Changes, called alterations or mutations, in certain genes make some women more susceptible to developing breast and other types of cancer. In breast tissue, alterations in the genes called BRCA1 and BRCA2 (Breast Cancer Gene 1 and 2) are involved in many cases of hereditary breast and ovarian cancer. BRCA1 or BRCA2 breast and/or ovarian cancer is usually associated with women who have families with a history of multiple cases of breast cancer, cases of both breast and ovarian cancer, one or more family members with two primary cancers (original tumors at different sites), or are of Ashkenazi (Eastern European) Jewish decent. However, not every woman who has an altered BRCA1 or BRCA2 gene will get breast or ovarian cancer. Approximately, 1 in 10 breast cancer cases involves an inherited altered gene, and not all inherited breast cancer involves BRCA1 or BRCA2. Therefore, genes are not the only factor that affect cancer risk.

According to a recent study conducted by Mary-Claire King, PhD, of the University of Washington, Seattle, and co-author Bernard Fisher, MD, Scientific Director, National Surgical Adjuvant Breast and Bowel Project (NSABP), the drug tamoxifen seems to reduce the incidence of breast cancer in healthy women who carry BRCA2 gene mutations that make them susceptible to the disease. Although this news appears to be significant for women with this mutation, tamoxifen does not seem to reduce the breast cancer incidence of healthy women with BRCA1 mutations. The Breast Cancer Prevention Trial (BCPT), which involved 13,388 women, demonstrated a significant reduction (49 percent) in breast cancer incidence among women who took tamoxifen. The benefit was evident in women who had mothers, sisters, and/or daughters with breast cancer, but it also seemed successful in women who had no family history of breast cancer. These findings led researchers to postulate that tamoxifen might also reduce the risk of breast cancer in women with BRCA1 or BRCA2 gene mutations.

Tamoxifen works by binding estrogen receptors (ER) in breast tissue with the receptor is termed ER-positive). Certain precancerous changes in the breast, however, may cause the loss of ER rendering tissues ER-negative. In the BCPT study, breast cancer, however, may cause the loss of ER rendering these tissues ER-negative. In the BCPT study, tamoxifen reduced the incidence of ER-positive tumors, but did not reduce the incidence of ER-negative tumors. Therefore, tamoxifen does not seem to be effective in women who develop ER-negative breast cancer.

The ER status of BRCA1 mutations appear different when compared to BRCA2 mutations. Several studies indicate that approximately 80 percent of breast tumors that occur in women with BRCA1 mutations are ER-negative. In contrast, other studies suggest that 80 percent of breast tumors that occur in women with BRCA2 mutations are ER-positive. Based on data from these studies, Dr. King analyzed the blood samples of women, without knowing who they were, participating in the BCPT for BRCA1 and BRCA2 mutations.

- Two-hundred and eighty-eight (288) BCPT participants, who developed breast cancer while taking either tamoxifen or a placebo were analyzed. NSABP BCPT researchers recorded the number of breast cancers among women receiving tamoxifen with that of those receiving placebo. From this data, Dr. King and her colleagues studied the two groups for BRCA1 or BRCA2 mutations finding that 19 women (6.6 percent) had at least one of the two mutations. And it is from these women that Dr. King's findings show that tamoxifen seems to reduce the incidence of breast cancer by 62 percent in healthy BRCA2 mutation carriers, but not in healthy women with BRCA1 mutations.

What does this mean for STAR participants? More definitive information on genetics, BRCA1 and BRCA2, and how they affect breast cancer is needed. To date, there is limited information about tamoxifen and genetics and none with regards to raloxifene and genetics. Dr. King's study is only the beginning to a long list of questions researchers have about the relationship between genetics and cancer. That is why your participation in STAR is so important. The more researchers understand about drugs such as tamoxifen and raloxifene and their effects on the human body the closer we will be to a cure. Dr. King’s article was published in the Journal of the American Medical Association (JAMA. 2001; 286:2251-2256).

It is important to note that this study addressed the incidence of new breast cancer cases among healthy women with BRCA1 or BRCA2 mutations, not the treatment of existing breast cancer. Among women with breast cancer that is ER-positive, tamoxifen has been shown (by NSABP and other studies) to reduce the risk of disease recurrence, regardless of the patient’s BRCA1 or BRCA2 genotype.
Some of you may have experienced personal tragedies within your families that have led you to this trial. Others may know someone who has had breast cancer. And still others, may be participating in this trial to ensure that future generations of women do not get this disease. But no matter what your reason is, all of us are here to hopefully prevent breast cancer before it has the opportunity to start, but we have to work in a way to go before this statement can hold true. As researchers, we do this study not only for your mothers, daughters, and nieces, but for ours as well. Therefore, I think of our relationship as an extremely large, extended family—united for one cause. As one of our STAR coordinators put it, “Alone you are a single STAR. Together we are a Constellation.” We are committed to finding a way to stop this disease but we need your continued support if this is to occur.

In July, STAR will be beginning its fourth year. Many of you have been with us since the beginning. Others may have just started, but let me update you on where we are today. As you can see by the side-bar to the left of this column, we are more than halfway to our goal with more than 13,390 women participating in this trial. However, we have touched many more women than this. As of May 30, 2002, more than 116,569 women have sent us their risk assessment forms so that we can calculate their risks and show them the importance of joining this trial, and if there is, you can just move along. We don’t want to force anything on anyone, this is not our intent. But, we feel that you will find that people will be interested in what you have to say. Your STAR program coordinator can provide you with some background materials, such as the STAR brochure and poster. The NSABP is currently working on a packet of information that will be geared toward helping you with these efforts. This packet will be made available to you through your STAR program coordinator when and if there is, you can just move along. We don’t want to force anything on anyone, this is not our intent. But, we feel that you will find that people will be interested in what you have to say. Your STAR program coordinator can provide you with some background information. As of this date, 10,473 women have been recruited to STAR as of May 30, 2002.

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Co-STAR: Cognition in the Study of Tamoxifen & Raloxifene ...from Pg. 1

How do ongoing studies of hormone replacement therapy (HRT) and dementia and cognitive aging relate to Co-STAR?

Since estrogen may have a positive effect on cognitive function and SERMs may replace traditional HRT for women who cannot or do not wish to take hormones, the question of the effect of SERMs on cognition comes to the forefront.

The Women’s Health Initiative Memory Study (WHIMS), designed to test the hypothesis that HRT reduces the incidence of all-cause dementia and Alzheimer’s disease in women aged 65 and older, is currently being conducted. Another ongoing study, WHISCA, a substudy to WHIMS is being funded by and conducted in collaboration with the National Institute on Aging and is focusing on the acquisition of data on memory, other cognitive abilities, and mood in WHIMS participants. WHISCA is the largest randomized trial of HRT on normal cognitive function; the study will provide invaluable data on the effects of hormone treatments on normal cognitive aging.

How is Co-STAR designed?

Approximately 2,000 women, 65 years of age and older, will be enrolled into Co-STAR over a three-year period. Following their enrollment into STAR and after being randomized to either tamoxifen or raloxifene, women will be recruited into Co-STAR. Those who agree to enter Co-STAR will undergo a baseline assessment comprised of tests for memory, other cognitive abilities, and mood. Participants will receive a similar test once a year for the next 4 years.

Who is eligible for Co-STAR?

STAR participants who are:

• at or near a STAR site participating in Co-STAR can volunteer;
• enrolled in STAR and have been assigned to either tamoxifen or raloxifene;
• 65 years of age and older;
• not, or have ever been, diagnosed with dementia; and
• willing to sign a separate consent form to participate in Co-STAR.

Co-STAR will only enroll 2,000 STAR women. With this in mind, each Co-STAR clinical center was selected based on its geographic location, ethnic diversity, and age appropriate period (65+ years). For more information on Co-STAR, contact your STAR coordinator to see if your site is participating in this study. If you need additional help finding a Co-STAR site, please contact the Co-STAR Central Coordinating Center toll-free at 866-716-9094.

For more information on SERMs & cognitive functioning in postmenopausal women, please consider reading the following:

Selective Estrogen Receptor Modulators: A New Paradigm for HRT

Baines K, et al

American Journal Obstetrics and Gynecology

179:1479-84, 1998

Selective Estrogen Receptor Modulators: A New Category of Therapeutic Agents for Extending the Health of Postmenopausal Women

Goldstein SR

American Journal Obstetrics and Gynecology

179:1207-13, 2001

Cognitive Function in Postmenopausal Women Treated with Raloxifene

Yaffe K, et al

New England Journal of Medicine

343:1207-13, 2000

Raloxifene Hydrochloride, A Selective Estrogen Receptor Modulator: Safety Assessment of Effects on Cognitive Function and Mood in Postmenopausal Women

Naidoo T, et al

Psychoneuroendocrinology

24:115-28, 1999

The Women’s Health Initiative Memory Study (WHIMS): A Trial of the Effect of Estrogen Therapy in Preventing and Slowing the Progression of Dementia

Shumaker SA, et al

Contemporary Clinical Trials


Reflections... was submitted by Suzanne Blanchard of Duxbury, Massachusetts, a STAR participant at Dana-Farber Cancer Institute. She has given permission for the NSABP to print this article in Constellation. The thoughts and words are her own and we thank her for sharing them with all of us. If you would like to share your experiences “inside a clinical trial,” please send them to the NSABP (address available on back page) and you too may see your story highlighted in an upcoming issue of Constellation.

I never expected my lovely daughter to teach me how to die, with such courage, love, and grace.

It all began with a call from Bambi, a 37-year-old mother of three, anxiously saying that overnight, her left breast had doubled in size. This had happened while she was on a field trip to Washington, DC, during the spring of 1998, with her son Peter. After speaking to her doctor, he told her that it was probably just an infection, and antibiotics were prescribed. After two days, the swelling and pain were worse. With Bambi’s insistence, a biopsy was scheduled. We all had trouble waiting those few days before the procedure was due, but we played over and over in our minds what her doctor had said and that it was very likely nothing to worry about. The diagnosis, unfortunately, was everything to worry about. Inflammatory breast cancer, a rare disease that claims the lives of nearly all its victims in three to eighteen months, often having metastasized before being discovered. In my daughter’s case, the cancer had already spread through most of the bones in her body. This type of breast cancer is indeed so rare that Bambi’s doctor in Dartmouth had never seen another such patient in his practice. On that lovely April day, the deep, raw wounds carved by breast cancer could be found. I’ll never forget the brightness of Bambi’s smile when I told her I had been accepted in this trial. “That’s great, Mom. I’m proud of you!”

Secondly, it is also for the many dedicated, wonderful doctors and nurses at Dana-Farber in Boston, that I wanted to continue her desire to find more answers to the many questions we still have about breast cancer. The staff treated Bambi with such skill and kindness, especially her key physician, Dr. Hal Burstein. He made her feel so special, so unique, and so loved. As Hal walked with her on that dreadful path to death, we could hear in his every word and step an echo of our sorrow and loss that one so kind, so exceptional, was not to be saved.

Yes, participating in STAR, I am hoping to be a small part of the army, which is now fighting this war... (to one day) hear the words, “Breast cancer—no longer a problem!”

—I am trying to be a star in the army of Bambi.
Leg Cramps*

A leg cramp is a painful involuntary muscular contraction that usually occurs in the calf or foot. A leg cramp is a painful involuntary muscular contraction that usually occurs in the calf or foot. Tonic Water: Many women have reported that they have received relief from the discomfort of leg cramps by drinking tonic water, which contains limited amounts of quinine. Tonic water may be taken either by itself or mixed with another liquid such as water or orange juice.

Vaginal Dryness*

The high estrogen levels of the premenopausal years help to maintain healthy vaginal tissue. As women begin menopause and their estrogen levels decrease, the vaginal lining becomes thinner and has less lubrication. These changes may cause women to experience vaginal dryness and pain with intercourse.

Practical Suggestions for Vaginal Dryness

• Take warm baths to alleviate itching and discomfort
• Wear cotton underwear
• Avoid douches, feminine hygiene sprays, and perfumed soaps or toilet paper

Hot Flashes*

Hot flashes usually begin as a sensation in the head, neck, upper chest, and back, and can spread to the entire body. The intensity and frequency of hot flashes vary; a woman may experience as few as one a day, or as many as three an hour. Hot flashes may interrupt sleep, causing irritability and insomnia.

Practical Suggestions for Hot Flashes

• Record the number of hot flashes per day/week
• Wear absorbent, cotton clothing
• Dress in layers
• Lower the thermostat
• Avoid caffeine and spicy foods
• Exercise regularly
• Learn relaxation techniques
• Try to identify “triggers” that may prompt hot flashes and avoid them

Over-the-Counter Interventions

• Vitamin E, 800 IU daily
• Vitamin D, 200 IU, daily
• Vitamin C plus bioflavonoids, (compounds found in plants) two tablets three times daily. Available over-the-counter as WellDerin®. This product is often not available in stores, but can be ordered through a pharmacist. It can also be purchased directly from the manufacturer (1-800-238-8542).

Leg Cramps

A leg cramp is a painful involuntary muscular contraction that usually occurs in the calf or foot. Leg cramps can be associated with the drugs used in STAR. Only a few women reported muscle cramps in scientific literature for the treatment of leg cramps. The following are suggested interventions that you may want to try if leg cramps become disruptive.

Practical Suggestions for Leg Cramps

• Exercise and Eating Right: Following a regular exercise program and eating foods that are high in calcium (i.e., low-fat milk) and potassium (i.e., banana) may help reduce leg cramps.

More Serious Potential Side Effects

Tamoxifen and raloxifene may also increase a woman’s chances of developing several rare, but potentially life-threatening health problems: deep vein thrombosis (blood clot in a large vein) and pulmonary embolism (blood clot in the lung). Tamoxifen use may also increase a woman’s risk of stroke and endometrial cancer (cancer of the lining of the uterus) at a rate similar to estrogen replacement therapy. In ongoing studies, raloxifene has not been associated with an increased risk of stroke or endometrial cancer. With your participation, STAR will help you to define the risks and benefits of tamoxifen and raloxifene therapy. Your STAR healthcare provider has provided you with detailed information about these types of side effects before you agreed to participate in STAR during the consent process.

This information was taken from the STAR Symptom Management Strategies brochure. If you would like a copy of this brochure, please contact your STAR healthcare provider.