

# Constellation

A Newsletter for All STAR Participants

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## Tamoxifen Reduces the Incidence of Breast Cancer in Women with Inherited BRCA2 Mutations:

*A Genomics Resequencing Project Embedded in the NSABP Breast Cancer Prevention Trial (BCPT/P-1)*



Changes, called alterations or mutations, in certain genes make some women more susceptible to developing breast and other types of cancer. Inherited alterations in the genes called BRCA1 and BRCA2 (*B*reast *C*ancer *G*ene *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 descent. 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 targeting estrogen receptors (ER) in breast tissue (tissue with the receptor is termed ER-positive). Certain precancerous changes in the breast, 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.

## Co-STAR: Cognition in the Study of Tamoxifen & Raloxifene

### What are the goals of Co-STAR?

The principal goal of Co-STAR is to compare the effects of tamoxifen and raloxifene, both selective estrogen receptor modulators (SERMs), on age-associated declines in memory and other cognitive abilities in women age 65 and over within the context of a randomized clinical trial. Therefore, Co-STAR will involve the collection of data on cognitive aging in a subset of STAR participants allowing a comparison of the two agents.

The secondary goal of Co-STAR is to compare the cognitive effects of tamoxifen and raloxifene with those resulting from hormone replacement therapy (HRT), specifically estrogen replacement therapy (ERT) and ERT plus progesterone, in the *Women's Health Initiative Study of Cognitive Aging* (WHISCA). Cognitive outcomes in Co-STAR participants will be compared with those from WHISCA participants. A comparison between the Co-STAR and WHISCA participants will provide insight into the effects of SERMs and ERT or ERT plus progesterone on cognitive functioning within the context of a clinical trial.

### What are the study questions in Co-STAR?

- What is the rate of change in memory and other cognitive abilities in women receiving tamoxifen compared to women receiving raloxifene?
- Do tamoxifen and raloxifene have beneficial, neutral, or detrimental effects on age-associated memory and cognitive decline in women over age 65?
- How do the cognitive effects of tamoxifen and raloxifene compare to those of ERT and ERT plus progesterone?

### Why is Co-STAR being conducted?

Co-STAR is in response to the unique opportunity afforded by STAR to study the effects of tamoxifen and raloxifene on cognitive aging in women. As a substudy to STAR, Co-STAR will collect data on memory, other cognitive abilities, and mood in STAR participants randomized to either tamoxifen or raloxifene. Co-STAR data will provide unique information about the effects of these drugs on age-associated cognitive decline.

Co-STAR will provide critical information for clinicians and researchers on the effects of tamoxifen and raloxifene on cognitive aging. As physicians increase the frequency of recommending tamoxifen for protection against breast cancer among healthy women, and raloxifene for protection against bone disease, this study is important to allow aging women to make informed choices about the relative benefits and risks of various estrogenic compounds.

### What is known about the action of SERMs on neural tissue and cognitive functioning?

No data has been published on tamoxifen or raloxifene showing that these drugs impair memory. A recent publication from the *Multiple Outcomes of Raloxifene Evaluation* (MORE) study reported that treatment with raloxifene for three years did not affect overall cognitive scores. A Phase II study comparing raloxifene and placebo found no differences in cognition or mood.

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