

## CONSENSUS STATEMENT

# Treatment of Estrogen Deficiency Symptoms in Women Surviving Breast Cancer

CONFERENCE SPONSORS: THE HORMONE FOUNDATION, THE SUSAN G. KOMEN BREAST CANCER FOUNDATION, THE CANADIAN BREAST CANCER RESEARCH INITIATIVE, THE NATIONAL CANCER INSTITUTE OF CANADA, THE ENDOCRINE SOCIETY, AND THE UNIVERSITY OF VIRGINIA CANCER CENTER AND WOMAN'S PLACE\*

### Executive Summary of Consensus Statement

#### Problem

Several million women worldwide have survived breast cancer but are currently advised against the use of estrogen for management of menopausal symptoms and for prevention of early cardiovascular death and osteoporosis.

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Address correspondence and requests for reprints to: Dr. Richard J. Santen, Division of Endocrinology, University of Virginia Health Sciences Center, P.O. Box 334, Room 4023, Charlottesville, Virginia 22908.

\* Participants in the Boar's Head Workshop Conference "Treatment of Estrogen Deficiency Symptoms in Women Surviving Breast Cancer", Charlottesville, VA, USA, September 21–23, 1997: Dr. Tom Anderson, Edinburgh University (Scotland); Dr. C. Wayne Bardin, NICHD (USA); Dr. Elizabeth Barrett-Conner, University of California at San Diego (USA); Catherine Black, patient advocate (Canada); Margaret Borwhat, Patient Advocate Foundation (USA); Dr. Henry Burger, Prince Henry's Institute of Medical Research at Monash Medical Center (Australia); Dr. Thomas Clarkson, Bowman Gray School of Medicine at Wake Forest University (USA); Dr. Melody Cobleigh, Rush-Presbyterian-St. Luke's Medical Center (USA); Dr. Felicia Cosman, Helen Hayes Hospital Columbia University College of Physicians (USA); Mary Sue Douglas, RN, patient advocate (Canada); Dr. Andrea Dunaif, Brigham and Women's Hospital Harvard University (USA); Jane Ford, patient advocate (USA); Dr. Patricia Ganz, University of California at Los Angeles (USA); Sally Gleason, patient advocate (USA); Dr. Pamela Goodwin, Mount Sinai Hospital (Canada); Dr. Paul Goss, The Toronto Hospital (Canada); Bettye Green, RN, patient advocate (USA); Dr. Elissa Gretz, Cornell University School of Medicine (USA); Dr. Jennifer Harvey, University of Virginia (USA); Dr. Dr. William Hazzard, Bowman Gray School of Medicine at Wake Forest University (USA); Dr. Kathy Helzlsouer, Johns Hopkins University (USA); Dr. V. Craig Jordan, Northwestern University School of Medicine (USA); Dr. Robert Josse, University of Toronto (Canada); Dr. Joseph Kelaghan, National Cancer Institute - USA (USA); Dr. Michael Kleerekoper, Wayne State University (USA); Dr. Jacqueline Lewis, Sunnybrook Health Science Centre University of Toronto (Canada); Dr. Hilary Llewellyn-Thomas, Sunnybrook Health Science Centre University of Toronto (Canada); Dr. Charles Loprinzi, Mayo Clinic (USA); Dr. Meryl Mark, New York School of Medicine (USA); Andrea Martin, The Breast Cancer Fund (USA); Hugette Martin, patient advocate (Canada); Dr. Susan Miesfeldt, University of Virginia, (USA); Dr. Marcia Moore, University of Virginia (USA); Dr. Lisa Nachtigall, St. Elizabeth's Hospital (USA); Dr. Maria New, Cornell Medical Center (USA); Dr. Annette O'Connor, Loeb Research Ottawa Civic Hospital (Canada); Dr. Mark Olsen, University of Wisconsin (USA); Barbara Parker, Breast Cancer Coalition of North Carolina (USA); Dr. Howard Parnes, National Cancer Institute (USA); Dr. Jeffrey Perlman, Epimedix (USA);

#### Consensus Conference

The Consensus Conference, convened to address this problem at the Boar's Head Inn, Charlottesville, Virginia, September 21–23, 1997, was a unique meeting involving international experts and breast cancer survivors.

#### Recommendations

Recommendations of the conference are summarized as follows:

- Apply "tailored treatment strategies" to individual patients' needs. These strategies would avoid the use of estrogen while providing its benefits (short- and long-term).
- Establish research trials to evaluate the use of estrogens or estrogen alternatives in selected groups of women in whom benefits might potentially outweigh risks.
- Conduct clinical trials to exploit the highly favorable properties of selective estrogen receptor modulators (SERMs).
- Forge a "Partnership for Progress" between patient advocate groups and health professionals to facilitate research and education about treatment options.
- Develop further the "Partnership for Progress" by exploring the establishment of a patient-initiated registry to determine what alternatives or standard medical approaches patients are using to manage estrogen deficiency symptoms, and to promote prevention of cardiovascular disease and osteoporosis.

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Dr. Joann Pinkerton, University of Virginia (USA); Dr. Trevor Powles, The Royal Marsden Hospital (England); Dr. Jerilynn Prior, University of British Columbia (Canada); Dr. Kathleen Pritchard, Sunnybrook Health Science Centre University of Toronto (Canada); Dr. Joseph Ragaz, British Columbia Cancer Agency (Canada); Elda Railey, Susan G. Komen Foundation (USA); Nina Rumen, patient advocate (Canada); Dr. Mary Ropka, University of Virginia (USA); Dr. Ron K. Ross, USC Norris Comprehensive Cancer Center (USA); Dr. Richard Santen, University of Virginia (USA); Dr. Carol Sawka, Sunnybrook Health Science Centre University of Toronto (Canada); Dr. Rena Sellin, MD Anderson Cancer Center University of Texas (USA); Dr. Craig Slingluff, University of Virginia (USA); Dr. Sandra Swain, Comprehensive Breast Center (USA); Phyllis Tysenhouse, Virginia Breast Cancer Foundation (USA); Dr. Nelson Watts, Emory University School of Medicine (USA); Elizabeth Whamond, patient advocate (Canada); Dr. Michael Wills, University of Virginia (USA).

*Definition of problem*

Increased patient awareness, mammography screening, and the use of adjuvant therapy have resulted in earlier diagnosis of breast cancer and a greater probability of long-term survival. Consequently, a large and increasing number of women are alive who have survived breast cancer. In two-thirds of these patients, the onset of menopause had occurred before the diagnosis of breast cancer. In many others, ovarian failure resulted from adjuvant chemotherapy or occurred spontaneously. A large fraction of these women currently experience symptoms of estrogen deficiency and/or can expect premature heart disease and osteoporosis. At the present time, estrogen replacement therapy is considered by many to be contraindicated in these menopausal breast cancer survivors, because estrogens might accelerate the growth of occult metastases. How to treat the range of problems related to estrogen deficiency in these patients is largely unexplored at the present time. Both the short-term effects of estrogen deficiency, such as vasomotor instability and urogenital atrophy, and long-term consequences, such as osteoporosis and heart disease, represent important health and quality of life issues for these breast cancer survivors.

*Magnitude of problem*

There are several million breast cancer survivors worldwide. Specifically in the U.S.A., 180,000 women were diagnosed with breast cancer in 1997. Approximately 97,000 of these women have an extremely low chance of a recurrence of their cancer during their lifetimes. With an average age at diagnosis of 60, and a 25-year expected survival, the current number of breast cancer survivors in the U.S.A. may approach 2.5 million women. Because breast cancer is now being detected at an earlier stage than previously and because adjuvant chemotherapy may cause ovarian failure, there is an increasing number of women who are postmenopausal at a younger age after breast cancer treatment.

*Purpose of the conference*

This conference was convened 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.

*Participants*

Patient advocates as well as experts from a wide range of disciplines including medical oncology, surgery, gynecology, endocrinology, radiology, nursing, epidemiology, and the basic sciences were represented. The conference planners wished to fully integrate women with a previous diagnosis of breast cancer into the schedule of formal talks and discussions so that the perspective of the patient would receive appropriate emphasis.

*Specific topics*

The conference focused upon three specific areas and attempted to reach consensus or identify areas of divergent opinion in each. The first topic addressed the question of initiating clinical trials with estrogen replacement therapy in

subsets of women surviving breast cancer or who have been using estrogens before the completion of trials. The second topic evaluated the potential for the use of selective estrogen receptor modulators (SERMs) in treating the problems arising from estrogen deficiency. The third topic considered the use of surrogates for estrogen to treat specific problems related to estrogen deficiency. Key aspects of each topic are considered in this report, and areas of consensus and divergence are described under each topic. In addition, a consensus statement was prepared by the patient advocates to reflect their unique perspective on the issues discussed.

### **Topic I: Use of Estrogens as Treatment of Menopausal Problems**

*Background*

Menopausal women with a previous diagnosis of breast cancer, as with other women, experience a variety of hormonal changes that potentially affect every aspect of their lives. In addition, many of the therapies currently recommended after a diagnosis of breast cancer produce body changes that can worsen this situation. Lumpectomy, breast irradiation, mastectomy, axillary dissection—each produce changes in body and in body image. Most combination chemotherapies produce either complete menopause or at least some degree of ovarian dysfunction. Menopause can be produced abruptly in this situation, precipitating acute menopausal symptoms that add to the anxieties, symptoms, and concerns already associated with the diagnosis of breast cancer and its surgical, chemotherapeutic, or hormonal therapy.

A traditional belief of the medical profession holds that estrogen and/or progesterone therapy in women surviving breast cancer represents an unacceptable risk. This belief is not unreasonable, based on much that we know about the causes and treatment of breast cancer. Estrogen and progesterone exposure are closely related to the development of breast cancer. In established breast cancer, removal or reduction of estrogen often results in shrinkage of breast cancer or in prevention of recurrence. Thus, both physicians and patients remain extremely cautious about the routine clinical use of estrogen or progesterone in women who have ever had a diagnosis of breast cancer. On the other hand, recent studies in patients without breast cancer suggest that estrogen replacement therapy can lengthen life. Thus it is possible that withholding estrogen from women with a previous diagnosis of breast cancer could increase their mortality from cardiovascular disease. Small observational studies in women with breast cancer receiving estrogen replacement therapy have not shown more rapid recurrence, but properly randomized studies have not yet been conducted. Thus important information is lacking regarding the safety and benefits of estrogens in women surviving breast cancer.

*Consideration of clinical trials*

The conference participants considered whether any trials of estrogen replacement should be undertaken in survivors of breast cancer and, if so, in which subset of patients. The participants agreed that the ability to control menopausal symptoms with surrogates for estrogen, while effective in some patients, was limited in others. The majority of polled

participants, but not all, agreed upon the need to conduct trials of estrogen replacement therapy in selected groups of women surviving breast cancer. There was agreement that the currently ongoing trials, such as the HABITS trial (large multi-institutional Scandinavian and European Trial coordinated from the Uppsala University by Dr. Lars Holmberg) and others, will not provide all of the information needed. Those favoring trials believe that an answer to this question is required and that it would not be ethical to continue to make recommendations to patients without greater scientific evidence. Those arguing against clinical trials of estrogen replacement believe that major difficulty will be encountered in entering a sufficient number of patients to answer the safety questions with acceptable statistical power. One participant suggested that information regarding safety might be gained from case control observational studies resulting from the establishment of a patient registry.

Most agreed that the initial trials should focus on short-term studies to relieve symptoms of vasomotor instability and urogenital atrophy but not upon prevention of osteoporosis or heart disease. Safety issues under these circumstances would involve risk of accelerating growth of occult metastases but not initiation of new second primary breast cancers. One group favored trials in patients at lowest risk of adverse effects from estrogens, namely women with estrogen receptor negative tumors. Another favored trials in women with receptor positive tumors, arguing that this group would provide stronger evidence of safety if recurrences were not increased. The latter group was also thought to provide higher statistical power to detect significant differences in recurrence. The pros and cons of these two approaches were felt to be a dilemma with no easy resolution.

Review of an ongoing trial and strong opinions expressed by patient advocates suggested that only a small fraction of breast cancer survivors would accept the use of estrogen replacement therapy, even if studies suggested relative safety. Consequently, trials with other approaches designed to relieve menopausal symptoms should also be carried out to develop safe, acceptable alternatives for women. Some participants felt that the use of progestins might not be safe in this setting, even though megestrol acetate is known to be an effective treatment for advanced breast cancer, albeit at higher doses than those used for vasomotor instability.

The participants discussed at length but could not agree upon specific groups of women to be involved in initial trials of hormone replacement therapy. Many reasoned that women undergoing chemotherapy-induced menopause experience particularly severe symptoms and should be targeted for initial trials of hormone replacement. Most agreed that such trials should commence only after subsidence of chemotherapy-related symptoms, to avoid confounding of interpretation of results. Patient advocates and others expressed the opinion that women in this category would be most frightened of the adverse effects of estrogen and that accrual into such trials would be too small to obtain meaningful information.

Substantial discussion addressed clinical trials of the combined use of tamoxifen and replacement estrogen in patients with estrogen receptor positive tumors. Concepts had been formally presented regarding the stoichiometry between ta-

moxifen and estrogen for the estrogen receptor and the differential agonistic and antagonistic effects of tamoxifen on various target tissues. It was noted that tamoxifen is an effective antitumor agent for advanced breast cancer in cycling premenopausal women with estradiol levels of 1000–2000 pmol/L. Based upon this observation, tamoxifen should remain an effective antitumor agent in postmenopausal women given small amounts of replacement estradiol sufficient to increase plasma levels only to the 150–450 pmol/L range. Under these conditions, the effects of estrogen might relieve hot flashes and symptoms of vasomotor instability without stimulating tumor growth. Preliminary biochemical data were presented to the participants regarding patients receiving both tamoxifen and conjugated estrogen.

Based upon this information, the participants believed that the combination of tamoxifen with estrogen or progesterone might potentially relieve menopausal symptoms without increasing the risk of tumor recurrence. It was agreed, however, that the data presented were insufficient to conclude that symptoms would be fully relieved by this approach. Most participants agreed that small pilot studies to determine efficacy of relief of symptoms should be followed by large randomized controlled trials to ensure safety. This approach was favored particularly for women with estrogen receptor positive tumors.

The conference participants initially attempted to design prototype clinical trials of hormone replacement therapy during the consensus building period. This was found to be impossible and, as expressed by several discussants, not the purpose of the consensus conference. The panel then agreed to establish general principles upon which such trials could be based. A consensus was reached that trials of hormone replacement should initially involve women who are symptomatic and not women where prevention of osteoporosis or heart disease is the primary goal. Trials should be short-term to minimize concerns about stimulation of occult micrometastases. Only with long-term estrogen replacement would the initiation of new second primaries be an important consideration. Groups of women selected for such trials should have findings suggesting that the benefits of hormone replacement therapy are likely to outweigh the risks. These might include women on tamoxifen; patients with small, node negative or low histologic tumor grades where the likelihood of long-term survival is great; women with receptor negative tumors; and women with a long disease-free survival before treatment with estrogen.

#### *Use of estrogen replacement therapy before completion of clinical trials*

The participants considered at length whether it might be appropriate to offer selected women hormone replacement therapy, as an interim measure, before the completion of clinical trials. All agreed that other established means of controlling symptoms or preventing osteoporosis or heart disease should be utilized before considering estrogen therapy. In those women not responding, entry into a clinical trial would be the preferable approach. However, nearly all agreed that a subset of women continue to experience severe problems from estrogen deficiency that might only be con-

trolled by hormone replacement therapy. The participants agreed that an informed woman, knowing all the potential benefits and risks of estrogen could choose to take estrogen and would be supported in that decision. Under those circumstances, informed consent by the patient should precede use of estrogens (most, but not all, felt this should be written informed consent). The unknown but potential risks of stimulating occult metastases or of causing a new cancer should be fully discussed. A clear distinction was made that there was not a consensus to recommend estrogen in selected patients, but that a woman is free to make her own decision provided she is fully informed. Estrogens or progestins in this setting should be prescribed in lowest doses, for the shortest duration of time, and only after full discussion. This strategy considers the informed patient as the final decision maker. The health care provider serves to guide the patient through the difficult process of assessing known and unknown risks and benefits.

To capture the essence of the discussion, a comprehensive statement was offered to the participants and agreed upon. "In women who have had an established diagnosis of breast cancer, we should seek other established symptomatic or health promoting interventions before considering the use of estrogens. When estrogen is used as a last resort, it should be used in the lowest dose for the shortest duration of time and only after full discussion of concerns regarding potential risks with respect to breast cancer outcomes. When estrogen is being considered, the role of the informed woman as the final decision maker should be accepted by the health care practitioner."

#### *Summary of consensus points*

- Studies of a variety of methods to control the short-term effects of estrogen deficiency in breast cancer survivors are necessary. One approach is to examine the efficacy of surrogates for estrogen. The other is the use of estrogen itself where the primary goal should be to examine the efficacy and safety of estrogen and progesterone replacement therapy.
- Initial emphasis should be on trials for relief of menopausal symptoms including hot flashes, vaginal dryness, urinary symptoms, and painful intercourse.
- Carefully designed trials should be undertaken to explore the effectiveness and the safety of estrogens and/or progesterone in women with a previous diagnosis of breast cancer who are also receiving tamoxifen.
- Well-designed trials, starting with smaller pilot studies to determine efficacy and followed by large randomized controlled trials to ensure safety, will be required to establish the indication for combined estrogen and antiestrogen therapy.
- Because only a small fraction of women surviving breast cancer will accept hormone replacement therapy, trials of alternative therapies to relieve symptoms are required.
- A series of principles intended to guide initial clinical trial design included the following:
  - Clinical trials should include only symptomatic women and hormone replacement therapy given short-term.
  - Well-designed, randomized trials are required.

—Studies should involve women in whom the benefits of hormone replacement therapy are likely to outweigh the risks. Specifically this might include:

- women with small, node negative or low histologic grade tumors
- women receiving tamoxifen
- women with receptor negative tumors
- women with a long disease-free survival

### **Topic II: Use of Selective Estrogen Receptor Modulators (SERMs):**

#### *Background*

Substantial data link estrogen exposure to breast cancer. Breast cancer occurs predominantly in women, and risk factors are related to lifetime exposure to estrogen. It is therefore logical that antiestrogens, substances that would block the effect of estrogen on the breast, should be developed to prevent breast cancer. By far the best studied antiestrogen is tamoxifen. When being evaluated, it was unexpectedly found to have estrogen-like properties on certain tissues—specifically, it prevented the bone loss induced by estrogen withdrawal in animals and mimicked estrogen in reducing cholesterol levels. These observations changed perspectives regarding antiestrogens and led to the concept that drugs could be developed that might mimic the favorable effects of estrogen on bone, blood vessels, and perhaps brain, while preventing the unwanted effects of estrogens on the breast.

Tamoxifen has been on the market for nearly 20 years for treatment of breast cancer and in the past decade has been evaluated for its ability to prevent breast cancer. A problem with tamoxifen is that it retains estrogen-like effects on the uterus and increases the risk of uterine cancer. Hence, there has been a need for better target-site specific drugs. The hope was to find an agent that would prevent osteoporotic fractures and lower the incidence of heart disease while preventing breast and uterine cancer. Such a drug would also benefit breast cancer survivors who could reap the benefits of estrogen replacement without the associated risks.

The participants of this conference heard presentations regarding a new class of compounds with target-site specific actions: selective estrogens or SERMs. These data provided the background for deciding whether the SERMs might be ideal agents to study as a strategy for treating estrogen deficiency symptoms in women surviving breast cancer.

#### *Actions of raloxifene*

The conference organizers chose to invite speakers to discuss the effects of raloxifene, as it was known to be on the fast track for approval at the time of planning of the consensus conference. It has now been approved by the Food and Drug Administration for use in the United States for prevention of osteoporosis. Published and unpublished data were presented to the meeting participants for their consideration. Two-year data from a large multicenter study involving about 7000 women were reviewed, indicating that raloxifene shows promise for prevention of osteoporosis and potentially of heart disease, but without risk of increasing the incidence of uterine or breast cancer. The number of patients

in this study who developed new breast cancers was small. Nonetheless, trends suggested a reduction in breast cancer risk in patients receiving raloxifene. These findings should be considered with caution as this trial was not designed as a breast cancer prevention study. Upcoming three-year data were considered to be potentially quite important. The preliminary data regarding blockade of bone resorption are favorable. Effects similar to those of estrogens but of somewhat smaller magnitude were observed. A reduction of lipid levels occurred that was significant but lesser in magnitude than occurred with estrogen replacement. Effects on the cardiovascular system, independent of the lipid effects of raloxifene, appeared to be less than observed with estrogen, as assessed in a model system in cynomolgus monkeys.

Raloxifene does not appear to act as an estrogen to reduce the frequency of hot flashes and will not therefore serve as an effective agent to relieve the symptoms of vasomotor insufficiency. No data are as yet available on the actions of raloxifene on the central nervous system with respect to cognitive function, mood, or memory.

Substances similar to raloxifene occur naturally, for example in soybeans, and are called phytoestrogens. New data were presented on the effects of these estrogens in postmenopausal primates. Heart disease reduction was similar to that produced by estrogen without stimulatory effects on the breast or uterus. Clinical trials of these compounds are currently under way.

#### *Potential clinical use of SERMs*

The conference participants agreed that the SERMs and phytoestrogens represent new possibilities for the long-term treatment of breast cancer survivors as well as of women who fear breast cancer. The SERMs do not relieve acute symptoms of menopause such as hot flashes and problems with urogenital atrophy. This class of agents would not serve as surrogates for estrogen for treatment of these acute symptoms. In contrast, the SERMs would provide lipid lowering effects for potential prevention of heart disease and would block bone resorption as a means of preventing osteoporosis. The participants concurred that raloxifene should become a major focus for study in women surviving breast cancer. The design of specific trials was not discussed, but the group generally felt that the aim of these studies should be to evaluate the use of SERMs for prevention of heart disease and osteoporosis. The participants expressed a major interest in the three-year follow-up data to determine if raloxifene will reduce the incidence of new breast cancers. This effect would be quite attractive for survivors of breast cancer who have a 0.5% yearly risk of developing a second primary. Evaluation of phytoestrogens by clinical trial was viewed with interest but considered by some to be preliminary at present.

#### *Summary of consensus points*

- The SERMs and phytoestrogens potentially represent important new agents for long-term treatment of breast cancer survivors.
- These agents are beneficial to reduce bone loss and to lower total and LDL cholesterol levels but do not cause relief

of vasomotor instability symptoms nor of urogenital atrophy.

- In contrast to tamoxifen, the new SERMs apparently do not stimulate the endometrium and thus may not increase the incidence of endometrial cancer.
- The SERMs should be tested long term in clinical trials in survivors of breast cancer for prevention of osteoporosis and heart disease but not for relief of short-term menopausal symptoms.
- More data are required regarding the phytoestrogens before initiation of large clinical trials.

### **Topic III: Tailored Treatment Strategies**

#### *Background*

Surrogate drugs that can be used to bypass the need for estrogens in women surviving breast cancer are currently available. Some of these do not need further clinical trial, whereas others are efficacious but require further safety testing. Use of these agents must be tailored to the specific problems of individual patients. For this approach, it is necessary to identify the five separate medical problems that occur as a result of menopausal estrogen deficiency. These include:

1. Increased risk of developing heart disease
2. Increased risk of osteoporosis with resultant fractures of the hip, wrist, and spine
3. Urogenital atrophy (dry vagina, dyspareunia, urinary incontinence, and increased risk of urinary tract infections)
4. Vasomotor instability (hot flashes, sweats, and frequent awakening from sleep with resulting daytime fatigue)
5. Central nervous system problems with mood disorders, depression, memory loss, and sleep disorders

#### *Discussion of treatment options*

The conference participants listened to and discussed presentations regarding each of these issues. They reached a consensus that it is possible to tailor specific treatments to each of these problems in individual patients, but that some treatments are not as effective as estrogen and others require further study. The physician and patient need to identify which of these five problems are specifically relevant to the individual patient. This approach requires assessment of specific symptoms or risk factors for heart and bone disease as part of a medical evaluation. Together, the physician and patient can tailor effective treatments for that specific patient and her particular problem.

*1. Heart disease prevention.* Individual patients are evaluated for their risk of developing new cardiovascular events. Various risk factors include abnormal levels of low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol, LDL/HDL ratio, and triglyceride levels; family history of coronary artery disease; hypertension; smoking history; presence of obesity; presence of heart disease currently; and life style factors such as alcohol intake and exercise. If the risk is substantial, the usual approach in a woman without breast cancer would be to recommend estrogens. However, a class of cholesterol-lowering drugs called HMG-CoA reductase inhibitors or "statins" has now

been shown to reduce lipid levels and the risk of new cardiovascular events and mortality. These drugs, when compared with estrogens in randomized trials, lower cholesterol to a greater extent than does estrogen. They reduce new cardiovascular events by approximately 30% in prospective, randomized trials. The long-term safety and side effect profiles appear favorable, but further experience is necessary. They provide surrogates for estrogen and an effective way to bypass the need for estrogens while accomplishing the same goal, prevention of heart disease. It should be noted, however, that the protective effects of estrogens are considered to result from both lipid lowering actions and by direct effects on the vasculature. The statin drugs only act by lowering lipids.

It should be noted that, at the present time, no prospective randomized trials have examined the effect of estrogen in reducing the frequency of new cardiovascular events or mortality. The only data regarding estrogen therapy are from observational reports. No studies have yet compared the statin drugs with estrogens prospectively with end points of cardiovascular events or mortality. Until such studies are completed, one can only conclude that the statins are effective in cardiovascular disease prevention, but their precise efficacy *vs.* estrogen, while apparently similar, is unknown.

**2. Prevention or treatment of osteoporosis.** The approach to use of estrogen surrogates for osteoporosis prevention or treatment is also based on an individual risk-based strategy. The various risk factors for osteopenia are assessed including family history, history of calcium intake, smoking, alcohol use, medications that induce osteopenia, weight, race, and degree of exercise. Taking into account these factors, a dual energy x-ray absorptiometry scan is obtained to determine the individual fracture risk. T scores of greater than  $-2.5$  are considered osteoporosis, and patients are treated with standard measures of appropriate calcium intake, vitamin D if needed, exercise, and either a bisphosphonate or nasal calcitonin. The bisphosphonates are considered to exert similar antiresorptive and antifracture potency as estrogens, with the caveat that head-to-head comparisons are as yet not completed. Women with bone densities between  $-1.5$  and  $-2.5$  are considered for treatment or are followed with repeat bone density measurements at intervals. With approval of raloxifene for prevention of osteoporosis, women with osteopenia could now be considered candidates for this SERM.

**3. Urogenital atrophy.** Severe symptoms of urogenital atrophy occur in nearly half of postmenopausal women surviving breast cancer. A consensus was reached that vaginal moisturizers and lubricants can be helpful but do not completely relieve symptoms in the majority of patients. Newer methods of delivering estrogen locally into the vagina without systemic absorption were discussed. One of these, a vaginal estrogen ring device (Estring, Upjohn-Pharmacia), was first introduced for use in the United States in February of 1997, and was recently made available in Canada. This device provides nearly complete relief of symptoms. In open label studies (but with blinded review of vaginal cytology), similar efficacy was observed with the vaginal ring device and with conjugated estrogens. Data reviewed indicate minimal sys-

temic absorption from this device, but more studies are needed to be certain that these methods do not cause an increase in systemic estrogen levels. Use of very low dose vaginal estrogen creams also exert predominantly local effects once the vaginal mucosa has matured. Estrogen absorption is enhanced at the onset of therapy when the vaginal mucosa remains atrophic. Available data indicate minimal systemic absorption of estrogen after correction of atrophy, but further study is required. While awaiting the results of such trials, physicians should discuss these local methods of estrogen delivery with patients whose symptoms are not relieved by other measures.

**4. Vasomotor instability.** The use of a placebo consistently reduces the number and severity of hot flashes by about 25%. Clonidine and to a lesser extent Vitamin E induce a statistically significantly greater reduction of hot flashes than observed with placebo but not to the degree produced by estrogens. Megestrol acetate at a dosage of 40 mg daily, on the other hand, appears to be as effective as estrogen. The consensus panel concluded that use of these agents should be offered to patients for control of symptoms. Caution was raised that long-term safety effects of megestrol acetate in patients surviving breast cancer have not been well studied. Based upon discussions of the stimulatory effect of progestins on breast tissue, several participants expressed concern about the use of megestrol acetate. The panel agreed that short-term use for control of severe hot flashes would be more acceptable than long-term use. Additional research to find more acceptable estrogen surrogates is warranted. The SSRI (Selective Serotonin Reuptake Inhibitor) class of drugs appears promising.

**5. Central nervous system (CNS) symptoms.** Symptoms of sleep disturbance and depression should be identified and treated, but no specific recommendations were made. More research is needed to identify the frequency and severity of these symptoms and the use of nonestrogenic medications for their treatment. No data are as yet available regarding raloxifene and CNS symptomatology, but SSRIs should be considered.

#### Summary of consensus points

- Effective means are now available to treat or improve problems associated with menopause without using estrogen replacement therapy.
- A tailored treatment strategy that identifies the needs of each individual patient is recommended. The physician and patient can then make informed choices to address specific problems and to treat each patient individually.
- Treatments now exist for prevention of heart disease and osteoporosis that can be used in place of estrogen.
- Provision of low dose estrogen to the vagina locally, via either vaginal ring or cream, provides relief of symptoms of urogenital atrophy without increasing plasma estrogen levels substantially. Further studies of plasma estrogen concentrations with highly sensitive assay methods are necessary to determine if increments in systemic estrogen levels occur with these local delivery methods.
- Treatment of the symptoms of vasomotor instability is highly effective with megestrol acetate, less so with

clonidine, and marginal with vitamin E. Further studies of the safety of long-term use of megestrol acetate are required.

- Symptoms related to the effects of estrogen deficiency on the CNS may respond to CNS active agents such as antidepressants, but this area requires further study.

*Consensus statement developed by the patient advocates*

Breast cancer advocates have partnered with the scientific and medical community in a landmark conference that discussed treatment options for menopausal symptoms in women diagnosed with breast cancer. Advocates from the United States and Canada presented their perspectives and insights on this issue.

Because estrogen use has been associated with an increased risk of developing breast cancer, women diagnosed with breast cancer are averse to the use of hormonal therapies to address both short-term menopausal symptoms and long-term concerns of heart disease and osteoporosis. They are frustrated by the lack of options. Patients often think of hormonal therapy as the only option, so they are encouraged by discussion of current choices and future developments presented at the conference. These options enable treatment to be tailored to the individual. The patient and her physician need to discuss the risks and benefits of agents that will address her specific needs. This allows the breast cancer survivor to make informed decisions.

The conference participants recognized the value of forging a partnership between patient advocates and the medical community that will result in more rapid progress in addressing issues of specific concern to patients. This partnership would facilitate research design to address quality-of-life issues. This partnership would also facilitate the recruitment and accrual of patients into studies, because the patient advocate organizations would share in the dissemination of information about studies and the education of patients regarding the goals and rationale for specific studies.

Catalyzed by the comments of the patient advocates, the other conference participants identified the need for a comprehensive registry to gather information from women diagnosed with breast cancer to facilitate future research. A consensus was reached that a registry originating from patient advocate groups would be more successful in obtaining information regarding current use of alternative therapies. Patients are reluctant to share information with their physicians regarding use of herbal medicine, nutritional strategies, and life style changes. A registry originating from patient advocate groups could obtain this important information and provide much needed data to patients and their health care providers.

*Summary of consensus points*

- The health care community should acknowledge that most breast cancer survivors are fearful of taking estrogens for relief of menopausal symptoms and prevention of osteoporosis and heart disease.
- Encourage physicians to discuss “tailored treatment options” that do not involve the use of systemic estrogen therapy for menopausal symptoms or for prevention of the problems associated with estrogen deficiency
- Forge a “Partnership for Progress” between patient ad-

vocate groups and health professionals to facilitate research and education about treatment options

- Further develop the “Partnership for Progress” by exploring the establishment of a patient registry to determine what patients are currently doing and thinking about with respect to estrogen deficiency symptoms, cardiovascular disease, and osteoporosis prevention

**Meeting Summary**

The full meeting summary is in preparation for publication in the journal *Obstetrical and Gynecological Surveys*. Full discussion of all major issues raised at the Boar’s Head conference is contained in this publication. Several controversial topics are covered at length there, as a consensus document is limited in scope. Issues such as the nature of menopause and whether it is a natural life event or a disease state are discussed, particularly by patient advocates. Substantial event rate data for osteoporosis and prevention of heart disease are provided there. The interested reader is referred to this document.

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