Treatment of Estrogen Deficiency Symptoms in Women Surviving Breast Cancer, Part 1

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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 47 breast cancer experts and 13 patient advocates participated. The proceedings of the conference will be published in six installments in successive issues of oncology. This first part defines the problem and explores its magnitude and ramifications for patient management. [ONCOLOGY 1(13):109-136, 1999]

Introduction

Henry Burger, MD: Estradiol levels are well preserved until the onset of the menopausal transition—a phase in a woman’s life marked by physiologic changes that indicate the approach of menopause. During that transition, hormone levels may fluctuate widely and symptoms begin to occur. Concentrations of estradiol fall by about 90% during the time when the final menses are experienced, although the lowest levels are not usually reached until 1 to 3 years later.

Interestingly, despite that very marked fall in estradiol, the impact of menopause may vary from woman to woman in the same community and among women in different communities and different countries. Community surveys indicate that the impact of menopause is not very great for the majority of women but is very great for a minority.

Clinical Indications for HRT

Hormone replacement therapy (HRT) may be used for both short-term symptom control and for the long-term prevention of a number of disorders resulting directly or indirectly from menopause (Table 1). Short-term symptom control may be required for hot flashes; symptoms that result from lower genital tract atrophy, such as difficulty with intercourse or urination; sleep disturbances; or mood disturbances.

For long-term disease prevention, a number of indications for systemic hormone therapy are generally accepted. Apart from the preservation of postmenopausal quality of life, however, none of these indications has been rigorously established. The consensus view is that established indications include a reduction in the risk of osteoporotic fracture, treatment of established osteoporosis, and a reduction in atherosclerotic cardiovascular disease risk, particularly myocardial infarction.

Reducing Osteoporotic Fracture and Treating Osteoporosis

Osteoporosis is a major cause of morbidity, mortality, and health expenditure but with variable prevalence worldwide. About 75 million women in the United States, Europe, and Japan are affected. One in three postmenopausal women will suffer from the consequences of this disease, the majority being elderly. In US women, about 1.3 million osteoporotic fractures occur annually, at a cost of $10 billion to the health-care system. Most significant is hip fracture, which may result in a 1-year mortality of 12% to 20% and frequently leads to a loss of the woman's independence. Estrogen deficiency increases bone remodeling and leads to bone loss. Estrogen administration reverses that process, although all of the mechanisms involved are still unclear. The effect ceases
when therapy is discontinued. Many believe that the greatest benefit of estrogen is seen when treatment is initiated within 5 years of menopause, although there is no consensus on when treatment should be initiated or for how long it should be continued. No controlled clinical trials have shown a reduction in hip fracture in women given estrogen replacement therapy. In placebo-controlled studies, only a small number of patients have shown actual reductions in fractures, such as vertebral fractures. The dose of estrogen is important, while the route is probably not. The effects of progestins on bone mineral density are variable.

**Reducing Cardiovascular Disease**
The impact of HRT on cardiovascular disease is generally regarded as a major focus of research. Mortality data from Australia in 1993 showed that 47.5% of all deaths in women were due to cardiovascular disease and 23.8% were due to coronary heart disease.[1] In contrast, breast cancer accounted for 4.7% of deaths, which is approximately one-fifth of total coronary heart disease mortality.

Mortality from breast cancer, when compared to mortality from heart disease, varies as a function of the age group in which that comparison is made. Rather old US data on age-specific death rates indicate that breast cancer mortality never reaches the figure for heart disease. However, more recent data suggest that the prevalence rates may converge, particularly in the 50- to 60-year-old age bracket.

To demonstrate an effect of estrogen in the prevention of coronary heart disease, randomized, controlled clinical trials are required. Observational and case-controlled studies show that estrogen probably reduces the risk of heart disease, and the general consensus favors that conclusion. Rigorous proof will be lacking, however, until the proper studies are reported.

**Primary Prevention**—With respect to primary prevention, a variety of observational epidemiologic studies have shown that estrogen users have a reduced risk of developing heart disease; generally, the magnitude of this reduction is approximately 50%. Estrogen administration has demonstrated acute and chronic effects in both human and animal studies that are consistent with such a protective effect. The mechanisms of estrogen’s effects are large in number and include favorable effects on serum lipids, as well as a wide variety of direct effects on the vasculature. Despite figures to the contrary, the more recently published major studies suggest that progestins do not exert a major influence on the beneficial effects of estrogen.

**Secondary Prevention**—With respect to secondary prevention, a number of observational studies show that estrogen therapy produces an even greater risk reduction of up to 80% in subsequent disease or death among women who have already had a heart attack or who have clear clinical evidence of coronary artery disease. A number of prospective studies focusing on secondary prevention are underway. One of these trials, the Heart and Estrogen-Progestin Replacement (HERS) trial, was recently reported.[2] [Editors’ Note: Although the HERS trial was reported after the 1997 conference, its results were considered important enough to be added to the published proceedings.] This study examined the effect of conjugated estrogens (Premarin) plus continuous medroxyprogesterone acetate in the secondary prevention of heart disease. Of interest was the observation of an increase in new cardiac events during the first year of the study when estrogen-medroxyprogesterone was compared with placebo. During the third to fifth years of observation, a reduction in new coronary events occurred. These results suggested an initial prothrombotic effect of estrogen and a longer-term beneficial effect. However, no overall effect of estrogen was documented. Longer-term studies that rigorously control for all possible variables are now needed and should be forthcoming.

**Other Possible Indications**
Several other conditions can be considered as possible indications for hormone replacement therapy. One that has arisen recently is the possibility of reducing the risks of and even treating Alzheimer’s disease. A number of studies also suggest that HRT may reduce the risk of colon cancer and some forms of arthritis. Although there are very little data, estrogens also may be beneficial in treating a number of complications related to macrovascular disease in diabetics.

**Alzheimer’s disease** is an idiopathic degenerative disease of the brain, the risk of which increases progressively beginning at 40 years of age. Its prevalence may be as high as 5% in people over the age of 65 and is much higher in those over age 85. Alzheimer’s disease is probably more frequent in women, although this has not been established with certainty, and men may have more vascular dementia than women.

A number of symptoms characterize Alzheimer's disease. These initially include memory loss and a number of other clear-cut neurologic disorders; personality and emotional changes occur later.
Progression of Alzheimer’s disease leads to incontinence, gait disturbance, mutism, and dependency, typically over a 6- to 12-year period.

There are several theories relating estrogens to Alzheimer’s disease. Evidence exists that women with a history of myocardial infarction and menopausal women, who, by implication, have lower estrogen levels or lower estrogen exposure, have an increased likelihood of developing Alzheimer’s disease. Most women with Alzheimer’s disease are thinner and, as a result, would have lower estrogen levels. They are also more likely to sustain hip fractures, which suggests an association with estrogen deficiency.

Oophorectomy may lead to rather specific deficits in some aspects of cognitive function, such as verbal recall, which are corrected by giving estrogen. Experimental evidence shows that estrogen has direct trophic effects on the basal forebrain cholinergic neurons. The degeneration and loss of the synapses of these neurons are believed to be major factors in the pathogenesis of Alzheimer’s dementia. Estrogen, which may maintain the levels of nerve growth factor and brain-derived growth factor, may thus be relevant to the disease.

Several observational epidemiologic studies have shown a 25% to 50% reduction in the relative risk of Alzheimer’s disease with the use of estrogens. A relationship to duration of use is apparent in some studies but not in others. A number of very small treatment studies suggest that estradiol itself and estrone sulfate may improve both cognitive and affective function in women with probable or relatively early-stage Alzheimer’s disease.

Thus, a decreased risk of Alzheimer’s disease may be a reason to consider postmenopausal hormone therapy. There is considerable debate over whether progesterone may reverse the beneficial effects of estrogens on Alzheimer’s disease.

Perhaps one of the more striking studies on the effect of estrogen is a paper by Tang and colleagues published in 1996.[3] This community-based study of aging in New York City involved 1,282 nondemented elderly women who, at the beginning of the study, were 74 years old on average. Estrogen use was associated with a statistically significant, 40% reduction in the risk of developing Alzheimer’s disease: 6% of estrogen users vs 16% of nonusers developed the disease. The age of onset of the disease was later in estrogen users, and none of the 23 women who were taking estrogens at the outset of the study actually developed Alzheimer’s disease.

In 1996, Kuller published a very useful critical review of the data regarding estrogens.[4] He argued that, of the possible benefits of estrogen use in Alzheimer’s disease, only its vascular effects on the pathogenesis of the disease are solidly based. According to Kuller, there is little evidence of a major gender difference in the prevalence or incidence of Alzheimer’s disease. He contended that the data on estrogen’s effects on cognitive function are equivocal. There is also the paradox of individuals with higher estrogen levels having greater longevity and, hence, a higher risk of developing Alzheimer’s disease.

In Kuller’s view, clinical trials, although very expensive, are essential and probably worth the cost. His overall conclusion is that the possibility that estrogen therapy may prevent Alzheimer’s disease is a hope without solid basis at this point in time.

**Long-Term Risks of HRT**

The long-term risks of hormone therapy have been widely discussed. Unopposed estrogen substantially increases the risk of endometrial cancer, and concomitant progestin use largely abrogates this effect. There is some question as to whether the abolition is totally or only partially complete.

With regard to breast cancer, ever-use or short-term use of estrogen has not been associated with an increased risk. In a number of studies, long-term use appears to be associated with an increased risk on the order of 30%. Questions about surveillance bias and patient selection bias (ie, the withholding of estrogens from individuals at increased risk) remain as confounding factors. Also, the effect of added progestins is unclear.

Since current data indicate that breast cancer is more common than heart disease in women between 50 and 65 years old, perhaps we need to be particularly careful about recommending HRT in that age group. Most women, however, are likely to derive an overall benefit from estrogen because of the reduction in heart disease, with only a small increase in the risk of developing breast cancer.

“Established” contraindications to hormone therapy include a history of breast and endometrial cancer, liver disease, and venous thromboembolism. In some of the older publications, established heart disease was also thought to be a contraindication, and this has been reconfirmed by the HERS study results. Undiagnosed vaginal bleeding, pregnancy, and certain pregnancy-associated disorders are universally regarded as contraindications.
There remains great controversy over the use of hormone therapy in women with a history of breast cancer. A 1997 review by Vassilopoulou-Sellin et al suggested that hormone therapy does not appear to have a pronounced adverse effect on cancer outcome,[5] although the number of patients studied and the resulting amount of data are small. It will be important to discuss in this conference whether women with a history of breast cancer should be denied hormone therapy when there are other conditions present for which HRT is indicated. With regard to liver disease, a recent review[6] suggested that hormone therapy should be considered in all menopausal women with chronic liver disease, regardless of whether menopause was spontaneous or surgically induced, and regardless of the presence of primary or secondary amenorrhea. Women with primary biliary cirrhosis or sclerosing cholangitis from alcohol or tobacco use or those who are receiving long-term steroids for autoimmune hepatitis are at particular risk for osteoporosis and ought to be treated with estrogens.

With regard to venous thromboembolism, three observational studies published in late 1996 found an association between hormone therapy and venous thromboembolism, although that would only confer an extra risk of about 1 case per 5,000 women per year. Five other studies found no association. In a very good review published in 1997, Douketis et al[7] argued that all of these studies have methodologic problems that preclude one from making definitive conclusions about the association, and that the biological plausibility of the association is not convincing.

Summary

As summarized in Table 1, estrogens are generally indicated for women with symptoms of estrogen deficiency, such as hot flashes and urogenital atrophy, depending on their severity. For women without significant risk factors for heart disease, osteoporosis, and Alzheimer’s disease, the indications for hormone therapy are equivocal. For those with significant risks of heart disease or osteoporosis, the benefits strongly outweigh the risks.

Current contraindications to HRT should be viewed with skepticism, as most may not be valid. Finally, ongoing clinical trials hopefully will provide helpful guidelines for the use of hormone replacement. Other options must always be considered for management, including advice on lifestyle modifications, avoidance of smoking, dietary measures, exercise, lipid-lowering agents, and bisphosphonates.

Magnitude of Problem of Estrogen Deficiency in Breast Cancer Survivors

Sandra Swain, MD: The incidence of breast cancer in the United States in 1997 approached 180,000 new cases, with 44,000 deaths. With increasingly earlier detection, many more women have been diagnosed with stage I or in situ breast cancer during the past 10 to 15 years and are expected to survive the disease over the long term. What should be done both to treat menopausal symptoms in these women and to prevent heart disease and osteoporosis accelerated by estrogen deficiency? This conference is being held to address these issues.

Trends in Breast Cancer Incidence

Surveillance, Epidemiology and End Results (SEER) data provide precise information regarding breast cancer incidence rates, with the latest data reported in 1994. Approximately 18% of women currently diagnosed have carcinoma in situ and 50%, stage I disease. Consequently, over half of the 180,000 women with newly diagnosed breast cancer, or about 97,000 women, have curable disease. Approximately 25% of women with stage I disease experience a recurrence, but the majority (75%) do not. Black women have more stage II than stage I disease. The percentage of expected cures may differ in various subgroups of women.

Changes in incidence rates over the past 20 years are striking. From 1983 to 1994, among women under 50 years of age, carcinoma in situ increased by 107% in white women and by 166% in black women; stage I disease rose by 42% in black women and by 52% in white women in this age group. Among women over 50 years old, carcinoma in situ increased by 219% in white women and by 232% in black women, while stage I disease rose by 99% in white women and by 133% in black women. In contrast, stage II disease decreased by 15% in white women, and stages III and IV disease declined by 15% in both black and white women.

Age-Related Causes of Death

Consideration of age-related causes of death heightens the concern about breast cancer. For women 35 to 54 years old and 55 to 74 years old, cancer is the number one cause of death, followed by heart disease. Breast cancer is the leading cause of cancer death in the 15- to 34-year age group, as well as the 35- to 54-year-old group. Lung cancer ranks first and breast cancer second as causes of cancer death in women 55 to 74 years old. In women over age 74 years, the leading cause of death...
is heart disease, and this age group has a larger number of deaths than do the younger age groups. In women over 74 years old, lung cancer is the number one cause of cancer death, followed by colon cancer and breast cancer.

Survival of women with breast cancer depends on age, stage, grade, and a number of other factors. For all women with a diagnosis of breast cancer, survival is actually reasonably good. For example, the 5-year survival rate of all women with node-negative breast cancer is 80%.

**Summary**

These considerations suggest that a substantial number of women are cured of breast cancer and require attention to related issues, such as menopausal symptoms and early heart and bone disease. The challenge is to integrate data regarding the risks and benefits of various therapies for menopausal problems. A strategy must then be developed to assess the risk-benefit ratio for an individual patient and to provide various options for that woman.

**HRT and Risk of Second Primary Breast Cancer**

**Duration and Dose of HRT: Data from a Meta-Analysis**

Karen Steinberg, PhD: Meta-analysis represents a quantitative summary of research. A number of rules exist for meta-analysis that allow for objective application of the results. The greatest strength of a meta-analysis is that comparisons among studies highlight differences observed in particular studies. One can then try to determine whether factors specific to individual studies may explain the differences in the risk estimates among studies. A weakness of meta-analysis is that biases present in each individual study will be reflected in the meta-analysis, which, in itself, does not eliminate bias.

In making a checklist for a meta-analysis, it is important to: (1) define the study objectives; (2) list inclusion and exclusion criteria; and (3) ensure the inclusion of all of the studies that have been done in the area, including those published in different languages. If only published studies are included in the meta-analysis, the results may be subject to publication bias, since positive studies are more likely to be published than negative ones. However, use of unpublished data can create other problems, for example, poor quality of data and added expense. Evaluating the magnitude of heterogeneity, as well as the sources of that heterogeneity, is of primary importance in a meta-analysis.

As part of an attempt to find sources of heterogeneity among studies, my colleagues and I at the Centers for Disease Control (CDC) examined time trends in the studies of HRT in relationship to breast cancer (Table 2). During the 1970s, most studies were negative but primarily used hospital control groups. In later studies, community-based controls were used, and when women had taken estrogen for longer durations, the studies began to show a positive relationship between long duration of estrogen use and the development of breast cancer. Three of the largest studies—the Cancer and Steroid Hormone Study (CASH), the Nurse’s Health Study, and the Breast Cancer Detection and Demonstration Project—reported an effect with long duration of use.

For this meta-analysis, we used two models. One model assumed that women who decided to take estrogens were probably at the same risk for breast cancer before they took estrogens as women who decided not to take estrogens. The other model did not assume that these groups were at equal risk. This meta-analysis also separated case-control studies from follow-up studies, and studies using hospitalized women as controls from studies using community-based controls.

**Results of the Meta-Analysis**—When only case-control studies that had community controls were included in the meta-analysis, using either model there was a 20% to 30% increase in the risk of developing breast cancer after 10 years of estrogen use. In-follow up studies, there was about a 50% increase in risk.

We found, in our quantitative literature review (meta-analysis), as did Barbara Hulka in her qualitative review, that ever-use of HRT did not seem to increase risk of breast cancer (ever-use is usually short-term use). However, we were unable to rule out an effect of long-term use, and believe that there is about a 30% to 50% increase in risk after 10 years of estrogen use. There seems to be an emerging pattern of association of breast cancer risk with long duration of estrogen use, but not a strong association.[8,9]

Put another way, postmenopausal US women have a 3% to 4% risk of developing breast cancer over a 10-year period. If one assumes that estrogen replacement increases that risk by 30%, women who use estrogen will go from having a 96% to a 95% chance of not getting breast cancer over a 10-year period (Marcia Angel, New York Times).

**Summary**
Increasing consistency among study results and biological plausibility support a link between HRT and the development of breast cancer in some women. However, when an odds ratio is less than 2.00, one cannot rule out the possibility that it is due to bias. It is important to examine specific subgroups, such as those at genetic risk, to determine whether their risk of breast cancer with long-term HRT use is different from that of the rest of the population. Genetic risk infers genetic polymorphisms that may slightly increase risk, such as the polymorphic forms of estrogen-metabolizing enzymes, and highly penetrant gene mutations that greatly increase risk, such as BRCA1 mutations.

**Discussion**

Drs. Melody Cobleigh and Kathy Helzlsouer asked whether women taking estrogen for a period of time and then “resting” for a year or two would experience less risk. Dr. Steinberg stated that this question could not be answered based on the results of current studies. Dr. Helzlsouer also questioned why the risk disappears when women stop using estrogen, even if they had been using it for a long time. Dr. Steinberg replied that the reasons for this are unclear.

Drs. Joseph Ragaz and Elizabeth Barrett-Connor raised the issue of overall mortality vs increased incidence of breast cancer in women who have used HRT. Dr. Ragaz pointed out that the relative risk of increased mortality is lower than the increase in incidence of breast cancer in many studies. Dr. Barrett-Connor agreed but stated that the Nurse’s Health Study has found an increase in mortality due to breast cancer in women who have used estrogen replacement. Dr. Barrett-Connor argued that the Nurse’s Health Study, because of the large numbers of women involved, outweighs all of the other studies in the available meta-analyses. She also pointed out that because of the young age of most of the women in the Nurse’s Health Study, most of those who have been taking estrogens for a long period are women who had a very early oophorectomy. This may not be the same as giving hormone replacement to women who have gone through natural menopause.

Dr. Barrett-Connor reviewed data from a National Osteoporosis Foundation study that was presented at a American Society of Bone and Mineral Research Meeting.[R. Heaney, unpublished data] This group recently sponsored a cost-benefit analysis of estrogen use. From these data, they were likely to recommend that the most effective time to start estrogen for the prevention of osteoporosis would be after 60 or 65 years of age. This strategy would avoid long-term hormone use for women who are not experiencing acute menopausal symptoms.

Dr. Richard Santen asked questions about communication of risk to the patient and about the differences between estrogens (conjugated vs nonconjugated estrogens). Dr. Steinberg stated that discussing risk presents a difficult challenge for the physician. She also indicated that different estrogens may confer different risks, but that such a conclusion is not possible from currently available data.

In response to a question from Dr. Michael Kleerekoper, Dr. Steinberg stated that, in her meta-analysis, risk was enhanced in patients who had a family history of breast cancer and took estrogen. There was no additive or synergistic effect between estrogen and other factors.

**Overall Perspectives on Breast Cancer Risk From HRT**

**Ronald Ross, MD:** The total body of indirect evidence regarding estrogens and the risk of breast cancer is so compelling that it is probably indisputable. The first evidence that estrogen might be involved in breast cancer came from the work of Bittner and Huggins in the early 1940s. Bittner first showed that administering estrogens to rodents could induce mammary tumors. Since that time, scores of studies have confirmed this finding. Bittner also showed that the removal of estrogen totally eliminates the high spontaneous tumor incidence in a particular strain of mice.

In my view, there is little doubt that estrogens are important in cell proliferation in the breast. To the extent that cell proliferation is important in the carcinogenic process, one would expect estrogens to be important as well.

Studies relating estrogen levels to breast cancer risk are very difficult to conduct. The better-designed studies of this type tend to show that populations at high risk of breast cancer, such as white women in the United States, have higher estrogen levels than do populations at lower risk for breast cancer, for example, Japanese women born and raised in Japan. This is true even among postmenopausal women.

Case-control studies are even more difficult to conduct than are cohort studies of healthy women. The more well-designed studies do suggest that women who develop breast cancer have higher estrogen levels than women in control groups. A few prospective studies have now been performed that verify this.
Moreover, a whole series of reproductive factors relate to breast cancer risk. Many of these are clearly related to ovarian function and thereby implicate ovarian steroid hormones and, presumably, estrogens.

**Results of Meta-Analyses**

One of my colleagues, Dr. Malcolm Pike, carried out a meta-analysis that included only population-based studies. Like Dr. Steinberg, Dr. Pike found that the risk of developing breast cancer was increased by 3.1% per year of use of HRT. These are not large effects epidemiologically, but that they are certainly meaningful for a disease as common as breast cancer and for a category of drugs as commonly used as estrogens.

The data from Dr. Pike’s meta-analysis correspond well with those of the analysis of Dr. Steinberg and colleagues. After 10 years of use, the risk would be expected to increase by about 30%. There is likely to be a linear relationship between HRT and breast cancer risk, so that if risk is increased 30% after 10 years, it is probably increased by roughly 15% after 5 years. Risk levels are low enough in the first few years of use that they cannot be detected by epidemiologic studies. When Pike’s analysis is limited to studies that focused only on conjugated estrogens, the risk is even lower, about two-thirds that of all estrogens combined.

Persson from Sweden summarized overall risk levels from individual studies and noted that with ever-use of HRT, the risks tend to cluster around 1, whereas with long-term use, the risk level rises. Also, Vert and colleagues at Oxford recently carried out a meta-analysis in which they used raw data from 51 studies looking at exogenous hormone use and breast cancer. They subcategorized the data by recency and duration of hormone use, and obtained results highly compatible with those of the meta-analyses by Pike and by Steinberg et al. The Oxford group separately analyzed women who had discontinued estrogen use 5 years previously and found that even they had a small residual increase in risk.

**Why Is the Estrogen-Breast Cancer Link Difficult to Establish?**

Why has it been so difficult to prove that estrogens cause breast cancer? This difficulty relates to two issues: (1) statistical power and (2) confounding factors.

**Statistical Power**—The issue of statistical power relates to the fact that the anticipated risk is relatively small, and, therefore, very large studies are required to show it. This may reflect the possibility that the only estrogen that matters to the breast is estradiol. Postmenopausal women have a circulating estradiol level that averages 10 pg/mL. Women who are taking 0.625 mg of conjugated equine estrogens have an average circulating estradiol level of about 25 pg/mL. Thus, if the increase in breast cancer risk in postmenopausal women were due entirely to estradiol levels, one might expect that breast cancer risk would be increased by an additional 2.5% per year in women taking estrogen—a result that is compatible with the results from all of the available meta-analyses.

This type of analysis makes two questionable assumptions. One is that the increase in breast cancer risk after menopause is due entirely to circulating estradiol levels. The other questionable assumption is that the other estrogens in drugs, such as conjugated estrogens, are, in effect, inert to the breast.

In any case, since these risks are small and based on empirical data, larger studies are clearly needed. Very few individual studies have had sufficient statistical power to determine these kinds of risk levels.

**Confounding Factors**—Of the possible confounding factors, body weight is an important one. It is known that heavy women are less likely to take estrogen replacement than are thinner women. Thus, failure to totally adjust for body weight in an analysis will tend to underestimate estrogen use in cases relative to controls and thereby underestimate the true relative risk.

It is relatively easy to control for body weight in an analysis. A more difficult variable may be a woman’s age at menopause. Late age at menopause is known to be associated with a low frequency of use of HRT. Once again, failure to adjust adequately for this variable would tend to underestimate the true relative risk in case-control studies. This may be more important as a confounding factor than body weight, since age at menopause is much more difficult to determine, particularly in women who are taking HRT and may have bleeding as a result.

**Need for Study of Specific Subgroups**

I believe that there is nothing more to be learned from additional study of the overall relationship between HRT and breast cancer. Further study of the relationship would only provide the same answer; namely, that there is a low level of risk, the importance of which can be debated. Instead, it is important to examine subgroups of women in whom the relationship may be more clear. Our group has a particular interest in women with a family history of breast cancer. The early data from
the Oxford Collaborative Group analysis regarding family history are encouraging,[12] but there is not yet a final answer.

Obesity is also an interesting covariate. It has been consistently found that heavier women are at lower risk for breast cancer following HRT, compared with thinner women, perhaps because they already have higher circulating endogenous levels of estrogen.

Very few empirical data are available in women who have already had a diagnosis of breast cancer with regard to late metastases and contralateral primary breast cancer. Looking at surrogate variables may be helpful in this setting. One possible surrogate variable is the effect of obesity on recurrence and death in women who have had breast cancer. It has been well-documented that postmenopausal obesity increases the risk of recurrence and death among postmenopausal women who have had breast cancer. The same is also true for premenopausal women with a history of breast cancer.

The latter finding suggests that estrogen may not be the mechanism involved, since premenopausal women have high levels of estrogen even if they are not obese. However, women treated for breast cancer frequently become anovulatory, and in this situation the effects of adipose tissue estrogens may be greater than one might expect in women who are ovulating regularly.

The average circulating estradiol level in postmenopausal women is about 10 pg/mL. Estradiol levels tend to increase by 1 to 2 pg/mL for every 10 pounds of increase in body weight. Thus, in women who weigh as much as 200 pounds, estradiol levels average 20 pg/mL.

Estradiol levels in women taking conjugated equine estrogens are even higher. Based on these data, therefore, one could argue that if the mechanism were the same in obese women and women receiving HRT, there could be a substantive increase in risk of recurrence if women who have had breast cancer are given HRT. Strong support for a relationship between estrogen and breast cancer derives from studies of the effect of oophorectomy in young women.

Adding Progestin to Estrogen May Increase Breast Cancer Risk

Over 10 years ago, my colleagues and I warned that adding progestins to estrogen replacement might be harmful to the breast. One animal model suggests that at least one type of progestin, injectable medroxyprogesterone acetate (Depo-Provera), may cause breast cancer. Certainly, there are breast cancer risk factors that suggest that estrogens in combination with progesterone may be important in determining breast cancer risk.

Few relevant data are currently available on this issue. Data from the Oxford Collaborative Group show that the risk for combination therapy in recent long-term users is 1.53,[12] which is a much higher risk than that seen with estrogen alone. However, these numbers are very small and totally inadequate to form a conclusion about the true effect on breast cancer risk of adding a progestin.

Discussion

Dr. Rena Vassilopoulou-Sellin raised the question of other hormonal changes in women with different reproductive histories (such as infertility and late menarche) and in obese women. From an endocrinologic point of view, ovarian dysfunction is often associated with hyperandrogenism and obesity with hyperinsulinism. There has yet to be thoughtful discussion about the possible effects of these other hormonal changes on the development of breast cancer. Dr. Ross agreed that these are important issues, and that thinking about the reproductive factors just in terms of estrogen and progesterone alone is obviously simplistic.

Dr. Robert Josse added that there are a number of different types of obesity. Visceral obesity, for example, is characterized by differences in metabolic activity, when compared with nonvisceral obesity, and by hyperinsulinism. Dr. Ross agreed that, again, the issues relating obesity have been discussed in a simplistic way, by using weight and height and a combination of both to calculate body mass index. He added that there may be much more to learn by examining the different types of obesity.

Dr. Kleerekoper pointed out that there is a difference in the relationship between body fat mass and estradiol and estrogen levels in postmenopausal African-American women compared to non-Hispanic white women. Thus, obesity is not just one condition.

Dr. Pamela Goodwin described her meta-analysis of obesity as a prognostic factor in breast cancer,[13] which showed that obese women have a relative risk of 1.9 of developing breast cancer and a similar relative risk of dying from the disease. A prospective study of over 500 women begun in 1990 that will be analyzed over the next 18 months will allow her to look at the prognostic effects of obesity at diagnosis, weight gain after diagnosis, distribution of body fat, and other body measures on risk of recurrence and risk of death from breast cancer. In addition, Dr. Goodwin will examine a number of physiologic mediators, including insulin.

Dr. Goodwin also pointed out that certain studies, particularly in the context of randomized trials
conducted by cooperative groups, have shown no effect of obesity on breast cancer prognosis. It is likely that some of these negative studies would remain unpublished and, thus, not be included in meta-analyses, including her own.

Dr. Kathleen Pritchard asked Dr. Ross for confirmatory data supporting the statement that HRT is less likely to be taken by women who have a late menopause and by women who are overweight. Dr. Ross stated his belief that this is definitely true of overweight women and is probably related to the fact that they have fewer symptoms because their estrogen levels are higher. The same is true in women who undergo menopause at a later age, but he is not certain of the reason for that phenomenon.

Dr. Andrea Dunaif mentioned small studies suggesting that insulin resistance is an independent risk factor for breast cancer, and she reminded participants that progesterone exacerbates insulin resistance.

Dr. Jeffrey Perlman noted that some studies have found a gradual decline in risk effect after discontinuation of estrogen replacement, even after long-term use. Dr. Ross agreed and noted that the Nurse’s Health Study is unique in showing increased risk only in current users. He pointed out that the Oxford meta-analysis shows that there is still an increase in risk as great as 12% 5 years after discontinuation of estrogen.[12,14] Thus, the effect of estrogen is not limited solely to current users. The recent user is more likely to be a long-term user, which has been a perennially confounding issue.

A participant questioned whether data exist regarding HRT and the risk of a second primary in women who have already had breast cancer. Dr. Ross noted that he has access to data on this but did not present them at this meeting. However, the highest risk of a contralateral malignancy appears to occur in the first year or 18 months after breast cancer diagnosis.

Dr. Cobleigh stated that National Surgical Adjuvant Breast and Bowel Project (NSABP) data suggest that the incidence of contralateral breast cancer is 0.5% per year, and that this is reduced to 0.25% per year in women who take tamoxifen (Nolvadex). Dr. Ragaz also pointed out that there is a different risk of contralateral breast cancer in younger women with primary breast cancer, who have a 6- to 8-fold increased risk; in 50- to 60-year olds, who have a 2- to 2.5-fold increased risk; and in women over the age of 60 years, who have a risk of only 1.

### Biological Basis for the Carcinogenic Effects of Estrogen

**Richard Santen, MD:** Compelling evidence that endogenous estrogen and breast cancer are associated comes from studies of breast cancer in women undergoing bilateral oophorectomy before age 35 years from 1920 to 1940.[15,16] These women were followed for 20 to 40 years after surgery to determine whether they would develop breast cancer. The control group consisted of age-matched women who had undergone unilateral oophorectomy.

Breast cancer developed 75% less frequently in women without functioning ovaries. This protective effect gradually increased over a follow-up period of more than 25 years (Figure 1 and Figure 2). Prospective studies conducted by Toniolo et al provide additional evidence of this association.[17] They found that women who develop breast cancer over a 5- to 10-year period have levels of estradiol approximately 20% higher than those who do not. As shown in Figure 3, these data have been confirmed by some more recent investigations[18-20] but not by all such studies.[21-23]

### Sources of Endogenous Estrogen

There are multiple sources of endogenous estrogen. The premenopausal ovary secretes estradiol, peripheral adipose tissues can aromatize androgen substrates to estrogens, and breast tissue itself contains aromatase and can synthesize estrogen in situ. Nearly 100% of endogenous estrogen originates from the ovary during the mid-cycle estrogen surge, whereas extraglandular production provides 50% at the time of menses. In postmenopausal women, the ovary produces no estradiol, whereas extraglandular sites predominate as sources.

Emerging evidence suggests the importance of estrogen production in situ in the breast. Study of the aromatase enzyme and its messenger RNA in breast tissue (via immunohistochemical and molecular biological techniques) in nude mice shows that the amount of estrogen made locally causes biological effects, and clinical studies of aromatase inhibitors in patients confirm this finding. Experiments in the nude mouse model have examined the relative importance of estradiol uptake from plasma vs local estradiol synthesis. These experiments show that autocrine effects of local synthesis predominate over endocrine effects of estradiol uptake from plasma. Additional evidence of the importance of aromatase is the finding that aromatase inhibitors block the development of spontaneously occurring benign and malignant tumors in aging rats.
Enhanced cell proliferation, induced by either endogenous or exogenous estrogens, increases the number of cell divisions and, by inference, the proportionate number of mutations. With an enhanced rate of proliferation, the time available for DNA repair is reduced. In addition, single-stranded DNA, present during cell division, is more susceptible to damage than is double-stranded DNA, and, thus, gene duplication can occur. This represents the predominant theory of estrogen-induced carcinogenesis at present.

**Metabolism of Estrogens to Genotoxic Metabolites**

Recently, numerous investigators have focused on another carcinogenic mechanism: the metabolism of estrogens to genotoxic metabolites. [Editors' Note: This hypothesis was the focus of a conference sponsored by the National Cancer Institute on March 15-16, 1998, at Chantilly, Virginia.] As shown in Figure 4, it is postulated that estradiol is metabolized first to 4-OH-estradiol and then to estrogen quinones. The quinones bind to guanine and are removed from DNA through glycosylation to form N-7-guanine-quinone conjugates (Figure 4).

The remaining segment of depurinated DNA forms G to T and A to T point mutations upon replication. In addition, the quinones can be reduced back to 4-OH-estradiol, which then participates in a redox cycle with oxidation back to quinones and generation of oxygen free radicals with each revolution through the cycle. These free radicals may activate polycyclic aromatic hydrocarbons to become carcinogenic or can activate other compounds to produce stable DNA adducts.

Evidence for the relevance of this metabolic pathway comes from measurements of the enzyme catechol-o-methyl transferase (COMT). This enzyme can detoxify 4-OH-estradiol and prevent its metabolism to genotoxic compounds. Yager and colleagues (as noted in a paper by Lavigne et al; see reference 24) recently showed that postmenopausal women with low levels of COMT and decreased ability to detoxify 4-OH-estradiol have a 3.7-fold increased risk of breast cancer.

Our laboratory is working on the hypothesis that aromatase overexpression in breast tissue provides sufficient substrate to allow the estradiol metabolites to be formed in biologically meaningful amounts. This hypothesis is supported by the observation that a carcinogenic oncogene in the mouse, formerly termed Int-5, is the aromatase gene. Its expression is turned on by insertion of a viral promoter into an untranslated portion of one of its exons. In addition, Tekmal and colleagues have developed a transgenic mouse that overexpresses aromatase in breast tissue and develops premalignant lesions, such as atypical ductal hyperplasia and dysplasia.[25]

These data provide potential mechanisms for the carcinogenic effects of estrogen. The proliferation concept and the metabolic concept could work in concert in an additive or even synergistic fashion to produce genetic mutations and ultimately cancer. However, if local estrogen synthesis proves to be a reality, it will be important for future studies to measure tissue estrogen levels rather than levels in plasma or urine.

**Discussion**

Dr. Santen responded to a question regarding which breast cell type overexpresses aromatase by indicating that epithelial breast cells, as well as adipocyte fibroblasts and macrophages, contain aromatase. The precise contribution of each cell type is unknown, but fibroblasts, when grown in tissue culture with a “cocktail” of transcriptional enhancers, can be stimulated to increase aromatase activity by as much as 10,000-fold. These data may provide a link between obesity and breast cancer, and again emphasize the need to measure estradiol directly in breast tissue.

Dr. Ragaz mentioned recent data indicating that, in normal women, the upper outer quadrant of the breast contains the highest level of aromatase and that this quadrant is also the most common site of breast cancer development. He noted that these data complemented Dr. Santen’s hypothesis. He also questioned whether the possibility of local estrogen formation raises issues about the relationship between exogenous and endogenously produced estrogen. Dr. Santen responded by speculating that the reason why the incidence of cancer may not be higher after use of exogenous hormone replacement may be that exogenous hormone does not produce tissue levels as high as those occurring from increased in situ synthesis of estradiol directly in the breast.

Another question focused on what form of estrogen is synthesized in tissue. Dr. Santen responded that both estrone and estradiol are made, but that an enzyme, 17-beta hydroxysteroid dehydrogenase is present to convert estrone to estradiol.

Dr. Josse asked how estrogen could act as both an antioxidant and a hormone, which can generate free radicals of oxygen when metabolized. Dr. Santen acknowledged that this is a paradox, but added that estradiol could have these two different effects, depending on the tissue in which it is synthesized and the amount of enzymes present to metabolize it.

**Progestins as Mammary Mitogens**
Thomas Anderson, MD: Our group has conducted investigations relating proliferative changes in the breast to phases of the menstrual cycle. Using tritiated thymidine-labeling techniques, we demonstrated that the greater degree of proliferation of resting breast tissue occurs in the luteal phase, or days 14 to 28 of the cycle (Figure 5). Increased breast tissue proliferation is also associated with use of oral contraceptives (Figure 6).

With respect to the increasing age of the breast (either considered chronologically or biologically with respect to time since menarche), the degree of proliferation is inversely correlated. Taking into account the confounding factors of age and parity, oral contraceptives categorically raise the level of breast proliferation. Nulliparous patients show the most marked increases in proliferation in response to oral contraceptives.

Distribution of Estrogen and Progesterone Receptors

With regard to steroid responsiveness, the localization of estrogen receptors in epithelial nuclei was diffusely distributed in breast cancer tissue, but only focally in normal breast lobules. It is possible to have no estrogen receptors in many cells and other scattered cells that have clearly detectable amounts of nuclear receptors. This focality makes it difficult to quantitate receptor levels to determine variations during the menstrual cycle. Nonetheless, cases expressing a high level of receptor were probably unresponsive with respect to labeling index.

In contrast, there was a reduction in the frequency of cases with low to moderate mitotic activity and a corresponding increase in those that were receptor negative. This would be an expected effect since progesterone down-regulates the estrogen receptor. In addition, women receiving oral contraceptives have a high proportion of estrogen receptor-negative lobules in their biopsies, in keeping with an effect of progesterone.

Further studies showed that progesterone receptor levels, scored in the same way, remain at a constant high level throughout the natural cycle and increase steadily during oral contraceptive use. The breast has continuous high levels of progesterone receptors during the entire cycle, which contrasts with the uterus, in which levels change substantially during the cycle. This finding emphasizes another major difference in response between the breast and the uterus.

Chang et al studied the effects of topical estrogen, progesterone, or placebo gels applied to the breast for 11 to 13 days after the onset of menses.[26] Surgery was then performed, and mitotic level proliferative cell nuclear antigen (PCNA) immunohistochemical values (as a marker of cellular proliferation) were assessed microscopically. These investigators found low mean activity in the placebo-treated breast, somewhat lower mean proliferative activity after progesterone, and higher mean activity in the estrogen-treated breast. The combination of estrogen and progesterone reduced activity to levels seen with placebo.

Chang et al concluded that progesterone decreased proliferation. However, the levels of steroid used in this study were far from physiologic. Also, levels of both estrogen and progesterone in the breast were very high; for progesterone, almost 100 times greater than after placebo and for estradiol in the nanogram per gram range. (Normally, tissue levels are 10-fold lower.)

Swedish researchers studied paired fine-needle aspiration (FNA) samples obtained in the follicular and luteal phases in 42 women.[27] Using MIB1-positivity as a measure of proliferative index, they showed an increase in proliferation from the follicular to the luteal phase in ovulating women. Proliferation correlated positively with serum progesterone level at aspiration, but not with levels of estradiol or various other hormonal factors.

Summary

In summary, published data regarding progesterone and resting breast proliferation are conflicting. Nevertheless, I believe that progesterone does act to increase breast tissue proliferation. Progesterone does not protect the breast—as it does the uterus—by reducing proliferation. This contention is supported by the work of Sutherland et al from Australia.[28] They demonstrated that estrogen stimulates proliferation, whereas progesterone has two effects: It inhibits this stimulatory effect of estrogen at the early G1 phase of the cell cycle and stimulates proliferation at a later G1 phase. Since most resting breast cells are in the inactive G0 phase, estrogen, perhaps in combination with progesterone, may elicit their progression into the active phases of the cell cycle. Thus, both estrogen and progesterone are involved in cell proliferation, and these effects probably result indirectly through stimulation of growth factors. The underlying effects of estrogen and progesterone in the breast may differ in various physiologic states, for example, in premenopausal and postmenopausal parous women, in nulliparous subjects, and in women receiving oral contraceptives. The same may be true for the level of breast cancer risk.

Discussion

Dr. Jerilynn Prior requested that Dr. Anderson to clarify several points about the collection of the
breast tissues. He replied that the 300 tissue samples came from women having breast surgery for benign breast disease in whom standard data were collected regarding cyclic menstrual function before and after surgery. Dr. Prior commented that women with benign breast disease frequently have anovulatory cycles, and added that hormonal confirmation of cycle phase was not available in the 300 reported cases.

Dr. Prior also noted that the finding of an increased tritiated thymidine uptake during the fourth week of the cycle among women taking oral contraceptives is difficult to explain. She asserted that increased progesterone levels always follow high follicular-phase estrogen levels. Thus, the increased progesterone levels after the oral contraceptives could reflect a prolonged increase in estrogen levels.

Dr. Santen then asked Dr. Anderson to comment on a study demonstrating that women with benign breast disease who received androgenic progestins (all 19-nor-testosterone derivatives including lynestrenol, norethindrone acetate, norethindrone, and ethynodiol diacetate) for 10 years had a 50% reduction in breast cancer incidence.[29] This study has been cited as evidence that these progestins prevent rather than increase the incidence of breast cancer.

The study involved 1,150 premenopausal women with nodular hyperplasia, fibroadenoma, fibrocystic disease, isolated cyst, isolated cyclic mastalgia, or nipple discharge (excluding galactorrhea). Biopsy evidence of benign breast disease was not required for study entry. The study demonstrated a reduction in breast cancer risk among women receiving the 19-nor-testosterone derivatives but not in those given other progestogens.

Dr. Anderson replied that the women in this study do not fall into the category of benign breast disease that carries any acknowledged increased risk for breast cancer, and that the numbers of women in the study were small. Also, only 29 breast cancers were found in the women receiving the 19-nortestosterone derivatives.

Dr. Charles Loprinzi commented that, for the purposes of this conference, the question is whether or not progestins increase the risk of breast cancer in patients, and that we don’t yet have the data to answer this question. Dr. Anderson agreed with that assessment, but emphasized that substantial data exist to indicate that progestins induce breast proliferation. The concept that progestins may be protective must be considered in this context.

Dr. Barrett-Connor then referred to the Nurse’s Health Study, and indicated that a paper presented at SER reported a 5% per year increase in risk of breast cancer with estrogens and a 9% annual increase with estrogens plus progestins.[G. Colditz, unpublished data] She speculated that this would be the next headline that physicians will need to discuss with patients.

Viewpoint of a Patient Advocate

Margaret Borwhat: The need for patients to become partners in the decision-making process is particularly important in the area of HRT, for which there is much conflicting information. Patient advocates are an important resource for suggesting ways that women may be informed about their choices, so that they understand the risks and benefits of each alternative. They can play an important role in suggesting clinical trials needed to guide women and their physicians.

Contralateral Breast Cancer

I will focus my remarks on a particular problem—contralateral breast cancer and its relationship to HRT. Women with surgically induced menopause have a 75% reduction in the risk of developing breast cancer, and chemotherapy-induced menopause may delay or prevent the occurrence of a second primary. Second primaries occur at a rate of between 0.5% and 0.7% per year, with a cumulative incidence of 15%. With these considerations in mind, perhaps avoidance of HRT may reduce the incidence of contralateral breast cancer.

With regard to the effect of contralateral breast cancer on prognosis and rates of recurrence, a study examining factors relating to prognosis in patients with contralateral breast cancer found that nodal status, age, presence of lobular carcinoma, and multicentricity all correlated adversely with outcome.[30] Another study addressed the issue of contralateral breast cancer using a proportional hazard model to assess competing risks. Adjuvant chemotherapy consistently reduced contralateral breast cancer, whereas lobular carcinoma, and age less than 55 years increased the risk.[31] A third study found that recurrence rates for contralateral breast cancer were equally divided between local and distant sites and among lobular cancer, invasive ductal, and lobular carcinoma.[32]

In addition to its impact on survival, development of a second primary may have other effects. One issue is that women taking HRT may be more commonly advised to undergo biopsy of the remaining breast, and this may engender a great deal of anxiety. Another issue is the increased lymphedema
resulting from surgery on the second breast, and the resulting limitation of activities and associated
depression. Physicians may underestimate this problem and its impact on the woman. Also, the
diagnosis of a second primary that occurs as a later event often results in additional chemotherapy,
with associated side effects and organ damage.

Clearly, physicians do not have adequate time to discuss all of these issues with patients, and
insurance does not provide sufficient coverage of these educational activities. Attention is required
to develop better means for communication and education. Use of patient resource rooms may
enhance patient understanding.

Attention also needs to focused on the problem of distortion of information by the media. For
example, coverage of the Nurse’s Health Study focused on the cardiovascular benefits of estrogen,
while the risks of breast cancer were underemphasized. Patients need verbal and written material to
better understand risks. Perhaps computer methods may be helpful in this area.

Discussion

Dr. Burger asked for advice about mechanisms for physicians to use in explaining complex
risk-benefit issues. Ms. Borwhat responded by focusing on the use of patient resource rooms, highly
trained, nonphysician patient educators, computer programs, and attention to identifying
appropriate written information for patients.

Dr. Annette O’Connor concurred about the need to synthesize evidence for patients and to help them
tsift through inconsistent results. Her patients use a self-administered educational tool, which is
subsequently reinforced by a practitioner. Dr. O’Connor agreed that information needs to be tailored
to the circumstances and needs of individual patients and that the computer may be a good tool to
achieve this goal. Someone, however, needs to sit next to the computer to provide guidance to the
patient.

Open General Discussion

Dr. Anderson discussed the concept that breast cancer is not just one disease, but rather, a very
heterogeneous group of diseases with a range of prognoses that range from excellent to poor.

Discussion of such issues as the risks and benefits of HRT first requires an assessment of the type of
cancer the patient has. If a patient has a tubular cancer, her chances of surviving are almost equal to
those of the general population. Even though it is an invasive cancer, this lesion is characterized by
excellent survival, and patients with this disease might well be encouraged to take HRT. In patients
with other lesions, however, the risk-benefit ratio may be quite different.

One needs to consider both the best- and worst-case scenarios as well. For example, HRT may not
affect the risk of developing a second breast cancer (best case), or it may affect it substantially
(worst case). If a woman is already at maximum risk because of a gene for familial breast cancer,
estrogen use may not increase that risk further. Reflection on these issues suggests the need for
well-controlled studies.

Dr. Vassilopoulou-Sellin commented on data regarding the outcome of patients diagnosed with
breast cancer while receiving HRT. Several studies suggest that their prognosis is at least as good
as, and probably better than, that of women who develop breast cancer while not taking HRT. This
information might be reassuring to the patient who develops a second breast cancer while receiving
HRT. On the other hand, several anecdotes have been presented regarding patients whose tumors
regressed after they discontinued HRT.

Patient Interaction Strategies

Strategy for Assessing Willingness of Breast Cancer Patients to Accept HRT

Hilary Llewellyn-Thomas PhD: In collaboration with Dr. Kathleen Pritchard, I am currently studying
a trade-off technique to assess the attitudes of women with a prior diagnosis of breast cancer toward
HRT. (Throughout this discussion, the acronym “HRT” will include both estrogen replacement
therapy and combined estrogen-progestin therapy). Background issues underlying this study include
the fact that more women are currently being diagnosed with breast cancer at a younger age and an
earlier stage. Both chemotherapy and tamoxifen, either of which can lead to premature menopause,
are now being used increasingly as adjuvant therapy in women who are at lower risk of breast
cancer recurrence, as data demonstrating benefit accumulate. At the same time, the benefits of HRT
in women without breast cancer are becoming more clearly established.

Accordingly, there has been considerable interest in reconsidering the role of HRT in women with a
previous diagnosis of breast cancer. There is, however, little information about the safety of HRT in
this setting, and about the attitudes of women towards its use. If HRT is to be seriously considered
for use in women with a previous diagnosis of breast cancer, a randomized controlled trial must eventually be done to establish its safety.

Preliminary data suggest that such a trial would need to be large enough to rule out even a relatively small increase in risk of recurrence of breast cancer (< 5%). Thousands of study participants would be required for such a trial. The maximal acceptable increase in risk of recurrence (MAIRR) for the use of HRT in women with a previous diagnosis of breast cancer is not known, nor are the attitudes of such women toward participation in a randomized clinical trial addressing that issue.

**Study Design**—We are conducting a prospective cohort study in 100 women with stage I-III breast cancer who are about to enter menopause, whether naturally or related to adjuvant chemotherapy or tamoxifen. These women are asked to respond to a probability trade-off task (PTO) administered at three points: (1) before menopause, (2) as the women enter menopause, and (3) 1 year after they enter menopause. Our objectives are to determine: (1) what proportion of women would accept an MAIRR of > 5% for HRT, and (2) what proportion would consider entry into a randomized trial of HRT.

The PTO task is an exercise in which risk-benefit information is used to assess a woman’s MAIRR for the use of HRT. This is done by presenting “bits” of information on cards that are presented one at a time in a clear, cumulative sequence and are arranged on a table in front of the participant.

The task begins with an introduction in which menopausal symptoms are described. Then, the beneficial effects of HRT (a major decrease in menopausal symptoms and potential prevention of osteoporosis and heart disease) are described. Next, the major potential risk (recurrence of breast cancer) is outlined; this card states that there are some data linking HRT with the development of a new breast cancer in women without breast cancer, but that to date no conclusive studies have been performed in women with a previous diagnosis of breast cancer.

Next, given this overall situation, the participant is asked to consider two hypothetical options: (1) that HRT offers beneficial effects (ie, reduced symptoms and increased protection from osteoporosis and coronary artery disease) and no potential risks (ie, no increased risk of recurrence); or (2) no HRT. The participant is asked to indicate which would option would be preferable; at this point in the task, participants are likely to choose the “dominated” option, which is HRT.

Then, the MAIRR for HRT is determined by systematically increasing the hypothetical risk of breast cancer recurrence (a sliding scale is used to illustrate this increase). For each participant, once the hypothetical risk of recurrence of breast cancer reaches a critical point, she will indicate that she would forgo HRT; this critical point is the woman’s MAIRR.

At each administration time, the PTO task is repeated using three different baseline risks of breast cancer recurrence (25%, 50%, and 75%). This permits the determination whether or not the MAIRR would shift given different baseline risks. Participants are advised that the probabilities in the PTO task are hypothetical and do not specifically apply to their own medical condition.

Finally, each woman is asked if she would be willing to participate in a randomized, controlled trial of HRT vs no HRT. For the purpose of that question, the patient is asked to base her decision on her own particular medical situation.

Thus, the task deliberately replicates the dilemma faced by an individual patient in real time who is facing a decision about treatment selection; such a decision requires consideration of the side effects of the various treatment options, as well as the possible outcomes of treatment, and the probabilities of attaining those outcomes. The goals of the study are to understand: (1) the additional risk of recurrence that a woman with a previous history of breast cancer might be ready to accept in exchange for relief of menopausal symptoms and potential prevention of bone and heart disease, and (2) her willingness to consider entry into a randomized, controlled trial of HRT.

**Efficacy of a Decision Aid for Healthy Postmenopausal Women Considering HRT**

**Annette O’Connor, RN, PhD:** Although healthy postmenopausal women are advised to consider their personal values when deliberating about the potential benefits and risks of HRT, feasible, effective methods of decision support in primary care have yet to be established. Using an explicit decision support framework, a self-administered HRT decision aid was developed and evaluated in two phases.

**Phase 1** was a before-and-after study of 94 women from six family practices. An audiotape guided women through an illustrated booklet that included: (1) detailed information about the benefits and risks of HRT (tailored to a woman’s clinical risk), and (2) a values clarification exercise to promote informed decision-making consistent with their personal values. After using the decision aid, participants had better general knowledge and more realistic personal expectations of the benefits and risks of HRT; and felt more certain, informed, and clear about their values, and supported in their ability to make decisions.

Women’s values elicited in the clarification exercise were 84% accurate in discriminating between
decisions. Women with polarized preferences at baseline did not change their minds but were better informed. Changes in preferences occurred in those who were uncertain about HRT prior to the study, with equal numbers accepting or declining HRT. Most of the study participants found the decision aid to be comprehensible, acceptable in length and pace, and balanced. **Phase 2 was a randomized**, controlled trial comparing the efficacy of a general educational pamphlet to the tailored decision aid. The pamphlet briefly summarized, in general terms, the benefits and risks of HRT and the features of women who were likely to benefit from such therapy. Compared to women in the pamphlet group, those in the decision aid group had statistically significant (P < .05) improvements in realistic personal expectations of the benefits and risks of HRT, decisional conflict, and perceived acceptability of the intervention. General knowledge about the main benefits and risks was comparable in the two groups.

We conclude that tailored decision aids better prepare women for decision-making than do general pamphlets. This approach may be useful in developing new decision support tools for women who already have breast cancer.

**Effects of Hormones on Mammographic Evaluation**

**Effects of Acute HRT Withdrawal on Mammographic Lesions**  
Jennifer Harvey, MD: Hormone replacement therapy confounds the interpretation of mammograms. In anywhere from 17% to 73% of women, HRT causes an increase in mammographic density that may be diffuse, focal, or multifocal. Although diffuse or multifocal changes are not worrisome, new or enlarging focal, circumscribed masses or developing densities can be a sign of early breast carcinoma and may prompt biopsy.

A recent study by Laya et al found a significant reduction in both the sensitivity and the specificity of mammography associated with current hormone administration. Thus, use of HRT in survivors of breast cancer may make it more difficult to follow patients for the development of a second primary lesion.

Mammographic changes from HRT are rapidly reversible. Thus, a strategy of repeating mammograms after acute cessation of HRT may be a practical means of assessing patients on HRT. From a group of 19,069 patients undergoing mammography at the University of Virginia from January 1995 until December 1996, 48 had a new or enlarging circumscribed mass or developing density while taking HRT. Hormone replacement was stopped for 10 to 30 days in these patients, and the mammograms were repeated.

Of the 48 patients, 35 (74%) had an interval decrease in size or resolution of the mammographic abnormality following hormone therapy cessation (see Figure 7). After 6 to 24 months (mean, 12.3 months) of mammographic follow-up, 26 of these patients have no evidence of carcinoma. Of the 12 patients with no change on mammography during HRT cessation, 4 had subsequent sonograms showing cysts, and 8 underwent biopsy. Histologic diagnoses included invasive lobular carcinoma (N = 1), typical hyperplasia (N = 4), fibrosis (N = 1), and normal breast parenchyma (N = 1). One patient elected follow-up rather than biopsy and had no change in mammographic appearance at the 6-month follow-up.

This retrospective study provided suggestive evidence that short-term cessation of HRT can induce regression of HRT-responsive changes and avoid unnecessary biopsies. Mammographic sensitivity may also be increased by use of this technique, provided that false-negative results do not increase. Because new, focal mammographic densities are common in women on HRT, these abnormalities could be dismissed as hormone-induced changes even though they usually carry a 9% to 11% risk of being carcinoma. Therefore, short-term HRT cessation may improve the clinician’s confidence that a persistent abnormality is of greater concern than an abnormality that regresses.

**References:**

1. Australian Study: Unpublished data on record at National Heart Foundation of Australia.


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