-term users; however, the overall mortality reduction, even with long-term use, was significantly lower among users compared to nonusers.

The Nurses’ Health Study also examined women with regard to cardiovascular (CV) risk factors, family history of breast cancer, smoking history, and body mass index. The women with the highest risk of CV disease derived the greatest protective effect from taking HRT. Among women at low risk of CV disease, HRT still exerted a protective effect, but it was of lesser magnitude. Reduction in overall mortality with HRT was similar for women with a family history of breast cancer, women who smoked, and across weight categories.

Risk-Benefit Analysis

A study by Grady et al.[25] examined the projected probabilities of selected diseases. For the average 50-year-old woman, for example, heart disease had a projected incidence of 46% and a mortality of 31%, respectively; stroke, a 20% incidence and 8% mortality; hip fracture, a 15% incidence and 1.5% mortality; and breast cancer, a 10% incidence and 3% mortality. For heart disease, Grady and colleagues estimated an odds ratio of 0.65 in ER users and a relative risk of 0.8 in combined HRT users. For stroke and hip fracture, there was no difference between ERT and combined estrogen/progestin replacement use. For endometrial cancer, there was an eightfold increase in risk for unopposed estrogen use among those who had not had a hysterectomy, but the use of combined estrogen plus progestin tended to eliminate that risk.

In the study by Grady et al, the net change in life expectancy for HRT users was positive for almost every risk group examined. For individuals with no risk factors, there was a 0.9-year gain in life expectancy with HRT use. For women who had undergone a hysterectomy and had no risk factors, there was a 1.1-year gain in life expectancy. For those with a history of coronary heart disease, there was an even greater gain in life expectancy. For women at high risk for breast cancer, there was still a mortality benefit overall. For women at risk for hip fracture, there was no real mortality benefit for ERT. The benefits were fairly similar for ERT and for combined HRT.

Symptomatic Relief and Other Benefits

Most women desire symptomatic relief of acute menopausal symptoms, such as hot flashes, problems with incontinence and urinary tract infections, and sexual dysfunction. However, women recognize that ERT may also reduce the risk of colon cancer and Alzheimer’s disease. Possible adverse effects of HRT on increasing the frequency of gallbladder disease have not really been a consideration.

Several studies show a benefit of long-term ERT in reducing colon cancer mortality. In one such study, conducted by the American Cancer Society,[26] with increasing years of estrogen use, there was a dose-response effect in lowering the risk of colon cancer mortality.

Decision Analysis

A recent study examining personal decision-making through risk-benefit analysis (Figure 3) focused on the hard end points of osteoporosis, heart disease, overall mortality, breast cancer risk, and elevated blood pressure.[27] The data suggested that women at high risk of breast cancer and low risk of CV disease might not choose HRT based on relative risk factor analysis. Women in most other groups would use HRT.

This study estimated gains in life expectancy from HRT at over 40 months for women at risk for heart disease but low risk of breast cancer. In almost every group except those at high risk for breast cancer and low risk for heart disease, there was some benefit in years or months of life gained. Similar data are not available regarding the relative risks and overall survival among women in whom breast cancer has already been diagnosed. Whether clinical trials can be performed to
address this issue is uncertain. However, if we are not going to prescribe hormones for women with a previous diagnosis of breast cancer, we need effective alternatives to alleviate menopausal symptoms and provide overall health benefits. We have to examine the reasons why women are seeking HRT and treat them accordingly.

Discussion

Jeffrey Perlman, MD, noted that an increase in mortality related to breast cancer was observed in the recent Nurses’ Health Study. Dr. Helzlsouer agreed with this statement, but commented that it did not totally offset the overall reduction in mortality. There was still a significant reduction in overall mortality, even in patients who had been taking ERT for the longest periods. The substantial reduction in heart disease mortality completely offset the statistically significant increase in mortality from breast cancer.

Dr. Helzlsouer was asked why a family history of breast cancer did not affect the apparent risk of using HRT. In the decision analysis that she cited, a positive family history weighed against the use of hormone therapy. Dr. Helzlsouer stated that this is a paradox, which relates to the model used. However, even among those with one risk factor for heart disease, the model showed a benefit of estrogen replacement. Dr. Helzlsouer added that, in her view, a positive family history was not a definite contraindication to ERT.

Dr. Barrett-Connor asked about data showing that duration of HRT use is an important covariate, and inquired whether such data raise concerns over using quality of life as a reason to take estrogen. She noted that other modalities are available to manage heart and bone risk, including some of the newer drugs (eg, lipid-lowering agents and potent antiresorptive agents to prevent or treat osteoporosis). While conceding the convenience of only taking one pill, she asserted that only with respect to relieving symptoms is estrogen much more effective than any other alternative.

Dr. Barrett-Connor then speculated that a patient might not require treatment for symptoms for a full 5 to 10 years, but rather, only for a few years. Patients might be relatively asymptomatic with 3 to 5 years of use, followed by gradual tapering. In fact, many women stop taking ERT when they become asymptomatic and no longer need it. Thus, she wondered whether it would be possible to prescribe estrogen for shorter periods, either in women with a previous diagnosis of breast cancer or those without such a history, without raising the risk of breast cancer too much.

Dr. Helzlsouer stated her belief that, for control of symptoms, estrogen is still the most effective therapy. She pointed out, however, that some women with a strong family history of breast cancer may also have a high family risk for heart disease, and that one has to weigh all of these issues.

British Columbia Analysis of the Impact of HRT on All-Cause Mortality

Joseph Ragaz, MD: The mortality from breast cancer over the last decade has declined significantly despite a continuing rise in incidence. This is probably due to earlier diagnosis by mammography and screening, as well as the use of adjuvant chemotherapy and hormonal therapy. As a result, however, more women are being given treatments that result in early menopause. Currently, because of insufficient research, however, most of these women are denied the potential benefits of hormone replacement.

Predicting Mortality Outcomes

In this analysis, overall (net) all-cause mortality outcomes of HRT were calculated, looking at the interaction of multiple conditions known to be affected by HRT. These include breast cancer, uterine cancer, cardiac events, colon cancer, hip fractures, and thromboembolic episodes. The calculations were based on previously published methodology of age-matched all-cause mortality, designed for mortality outcomes in association with tamoxifen.[28]

The analysis used death rates in Canada from 1991 to set the mortality values for nonusers as controls. Relative risks (RRs) of each condition (as obtained from the literature) were then applied to the mortality of controls (nonusers) in order to calculate the mortality for ERT users. The figures were expressed as absolute numbers per thousand and summed as the avoidance and excess of deaths in nonusers and users (Table 1). The methodology then defined a maximum limiting relative risk (RRlim) of breast cancer, which would be required to erase the mortality impact of all other causes (ie, nil increase or excess of overall mortality).

It is important to consider the results of analyses for women who start HRT at different ages. Thus, calculations showed that, for patients using HRT for 5 years, the overall numbers of avoided deaths at the follow-up of 10 years were 2.6, 10.4, and 34.5 for women 50, 60, or 70 years old, respectively. The increased proportion of avoided deaths with increasing age at the start of HRT was due, in large part, to the more substantial reductions in cardiovascular (CV) events due to estrogens.
For breast cancer in women ages 50, 60, or 70 years, the RRlim was calculated as 1.2, 2.2, and 3.8, respectively. This means that giving HRT to women age 50, 60, or 70 years, the RR values of breast cancer mortality could increase up to 1.2, 2.2, or 3.8, respectively, before overall (net) mortality outcomes from other conditions were reduced to 0. Similar analysis showed that if the calculations are projected to age 90, the HRT benefit would be increased, with the RRlim for breast cancer in women ages 50 and 60 years of 1.7 and 3.0, respectively.

The relative risks of incidence and of mortality due to HRT may not be the same, for a variety of reasons (eg, differentiating effects of hormones for conditions, effects of early detection). Indeed, there is evidence from recent epidemiologic studies that while the incidence of breast cancer due to HRT may be raised moderately, the mortality in HRT users is reduced compared to that of nonusers, perhaps because women on HRT tend to develop better-differentiated tumors.

In this newly developed methodology for calculating all-cause mortality outcomes, new values of RRs can be applied, as they become available in longer follow-up, to recalculate at any future time new overall (net) mortality outcomes in different age groups, as new data become available. While quality of life is important to these patients, these analyses were restricted to mortality calculations only.

**Discussion**

Sandra Swain, MD, asked whether it would not be better to use lipid-lowering drugs and bisphosphonates, and not estrogen, to attain the CV and bone benefits without increasing the breast cancer risks. Dr. Ragaz agreed that this was another approach, but that it might not have the quality-of-life advantages of using estrogen.

The issue of mortality benefits from 5 years of HRT was raised, along with the question of whether, in fact, the relative risks cited by Dr. Ragaz were actually related more to long-term use of HRT. Dr. Ragaz responded that the calculated outcome results are restricted only to ≤5 years of HRT.

Responding to queries about the way in which developing breast cancer and dying from breast cancer is factored into the analysis, Dr. Ragaz pointed out that breast cancer, like all of the other mortality causes outlined above, has been factored into these calculations, as indicated by the methodology,[28] in order to obtain survival estimates reflecting the overall (net) mortality impact of HRT. It was also asked whether the use of low-dose HRT has been tested in a model such as this. Dr. Ragaz responded that he did not know whether the half-dose HRT would have the same or proportionately lower relative risks and stated that half-doses were not used in this analysis because of insufficient published data.

**Vital Statistics Model of Longevity Effects of HRT**

Jeffrey Perlman, MD: The FDA-approved indications for ERT at the time of the 1993 National Cancer Institute (NCI) conference were for short-term relief of menopausal symptoms and long-term prevention of osteoporosis. Based on the Grady-Rubin-Petitti model, the main long-term benefit of hormone replacement appears to be the prevention of heart disease. This conclusion is based on incomplete data, since no randomized trials have as yet been conducted.

At the NCI conference, Dr. Robert Dickson reviewed a series of studies regarding hormones and breast cancer development. He showed that both estrogen and progesterone stimulate the development and progression of breast cancer. Most of the literature suggests that estrogens cause breast cancer, but more recent evidence also implicates progesterone.

Together, estrogen and progesterone contribute to uncontrolled proliferation and local invasion, although this effect decreases over time. Hormones probably play a greater contributory role in the early stages of breast cancer initiation than to metastatic progression. Thus, hormones may increase the incidence of second primary tumors more than they affect recurrence.

**A New Model**

Next, the NCI conference group considered the work of Harvey in Britain, published in 1985, showing that breast cancer survivors have a threefold increased risk of second primary tumors (ie, contralateral breast cancers). This was factored into the model. The group concluded that the increased risk of developing a primary breast cancer was 1.03 for ERT and 1.04 for HRT for every year of use.

A modeling exercise was carried out in which yearly death rates for coronary heart disease, breast cancer, hip fracture, and endometrial cancer among 1,000 controls were estimated, and the estimates were considered iteratively over a 45-year period. In this model, 1,000 women were then considered to be exposed to HRT and the death rates were adjusted for this effect.

With estrogen usage, the overall mortality estimates decreased. However, the disease-specific
mortality estimates from breast cancer increased. Mortality from hip fracture declined, whereas mortality from endometrial cancer mortality rose. Overall, women at no special risk for breast cancer who took estrogen enjoyed 1 extra year of life expectancy. For some women with a family history of breast cancer, estrogen use resulted in 2 additional years of life expectancy. For women at high risk of coronary heart disease, the increased life expectancy with estrogen was 1.6 years.

In the general population, the lifetime risk of breast cancer mortality was only 3.3%. With HRT, it increased to 4.2%. With respect to heart disease, there was a 22.3% lifetime mortality risk among the general population, which declined to 15.7% with ERT. Thus, there is a large reduction in heart disease (7%) and a small increase in breast cancer mortality (1%) with ERT. This explains the general mortality benefits seen in the average person.

**A Model for Breast Cancer Survivors**

Breast cancer survivors are different. First, the model had to take into account their altered risks of endometrial cancer and pulmonary embolus (related to tamoxifen). Three scenarios were assumed. The first was a worst-case scenario in which all breast cancer mortality would increase by 40%, a relative risk of 1.4. Then there was a best-case scenario, in which only the incidence of second primary tumors would increase and there would be no increased risk of recurrence. In the very-best-case scenario, there would be no effect of ERT. For baseline breast cancer mortality in survivors, the standard textbook explanation by Fox was used. In this explanation, breast cancer survivors fall into two groups: a high-risk group who die at a rate of approximately 25% per year, and a low-risk group who dies at a rate of 2.5% annually. Various combinations of these patient groups result in different scenarios.

First, using the model for breast cancer mortality in women with a previous diagnosis of breast cancer, the model was checked against known results of studies, such as the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-6 and B-14 trials. The predicted survivors from the model fitted very closely with what was actually seen in those two trials.

Next, the group looked at the worst-case scenario in which there was a 40% increase in all breast cancer, new second primaries, and recurrences. That model resulted in “a disaster.” Obviously, estrogen replacement would not be used in that situation.

In the best-case scenario, only new breast primaries were affected by ERT, and there was only a 4% increase in breast cancer mortality. Nonetheless, the increase in mortality from breast cancer in this group was of sufficient magnitude to outweigh the other benefits relative to CV events and deaths from osteoporotic fracture.

To summarize, taking ERT under the best-case scenario for 2 years, 10 years, 10 to 20 years, or > 20 years had no effect, either positive or negative, on survival. Consequently, in terms of long-term beneficial effects, there would be no point in taking ERT. On the other hand, if a woman wished to take estrogen replacement for symptom control, it would not have deleterious effects on overall mortality.

In seeking an explanation for this situation, one has to realize the most common cause of death in breast cancer survivors is breast cancer. The issue of competing causes of mortality comes into play when a benefit from decreased CV mortality may be offset by an increase in breast cancer mortality. Under the very-best-case scenario, HRT would not increase breast cancer mortality, which might lead one to believe that there would be an overall mortality benefit. In fact, however, women continue to die from breast cancer at such a high rate that the other effects are basically negligible. In other words, if a therapy does not an impact on breast cancer mortality in breast cancer survivors, it will not affect overall life expectancy to any great degree.

**A Model for Tamoxifen and Progestin**

Following these rather discouraging results, the group went on to model the case for tamoxifen and progestin. This model assumed that breast cancer mortality decreased by 14% in response to tamoxifen (as shown in clinical studies) and that the addition of progestin reduced the risk of endometrial cancer (an assumption only, as there are no relevant data available). The model factored in the risk of pulmonary embolus associated with tamoxifen.

The increase in life expectancy in the breast cancer survivor population exceeded the survival benefit expected in the general population from using HRT. This model assumed a 15-year effect from 5 years of tamoxifen use, which is known from published studies. The group suggested that since Loprinzi and coworkers have shown that megestrol acetate reduces vasomotor symptoms,[12] it might be a better drug than estrogen to study.

**Conclusions About Mortality Models**

Several conclusions may be drawn regarding applied mortality models.
1. A model is only as good as its weakest assumption, and there are many weak assumptions in this model.
2. Perhaps despite this, the model suggests that alternative forms of HRT (i.e., the tamoxifen/progesterone model) may be the best to pursue.
3. Although HRT probably increases life expectancy in the general population, it cannot do so in breast cancer survivors because of their high risk of death from breast cancer.
4. In a best- or very-best-case scenario, a short-term trial of HRT would probably be reasonable for symptom control. It would be very important, however, to establish that the worst-case scenario is not true for breast cancer recurrence, as this could be a disaster.

Discussion
Dr. Ragaz suggested that his mortality model reached conclusions similar to those of Dr. Perlman's model. Both models showed that, in breast cancer survivors, breast cancer mortality is by far the leading cause of death, and that the overall mortality from breast cancer could offset the potential benefits of HRT with respect to heart disease. It is very likely that HRT may slightly increase the risk of cancer relapse, and this possibility must be taken into account when weighing treatment options. Dr. Perlman emphasized that all of his observations point to the need for good clinical trials in which ERT can be tested safely.

Dr. Vassilopoulou-Sellin raised a question about the role of tamoxifen beyond 5 years and whether it was deleterious. Dr. Perlman stated that he was doing all of his modeling based on 5 years of tamoxifen, which is assumed to be the optimal duration of therapy based on currently available data. Dr. Swain asked whether the model considered or analyzed the possibility that the combination of tamoxifen plus progestin might reduce or negate some of the benefits of tamoxifen. Dr. Perlman replied that he had not considered that possibility.

Dr. Ragaz suggested that a very-best-case scenario might demonstrate that ERT could cause a reduction in mortality from breast cancer even though it increased the number of breast cancers. This would imply that fewer women would die from their breast cancer under these circumstances.

Dr. Perlman also pointed out that the Nurses' Health Study did show a reduction in breast cancer mortality for the first few years of HRT, and that sooner or later the breast cancer mortality catches up. For this reason, short-term use of hormone replacement might be a good idea, Dr. Perlman speculated.

Dr. Helzlsouer raised the issue of the quality-of-life effects of hormone replacement with regard to hip fracture and heart disease, and Dr. Perlman agreed that these effects are important. Dr. Burger questioned the 20% reduction in heart disease mortality used in the Perlman model. Dr. Perlman stated that in his best-case scenario, the reduction was estimated at 30%. Dr. Burger suggested that the decrease in mortality might be as high as 50%. Dr. Perlman agreed, but felt that in the breast cancer population, breast cancer mortality would still outweigh the benefit of such a reduction.

Perspective of a Breast Cancer Survivor
Andrea Martin: I speak as a representative of other women with breast cancer, as a patient twice diagnosed with breast cancer, as an engaged feminist, and as an educated breast cancer advocate. At the age of 42, only 5 months after a negative mammogram, I was diagnosed as having a 7-cm breast tumor with positive lymph nodes. I was the first person in my family to have breast cancer. I had to undergo mastectomy, chemotherapy, radiation therapy, and further chemotherapy after that. I chose not to have breast reconstruction.

I went through menopause after my first infusion of cyclophosphamide, Adriamycin, and fluorouracil (CAF), which was extremely difficult. I lost all libido, and also lost the ability to become pregnant. I worried that my 6-year-old daughter might someday develop breast cancer. I entered into a trial of residoronate vs placebo for bone density loss but was on the placebo arm and suffered considerable bone loss.

A new primary tumor less than 1 cm in size was found in my other breast 2-1/2 years after the first diagnosis. I had a second mastectomy and began taking tamoxifen. The hot flashes and night sweats that had started to abate recurred. My libido remained absent, but, ultimately, I sought help regarding this problem. Through practices that focus on communication, commitment, and consciousness in love-making, I have regained my sexual energy. Without the use of chemicals or creams, I am discovering a greater capacity for sexual fulfillment, sensuality, and intimacy than I had experienced before my breast cancer diagnosis.

I started the Breast Cancer Fund in order to improve knowledge about the disease and help my...
daughter and thousands of others avoid this problem. This fund-raising, grant-making, problem-solving organization now represents over 60,000 supporters nationwide.

I urge clinicians to exercise extreme caution in advising any woman who has had breast cancer to use estrogen replacement. I encourage creativity in designing interim alternatives and future research. I feel that it seems counterintuitive to prescribe estrogen until it has been proven safe in this setting. I stress this only because the endocrine system is very subtly balanced and, as you know, is easily disrupted.

References:


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