Position
Women need more information on the potential risks and benefits of taking tamoxifen, raloxifene, and aromatase inhibitors for breast cancer risk reduction. There is no current evidence that these drugs ‘prevent’ breast cancer; some studies suggest that they may reduce the chance that a woman will get breast cancer during a certain period of time. NBCC urges physicians to prescribe chemoprevention drugs cautiously and responsibly.

Introduction
All women are at risk for breast cancer, and there are very few actions a woman can take to reduce her risk of breast cancer. Chemoprevention -- giving drugs to women who do not have breast cancer -- is just one approach to risk reduction that scientists are currently researching. To date, there is no evidence that these drugs 'prevent' breast cancer, although some studies suggest that they may reduce the chance that a woman will get breast cancer during a certain period of time. As with most drugs, chemoprevention drugs have adverse side effects, and it is important that their benefits outweigh their risks.

Most scientists agree that chemoprevention drugs should not be given to every woman in the population because the majority of these women will not get breast cancer. Thus, as depicted in the trials described below, scientists have attempted to define a population of women who are most likely to gain some benefit from these drugs -- women who are at 'high risk' for breast cancer. High risk is defined by researchers at the National Cancer Institute (NCI) and the National Surgical Adjuvant Breast and Bowel Project (NSABP) as a 1.66% or greater chance of getting breast cancer within the next 5 years, which is the risk of an average 60-year-old woman. However, this is an arbitrary cut off point, and the use of this threshold to define 'high risk' is controversial. Most of these women will never get breast cancer; highlighting the importance of a risk/benefit analysis

The risk/benefit analysis for chemoprevention is different from the risk/benefit analysis for breast cancer treatment. Treatment drugs are given to women who already have breast cancer, while chemoprevention drugs are given to healthy women. Chemoprevention drugs will only benefit a small proportion of healthy women because most healthy women will never get breast cancer. Therefore, women must have reliable, quality information on all of the risks and benefits of chemoprevention drugs before deciding whether to take them. Unfortunately, past and current research studies were not designed to answer many important questions regarding the risks and benefits of these drugs.
The Research So Far

Until recently, in this country, clinical trials of breast cancer chemoprevention have focused primarily on two drugs - raloxifene and tamoxifen - that are selective estrogen receptor modulators (SERMs). A SERM is a drug that blocks estrogen from initiating cell division in specific tissues of the body, including breast tissue and certain types of breast cancer. SERMs also mimic estrogen and stimulate other tissues of the body, such as the endometrium (uterus).

The drug tamoxifen has been used for over 30 years as a treatment for women with advanced breast cancer and as a postoperative, adjuvant therapy for women with early stages of breast cancer. When used to treat women who already have breast cancer -- specifically, estrogen receptor (ER)-positive breast cancer -- tamoxifen prolongs some women's lives and reduces the rate of tumor recurrence. Tamoxifen also increases the risk of endometrial cancer, stroke, and venous thromboembolic disease. In women who have ER-positive breast cancer, tamoxifen treatment has been shown to reduce mortality (death rate). This may not be the case for healthy women who use tamoxifen to reduce their risk of getting breast cancer.

In addition to reducing the risk of tumor recurrence in breast cancer patients, tamoxifen also reduces a patient's chance of developing breast cancer in the opposite (contralateral) breast. This finding led researchers to hypothesize that the drug may be able to prevent breast cancer in healthy women at increased risk of developing the disease. In 1992, the NCI and NSABP began enrolling participants in a clinical trial, the Breast Cancer Prevention Trial (BCPT), to examine the hypothesis. This trial was also designed to look at whether taking tamoxifen would reduce the incidence of ischemic heart disease and bone fractures.

Based on the results of the BCPT trial published in 1998, tamoxifen was approved by the Food and Drug Administration (FDA) for reduction of breast cancer risk in women at high risk for the disease. In the study, tamoxifen reduced the 5-year risk of ER-positive breast cancer in a population of high-risk pre and postmenopausal women.

BCPT Study

The BCPT study followed 13,388 high-risk women – 6,707 women were assigned to a placebo arm (control group) and 6,681 women were assigned to the tamoxifen arm. The study was double-blinded, which means that neither the researchers nor the patients knew who was assigned to each treatment. Women were considered to be at high risk for breast cancer if they were 1) 60 years old or older, 2) between the ages of 35 and 59 years old with an elevated 5-year predicted risk of cancer (at least 1.66%), or 3) had a history of lobular carcinoma in situ (LCIS). About three quarters of the trial participants had a 5-year

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predicted breast cancer risk greater than 2.00%. The large majority of participants (97%) in the BCPT were white women.

The 7-year incidence of invasive breast cancer was approximately 4.3% in the placebo group and 2.5% in the tamoxifen group. The results of the BCPT were reported in terms of relative risk -- tamoxifen use resulted in a 42% reduction in the 7-year risk of invasive breast cancer. Although these results are substantial, they obscure the fact that the large majority of women in the study did not get breast cancer, regardless of whether they were given tamoxifen or not. Reported in terms of absolute risk, tamoxifen use 'prevented' clinically detectable breast cancer in only about 2% (4.3 - 2.5) of the women who took tamoxifen. Thus, many healthy women received a drug that benefited only a small percentage of the total study population. This will be the case with any breast cancer preventive drug that is given to a large population of healthy women.

The risk reduction in this trial resulted from a decreased risk of ER-positive breast cancer; there was no reduction in ER-negative breast cancer associated with tamoxifen use. The study also found that tamoxifen increased the risk of endometrial cancer, stroke, pulmonary embolism, and deep-vein thrombosis. In terms of benefits, tamoxifen led to a 32% reduction in hip, radius and spine fractures.

The incidence of endometrial cancer is usually much lower than the incidence of breast cancer in a population of healthy women. Thus, although tamoxifen more than doubled the risk of endometrial cancer in the BCPT, the drug was responsible for only a few cases of endometrial cancer - fewer than the number of breast cancer cases prevented by the drug. Since tamoxifen had several beneficial effects in the BCPT (e.g. reducing the number of breast cancer cases, bone fractures, etc...) and several adverse effects (e.g. increasing the number of endometrial cancer cases, strokes, etc...), it is difficult to determine whether the benefits of the drug outweigh the risks. A risk/benefit analysis of tamoxifen, based on the results of the BCPT, has been published. The main results of the study were:

- Women with a uterus - for all women over 60 and for many women 50-60, the benefits of tamoxifen *do not* outweigh the risks.
- Women without a uterus - for most women over 70 and for many women 60-70 without a uterus, the benefits *do not* outweigh the risks.
- For most women under 50 and for some women 50-60, the study found that the benefits *do* outweigh the risks. This is because, in the BCPT, younger women experienced fewer total adverse effects from tamoxifen.
- In general, the risks of tamoxifen outweighed the benefits for more black women than white women. However, the results for black women are much less reliable than the results for white women because there were so few black women in the BCPT.

These results apply to high-risk women in the general population. Although this risk/benefit analysis provides some useful information, long-term incidence and mortality data must be obtained in order to properly weigh the risks and the benefits of tamoxifen. It is important to

determine how many women die of breast cancer versus how many women die of the adverse effects associated with tamoxifen use. In addition, risk/benefit analysis is not an exact science—the calculation of risks and benefits in the study above were based on uncertain rates of disease in the population.

As part of the study design, the BCPT data were regularly reviewed by an independent Endpoint Review, Safety Monitoring, Advisory Committee (ERSMAC). At a regularly scheduled meeting of ERSMAC, the committee recommended to NSABP that the study be unblinded (treatment assignments revealed) because of the 'clear evidence of a reduction of breast cancer in the tamoxifen group.' In April, 1998, the study was unblinded less than six years after it was initiated; the average follow-up time for participants was about 4 years. At this point, participants in the placebo group were free to begin taking tamoxifen.

When participants of the BCPT began to cross-over from one group to another, researchers were no longer able to isolate the effects of tamoxifen. Thus, the long-term effects of tamoxifen on breast cancer incidence and mortality could not be obtained from the study. Nonetheless, in October, 1998, the Food and Drug Administration approved tamoxifen for the reduction of incidence in breast cancer for high-risk women, but did not approve it for breast cancer prevention.

Tamoxifen versus Raloxifene

In 1999, researchers conducting a study looking at the SERM, raloxifene, for the prevention of osteoporosis, noticed that patients taking raloxifene had a lower risk of breast cancer than the control group.5

This observation led to the Study of Tamoxifen and Raloxifene (STAR) trial, one of the largest breast cancer clinical trials ever conducted.6 The STAR trial led to the 2007 FDA approval of raloxifene for reducing the risk of invasive breast cancer in postmenopausal women with osteoporosis and in postmenopausal women at high risk for invasive breast cancer. This trial, conducted by the NCI and NSABP, showed that raloxifene works as well as tamoxifen in reducing breast cancer risk for postmenopausal high-risk women without some of the serious side effects (uterine cancers, blood clots) known to occur with tamoxifen. The National Breast Cancer Coalition (NBCC) had serious reservations, which are detailed below, about aspects of the STAR trial's design and conduct.

The STAR Trial Had Shortcomings

Due to the promising results of the previous clinical trials on tamoxifen and raloxifene,1,2,5 the NCI and NSABP designed the STAR trial to compare tamoxifen and raloxifene. The STAR trial followed 19,747 (analysis based on 19,471 with complete information) healthy postmenopausal women (mean age 58.5 years) for only five years. It did not include a placebo group, and it did not enroll premenopausal women. Tamoxifen can have life-
threatening, adverse effects, especially in older women - the same population enrolled in the STAR trial. In addition, we did not know enough about how raloxifene affects the population of women eligible for the STAR trial because raloxifene had never been tested in high-risk women. It was possible that both raloxifene and tamoxifen would not decrease breast cancer risk enough for a significantly large number of women to balance the drugs' adverse effects, but this was to be determined throughout the study.

Nonetheless, the study continued to completion, with 9,726 women assigned to receive tamoxifen daily for 5 years, and 9,745 women assigned to receive raloxifene. After 5 years of follow-up, there were 163 cases of invasive breast cancer in women assigned to tamoxifen and 168 in those assigned to raloxifene. There were fewer cases of noninvasive breast cancer in the tamoxifen group (57 cases) than in the raloxifene group (80 cases). There were more cases of uterine cancer (36 versus 23) and thromboembolic events – including deep vein thromboses and pulmonary embolisms (141 versus 100) in the tamoxifen group compared to raloxifene. The risk of other cancers, bone fractures, heart disease and stroke was similar for both drugs: 53 and 51 women had strokes in the tamoxifen and raloxifene group, respectively. Based on these results, researchers and the FDA concluded that raloxifene is just as effective as tamoxifen in reducing breast cancer risk, but without some of the serious side effects known to occur with tamoxifen.

However, in order to make decisions regarding chemoprevention therapy, women need to know the long-term effects and have an accurate risk/benefit profile of these drugs. Such a profile does not yet exist for tamoxifen and raloxifene, and will never exist unless a study is designed with adequate follow-up time, appropriate outcome measurements, and an appropriate study population.

Are Aromatase Inhibitors Potential Chemoprevention Drugs As Well?
Most recently, the focus has been on the potential of aromatase inhibitors (AIs) to prevent breast cancer in postmenopausal women. AIs work by blocking the enzyme aromatase, which turns the hormone androgen into small amounts of estrogen in the body. By blocking the action of aromatase, AIs stop the production of estrogen in postmenopausal women.

In June 2011 at the 47th Annual Meeting of the American Society of Clinical Oncology (ASCO), researchers presented study results on an aromatase inhibitor (exemestane) for prevention of breast cancer in postmenopausal women. The study found a reduction in invasive breast cancer for high risk women taking exemestane compared to women taking placebo, after merely three years.

A total of 4,560 women with at least one risk factor (over 60, Gail score over 1.66, prior hyperplasia, or DCIS with mastectomy) were randomized to receive exemestane or placebo in a double-blind trial. After a median 35 months of follow-up, 43 invasive breast cancers were diagnosed, 11 in the exemestane group and 32 in the placebo group. There were also 10 DCIS diagnoses in the exemestane group, compared to 27 in the placebo group. The

majority of cancers in both groups were ER-positive. The annual incidence for developing breast cancer was less than 1% in both groups, but exemestane reduced the annual incidence from .55% to .19%.

Symptoms and adverse events occurred in 88% of the women in the exemestane group and 85% of the women in the placebo group. Arthritis and hot flashes were more common in the exemestane group. One breast cancer death occurred in the exemestane group compared to 0 in the placebo group.

The study duration was too short to know what long term risks are associated with exemestane, and whether the reduction in breast cancer holds up over time. Exemestane has not yet been approved by the FDA for reduction of breast cancer risk.

Conclusion
Decisions made by healthy women regarding chemoprevention therapy are significantly different than decisions made by breast cancer patients regarding treatment. Women need more information about the risks and benefits of tamoxifen, raloxifene, and exemestane. NBCC supports more research into the long-term effects of chemoprevention drugs. The following questions about tamoxifen, raloxifene, and exemestane use in women who do not have breast cancer remain unanswered:

- Do these drugs prevent the initiation of breast cancer?
- Do these drugs effect the development of lethal, aggressive breast cancers?
- Do these drugs impact future development of metastasis?
- Can these drugs reduce breast cancer risk over the long-term (> 5 years)?
- Can these drugs reduce mortality and extend women's lives?
- Can these drugs reduce breast cancer risk and mortality in all sub-groups of high-risk women (e.g. non-white women, BRCA1/2 mutation carriers, etc...)?
- What is the optimal length of time for a woman to take these drugs?
- When is the optimal point in life when a woman should begin to take the drugs?
- What are the long-term incidences of the adverse effects of each drug, and what are the mortality rates associated with these adverse effects?
- If a woman uses tamoxifen or exemestane for risk reduction but still develops breast cancer, will the drugs be less effective as treatments?

Future studies must provide women with answers to all of these questions and should:

- have a follow-up period sufficient to determine disease-specific mortality rates and all cause mortality rates.
- assess the optimal length of time for a woman to remain on the drugs, and the optimal point in life when a woman should begin to take them.
- enroll adequate numbers of both white and non-white women.
- include a placebo arm so that the absolute effect of all three drugs on long-term incidence and mortality can be determined. A placebo arm is also necessary to determine the effect of these drugs on non-white women, as previous trials have not provided this information.
- have an informed consent that is very carefully designed and include information about the controversy over the trial.
enroll women that have the same 5-year predicted risk of breast cancer as the women who enrolled in the BCPT.

The makers of tamoxifen and raloxifene, and many in the medical community, are marketing both of these drugs to all women over 60 (as well as all other women who have a 1.66% risk of getting breast cancer in the next five years) for breast cancer risk reduction. NBCC believes that this enthusiastic endorsement of tamoxifen and raloxifene is irresponsible.

The Coalition urges physicians to prescribe tamoxifen and raloxifene responsibly. Physicians should fully understand the potential risks and benefits of tamoxifen before prescribing it, and they should make sure that women understand the risks and benefits as well.

More needs to be known about how to cure, treat and ultimately prevent mortality from breast cancer - and this needs to be learned from clinical trials. These trials must be well designed and well conducted, and advocates must be involved in the trial design, accrual and implementation.