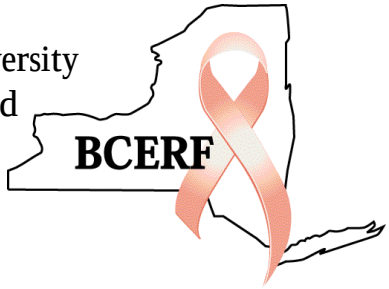
The Ribbon

A Newsletter of the Cornell University Program on Breast Cancer and Environmental Risk Factors in New York State (BCERF)



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The National Cancer Institute's Study of Tamoxifen and Raloxifene (STAR)

An Interview with Dr. Worta McCaskill-Stevens, Program Director for STAR, Division of Cancer Prevention, National Cancer Institute

What is your role at NCI (the National Cancer Institute) and in STAR?

I am a medical oncologist by training. I came to NCI having been Co-Director of the Breast Care and Research Center at Indiana University, so I came with breast cancer treatment experience. Another project of mine was investigating clinical trial participation among African Americans. I am the Program Director for the STAR trial. I do administrative work on the trial and provide clinical input into the National Surgical Adjuvant Breast and Bowel Project (NSABP) and the STAR Trial.

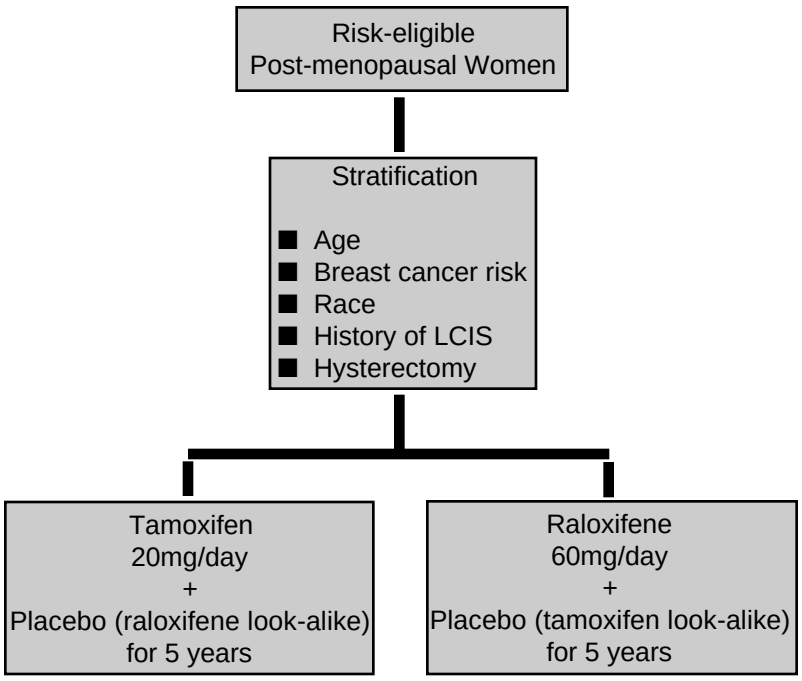
What are your hopes for the ultimate benefits to be gained by women as a result of this study, which of course, is a huge effort?

You are correct, it is a huge effort. We don't have operative biomarkers — although we are working on them — to make our clinical trials shorter. STAR is only the second largest US breast cancer prevention trial. It's an exciting area in that we are doing what the NCI/NIH does best: providing leadership in combating morbidity and mortality from disease through research, in this case, on breast cancer. Not only are we investigating the objectives of the trial, but because we are doing prevention and not treatment, we are also providing the women with many levels of information about breast cancer risk. There is a lot of education we can do about breast cancer risk and prevention, and that is not just for the lay public or the women, but also for health care providers.

When do you see us having a more complete understanding of the role of these types of drugs?

I think it's going to be a while because, as you know, this is a family of drugs — selective estrogen receptor modulators. Tamoxifen is the one about which we know the most. There are other drugs that are being developed at the same time, which is very characteristic of science – it's not a static environment. Obviously because tamoxifen has traversed from treatment and moved into prevention, we do know a lot about it. We know more about this drug than we do for most of our oncological treatment drugs. What's new, and all the questions that we don't have answered, are the long-term benefits of using a preventative agent. Ultimately we would love to have the "wonder drug" that would reduce the risk of developing breast cancer, with less or no risks. We would also like to be able to provide all the answers to questions such as "how long do the benefits last?" The only way that we are going to know those answers is through the investigation.

STAR Schema



In the first year, STAR enrolled 6,139 women, from the over 47,000 who went through the individualized, no-obligation risk assessment. Of the over 47,000, over 29,000 of these women were eligible based on their risk. These eligible women need to then make their choice based on their own understanding of their risk and an understanding of the two drugs' known risks and benefits. Can you describe the guidance they receive in doing so?

Each woman will receive an individualized risk assessment form which, in addition to providing a predicted breast cancer risk, will compare that risk to a woman who is of the same age and race, but without the increased risk factors of developing breast cancer. For each of the events (benefits or risks), women are provided an analysis, of the expected number of cases if 10,000 women were not treated to the expected cases that may be prevented or caused if all women were treated with tamoxifen. NSABP will make sure the women do not have any of the conditions which would render them ineligible from their medical history. Women come with a varying amount of information. Some, after receiving the information we make available to them, go to their family members, or other women, to their primary care physicians – to discuss the idea of their participation in the trial. In considering those roles, there are efforts from various angles to try to educate primary care physicians about explaining risks and benefits of chemo-prevention. Oncologists have been doing this for quite some time. This has not been the case with primary care physicians. There was a joint effort by Zeneca, various oncologists, and NCI as well, called Discovery International, which went to various sites throughout the country to teach primary care physicians how to counsel about risks and benefits. The second step of the Discovery International effort is going to be geared toward gynecologists. This is an important point because one of the issues that women often have to deal with is the question of hormone replacement therapy. These women seek the advice of their gynecologists.

Can these efforts reach all participating sites?

They haven't reached every site, but clearly in all participating sites in the STAR trial there are massive education and outreach efforts. Concomitant with those efforts are the probably more frequent efforts made by the membership of the NSABP – there is mandatory attendance of all principal investigators and coordinators at the STAR sites to the large cooperative group meetings. This last meeting in fact had workshops addressing many of these issues: the hormone replacement issue, minority recruitment issues, gynecological issues, etc.

At what point does a woman considering the trial need to come into contact with a professional?

At some point, she has to sit down with a health practitioner and go through everything, but she can initially fill out the forms by herself. As for the final decision-making process, this cannot be done without consulting with a health practitioner.

The lowest assessed risk which would make a woman eligible for STAR is equivalent to that of an average 60-year-old woman, or a 1.7% risk of breast cancer in five years (17 in 1,000). Some would argue that this is not "high risk." Do you feel that eligible women in this range of risk are self-selecting themselves out?

In the first Breast Cancer Prevention Trial (BCPT), 60 was the average age at which women developed breast cancer. Age, as you know, is the primary risk factor for breast cancer. If you are 60 years old, you are

approaching your peak. Even though it continues to increase, many of those women don't live, and secondly, they are often confronted with things that would prohibit them from considering breast cancer prevention at that point in time. So 60 is important, and it is high risk.

Two things about the women who participated in BCPT: 75% of them had a five-year predicted risk of greater than 2.0. In addition to that, the benefits of breast cancer prevention in BCPT traversed all age groups and all five-year risk groups as well. So as for the impact, even for the 25% of women with risk between 1.7 and 2.0, there was still a benefit for them in terms of reducing their risk of developing breast cancer.

The eligibility criteria for the two trials is different. For BCPT you could be 60 and that would render you eligible, but that is not the case for STAR. For STAR, age alone does not render you eligible, your assessed risk has to be greater than 1.7.

As for the breakdown of the percent of women enrolled in STAR to date by five-year breast cancer risk, we have that information (see chart).

Five-year Breast Cancer Risk	Percent of Women in STAR to date
1.7 - 2.0	10.3 percent
2.0 - 2.9	30.3 percent
3.0 - 4.9	32.2 percent
Greater than 5.0	27.2 percent

In the African-American community, the incidence of breast cancer is lower but the mortality is higher, and the population has not historically had access to the clinical trials. African American women come in to STAR knowing that they are more likely to die of breast cancer, which is true, but risk assessment is based on incidence, so the eligibility threshold is higher. These women have said they are ready to learn about their breast cancer risk and learn about clinical trials. They get to a level of trust, and then often find out they are not eligible. That's of course good news, except that for a community that has not been engaged in this process historically, it can be disappointing for them after they feel they had taken the steps to become proactive. This is an interesting challenge for us to work within. But we are providing women with information, and encouraging women to participate in better health care – and breast health care. In fact, this is not a static situation because age is a strong risk factor: the same woman may become eligible in a year when she's older. Her ultimate choice will be an informed choice.

You have said that "the benefits and risks of tamoxifen are the same in African-American and white women. Women of all races can feel comfortable about considering STAR if they are at increased risk of breast cancer." Indeed African-American women, who have historically been underrepresented in cancer trials, are being actively recruited for STAR. Can you comment on this?

Yes, our analysis showed that among 1200 women, tamoxifen is as effective in African-American women as it is in white women in reducing the risk of contralateral breast cancer. We also found out that the rates of the two main side effects, endometrial cancer and blood clots, were no greater in African-American women.

In terms of recruitment, what we learned from BCPT was that we need to go into the communities. Toward the end of recruitment of that trial, funding was put forward to five sites that were areas with significant minority populations. We hired an outreach coordinator to go in and provide information about the trial. This proved for that particular trial to be the most successful route. Of course, 3% (total minority participants in the trial) was not where we would want to be, so that approach has been massively expanded for the STAR trial. It's a great learning process for any investigators who are out there. You must have people who are out there in the community who understand the various cultures and the various languages. We now have the trial components available in Spanish. There are now ten, and going to be 14 sites to be targeted for minority populations. There are other infrastructures in place at NCI, and we are learning how to do it better. We have a minority-based community clinical oncology program; eight are now funded to provide clinical trials to areas that have 40% minorities in their areas.

We are working with all minority groups. The Philadelphia chapter of the National Medical Association, which is the African-American equivalent to the American Medical Association, is now a STAR site. I am also working among the Latino community, for example in New Mexico and in Puerto Rico. I am working among Native Americans to try to facilitate tribal approval of the STAR trial in light of Native

STAR Trial

Possible Benefits and Risks – Sample Case*

Severity Of Event	Type of Event	Expected Cases in Five Years Among 10,000 Women Not Participating in STAR	Potential Effect Among 10,000 Women If They All Participate in STAR and Are Treated for Five Years
Life Threatening Events			*Potential Benefits*
	Invasive Breast Cancer	1,375 cases expected	648 cases may be prevented
	Hip Fracture	116 cases expected	52 cases may be prevented
			Potential Risks
	Uterine Cancer	70 cases expected	206 more cases may be caused
	Stroke	72 cases expected	42 more cases may be caused
	Blood Clot in Lung	20 cases expected	39 more cases may be caused
Other Severe Events			*Potential Benefits*
	In Situ Breast Cancer	426 cases expected	211 of these cases may be prevented
			Potential Risks
	Blood Clot in Large Vein	47 cases expected	28 more cases may be caused
Other Events	*Potential Benefits*: Treatment may reduce the risk of a certain type of wrist fracture called Colles' fracture by about 39%, and also reduce the risk from fractures of the spine by about 26%.		
	Potential Risk: Treatment may increase the occurrence of cataracts by about 14%.		

*caucasian, age 62

Americans having had their history of atrocities with unethical medical trials. These are issues we need to be very sensitive about; it's all a learning process.

These are drugs that cannot be used on a long-term basis. Women with breast cancer who use tamoxifen for more than five years have an increased likelihood of recurrence. How should we think of this in terms of preventative effects? Perhaps when we are talking about a breast cancer "prevented" by either drug we are more realistically talking about a delay?

We don't know. When a woman has estrogen receptor-positive breast cancer in one breast, it does not mean that were she to develop a second primary tumor in the other breast, it would also be ER-positive. Our decision to intervene in the prevention arena for five years is based on treatment data. We have clear-cut data that there is not a treatment benefit beyond five years — however, it does appear that there is a prolonged benefit from taking tamoxifen for five years that extends out to ten years. We don't have confirmation of that yet for women taking tamoxifen for prevention for five years. There are studies that are continuing in the prevention arena, such as the European studies.

We don't know all the molecular answers to those questions. One of the criticisms of BCPT was that perhaps we were treating early breast cancer that already existed. Clearly one of the compelling elements of the BCPT trial was the 86% reduction in atypical hyperplasia, which is a pre-malignant condition. But we don't know all the answers about the physiology and pathology from a healthy breast to a diseased one.

Cancer takes a long time to develop. The Breast Cancer Prevention Trial was stopped early because the researchers felt that tamoxifen should not be withheld from the placebo group. Those placebo group members are being actively recruited for STAR. STAR does not have a placebo group. How will we be able to do long-term follow-up, to determine how the incidence of breast cancer in women who have taken tamoxifen or raloxifene compares to women who have taken neither?

1100 women from BCPT placebo group have gone on to STAR and another 600 have gone on to take tamoxifen, but we are left still with several thousand women who can be followed from the placebo arm of BCPT. As for the logic behind not having a placebo group in STAR, in my mind this is very clear. You cannot have a placebo group when you have a drug which leads to a 49% reduction in breast cancer risk in a trial of 13,000 women. It's not ethical.

Can you comment further on the issue of side effects?

Tamoxifen and raloxifene have side effects. It may help to put things into perspective to consider that

we are now getting more and more data that show the hormone replacement drugs are not the wonder drugs that everyone thought they were. Hormone replacement therapy has the same blood clotting risk, but unfortunately women have not been informed. If you ask women what they were told about hormone replacement therapy, many of them would tell you that they were not told much. The informed consent about the profile of these drugs was very poor. Women are becoming more savvy and coming to their decision-making with better information about their personal health. We know that there are women whose health situation is not going to permit them to address their high risk of breast cancer through the trial or tamoxifen. But there are women who are high risk and healthy for whom it may be appropriate.

Commentary on STAR

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The "Study of Tamoxifen and Raloxifene (STAR) in Postmenopausal Women at Increased Risk for Invasive Breast Cancer" (P-2) is a clinical trial currently being conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP). This large, multi-center trial is the first North American trial to compare two different pharmaceuticals, tamoxifen and raloxifene, as preventive agents for breast cancer. Tamoxifen, in the NSABP's Breast Cancer Prevention Trial (P-1), demonstrated a decrease in the incidence of breast cancer by about 50% in patients at increased risk for developing the disease (Fisher et al., 1998). An early clinical trial of raloxifene to evaluate its efficacy in preventing osteoporosis, the Multiple Outcomes of Raloxifene Evaluation (MORE), suggested that raloxifene may also decrease the incidence of breast cancer (Cummings et al., 1999). The STAR trial compares the effectiveness of these two drugs at decreasing the incidence of breast cancer as well as compares their associated side effects.

As expected from the NSABP, the STAR trial is well designed. It is a large, prospective, double-blinded, randomized trial involving approximately 23,000 women that will provide important information concerning raloxifene. Although the study design is well planned, there are some areas of concern. The STAR trial will not provide data on breast cancer associated mortality of the patients in the study (Osborne, 1999). Initially, the P-1 trial had patients in a placebo control group; but these patients were allowed to cross to tamoxifen when the results were published (Fisher et al., 1998). Because of the cross over there will be no control group to compare breast cancer mortality data. It will be difficult to establish a difference in mortality of patients taking tamoxifen, raloxifene or no drug. The use of historical controls is not appropriate as they may have different eligibility parameters compared to the STAR trial making it difficult to extrapolate data to patients on the STAR trial. Moreover, like most clinical trials, this data will not be available for many years (Osborne, 1999).

One of the criticisms of the tamoxifen prevention trial is whether patients are actually receiving treatment for an early, undetected breast cancer. It is postulated that some patients in the P-1 had early breast cancers that were not detected on mammography or physical exam. This means that some of the patients who developed breast cancer may not represent those at increased risk and did not have the disease. For the patients on tamoxifen, the drug would actually treat the cancer, potentially delaying its manifestation. However, for the patients on placebo, these cancers would continue to grow until detectable. This may account for the increased incidence of breast cancer in the placebo group as opposed to the tamoxifen group. The placebo data may have merely represented patients with early undetectable cancer that did not receive treatment. This may also be true for the STAR trial; tamoxifen is an agent that is proven to treat cancer, while raloxifene has never been tested or proven as such. However, intuitively it would seem likely that raloxifene will be equally effective as tamoxifen.

Additionally, it has consistently been a challenge to incorporate minority populations into research trials within the United States, as seen in the P-1 trial. The efforts put forth to incorporate minorities into the NSABP treatment and prevention trials are to be applauded. The directors of the STAR trial have gone out into the community and attempted to bring the

prevention trial to the minority populations. The challenge is not only reaching the different populations, but also assisting them in understanding the benefit-risk ratio in relation to them. In the past the comparable side effects of tamoxifen in other settings made it reasonable to apply the same criteria for tamoxifen use in all ethnic groups. Whether or not this will hold true with raloxifene is unknown. The experience with raloxifene is still rather limited in comparison (Cheblowski, et al., 1999).

Summary. The STAR trial will help to answer an important question related to breast cancer prevention. However, this trial is not without limitations. There is little information related to breast cancer mortality in this group of high-risk women. The use of a preventive agent may decrease the amount of breast cancer, however the number of patients that die from breast cancer may not be significantly different. Because the biology of breast cancer is still not completely understood, it is unknown if this prevention trial is actually treating occult breast cancers not yet detectable. Again, the hurdle with incorporating minorities in prevention clinical trials remains. Minorities are consistently underrepresented in clinical trials and incorporating them poses a challenge for the directors of the STAR trial. In addition, this trial specifically targets postmenopausal women who do not have breast cancer, but are at increased risk for developing it. The use of raloxifene to treat patients with breast cancer or a history of breast cancer is unproven. The information gained from this trial should not be interpreted and used to treat patients with breast cancer. Furthermore, the use of raloxifene as a preventive agent for breast cancer is unproven. Patients should not receive raloxifene as a preventive agent for breast cancer unless they are on a clinical trial (Cheblowski, et al., 1999).

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Research Commentary

Decision Analysis of Tamoxifen for the Prevention of Invasive Breast Cancer

Grann VR, Sundararajan V, Jacobson JS, Whang W, Heitjan DF, Antman KH, Neugut AI. (Herbert Irving Comprehensive Cancer Center, Department of Medicine, College of Physicians and Surgeons, Columbia University, New York) Cancer Journal of Scientific American 6(3):169-78, 2000.

Seema A. Khan MD, Associate Professor of Surgery, Northwestern Memorial Hospital

Women who are at increased risk for developing breast cancer and have completed child bearing now have the option of taking tamoxifen for five years in order to decrease their breast cancer risk. However, for many women this is a difficult decision to make, since tamoxifen does have some adverse effects, and the risk/benefit analysis is not straightforward. In an attempt to clarify some of these issues, researchers from Columbia University have developed a decision analysis model to aid physicians who are counseling women at increased risk of breast cancer regarding preventive therapy with tamoxifen.

The researchers have used a mathematical model to predict overall benefit in terms of quality adjusted survival for three different age groups of women: 35-49, 50-59, and over 60 years. They have made allowances for the side effects of tamoxifen, and the

cost of tamoxifen therapy, as well as the cost of treatment of any complications. Quality of life estimates for these calculations were derived from a recent study where women were asked how much added life-time they were willing to trade for time spent in three states: taking chemopreventive medication, diagnosis of and treatment for invasive breast cancer, and time living with metastatic breast cancer.

The model predicted that the greatest preventive benefit of tamoxifen would be seen in women who start treatment early in life (the 35-49 year age group). The actual time gained in this age group was surprisingly small (69 days), but this number needs to be interpreted with the understanding that in models such as these, the benefit of a particular treatment is actually being averaged across a large number of people who are being subjected to the treatment. When we consider individuals, the benefit will be large for a small minority (those who would have developed breast cancer, but did not because of preventive therapy), and zero for the rest (women who would never have developed breast cancer, with or without tamoxifen, and those who develop breast cancer despite tamoxifen).

In fact, most women will not benefit from preventive tamoxifen, because most women would not have developed breast cancer in their lifetimes even without tamoxifen. For example, the threshold for recommending preventive treatment with tamoxifen is a breast cancer risk of about 2% over five years. An 80-year-old woman belonging to this risk group, might have a lifetime chance of developing breast cancer of about 5%, and 95 out of 100 women in this age group, with this risk level, will die of other causes. On the other hand, a 40-year-old tamoxifen eligible woman with a five-year breast cancer risk of 2%, will have a lifetime risk of 25%. It is easy to see from these figures that a woman who is at high enough risk to be eligible for tamoxifen at a young age actually has a much higher lifetime risk for breast cancer than an older woman, even though their short term risk might be similar. In risk benefit calculations, the benefit of the treatment is usually found to be proportional to the risk of disease, and the model used in this study again validates this general principle, showing us that women at higher lifetime risk derive greater benefit.

The second part of the calculation of the risks and benefits of tamoxifen has to do with the adverse effects that might be experienced by women taking tamoxifen. Since the serious side effects of tamoxifen (uterine cancer, stroke, and clots in the deep veins of the legs which can travel to the lungs) become more common with age, older women who take tamoxifen have a higher chance of suffering serious side effects from tamoxifen, but have a smaller benefit as we have seen above. Thus when the higher risks of therapy are balanced against the smaller benefits in older women, the overall gain is small. For young women on the other hand, the benefits are larger, the risks are smaller (women in the tamoxifen arm of the BCPT did not suffer the adverse events associated with tamoxifen use at significantly higher frequency than women in the placebo arm of the trial) and the overall balance is in favor of using tamoxifen for breast cancer prevention.

The authors then looked at the cost of using tamoxifen for breast cancer prevention, and the costs of treating serious side effects, and estimated the cost per life year saved by tamoxifen use. Again, because the benefit is larger in younger women, and the likelihood of side effects is smaller, the cost per life year saved was smaller for younger women.

The results of the model were varied using different estimates of the duration of the beneficial effect of tamoxifen in terms of breast cancer protection. The available data from several different analyses suggest that this protective benefit outlasts the actual duration of tamoxifen use by at least 5 to 10 years, and perhaps longer. The authors redid the calculations assuming a 5, 10, and 15 year duration of tamoxifen benefit after stopping therapy. They found, naturally, that increment in longevity was greater, and the cost per year of life saved smaller, in all age groups as one assumes increasing duration of benefit. Again, the actual numbers they derived are used only for purposes of illustration and do not have any real meaning if they are applied to individuals. Assuming a 15 year duration of benefit after stopping tamoxifen, the quality adjusted survival (i.e. accounting both for the increased lifespan of women benefiting from tamoxifen and the effect of adverse side effects on this gain) is illustrated as follows:

> *Assuming a 15 year duration of benefit after stopping tamoxifen, the quality adjusted survival (i.e. accounting both for the increased lifespan of women benefiting from tamoxifen and the effect of adverse side effects on this gain) is 105 days for a woman starting tamoxifen at age 35, 66 days if starting at age 50, and 45 days if starting at age 60. The mean cost per quality adjusted life year saved is about $19,000, 41,000 and*

67,000 respectively for each of these groups. These costs are comparable to other life-extending interventions, such as mammography, but the cost benefit ratio is substantially less favorable for older women.

The advice that women who are considering tamoxifen can take away from this cost benefit analysis — which echoes the conclusions drawn from other analyses — is that women over the age of 60 or 65 have in general a lower expectation of benefit, at higher cost, from the use of tamoxifen for the prevention of breast cancer. In this age group it may still be advisable for women to take tamoxifen if they are at substantially increased risk of developing breast cancer, but the present threshold of a five year risk of 2% may not be sufficient to warrant the quality of life and financial cost of tamoxifen.

Activist Perspective

The Dark Side of the STAR Trial

by Andrea R. Martin
Founder and Executive Director
THE BREAST CANCER FUND

The promise is dazzling: not one but two pills to prevent breast cancer. Which one does a better job? That's the spin from the National Cancer Institute (NCI) about their multi-million dollar STAR trial (Study of Tamoxifen and Raloxifene) for breast cancer prevention. The goal: enroll 22,000 healthy "high risk" women, half of whom will take tamoxifen for five years, the other half will take raloxifene for the same time period.

During the first 18 months since the study was announced, only 6,139 women have signed up. So the NCI is revving up recruitment, particularly among African American women and other women of color, using scare tactics that distort the risk/benefit ratio of taking either of these drugs. The reality is that every woman in the trial is being exposed to drugs with potentially life-threatening side effects.

Therein lies the dark side of the STAR trial, the failure to ask the question: which drug does a better job than a placebo (i.e. a dummy pill which is like taking no drug at all)? The absence of a placebo group in the STAR trial is not just a design flaw; it is a lapse in ethics and a callous disregard for women's health. It is also an unconscionable misuse of public funds.

The Breast Cancer Fund has been concerned about STAR since its inception, just months after the premature termination of the Breast Cancer Prevention Trial (BCPT), also known as the tamoxifen trial. Women in the BCPT took either tamoxifen or a placebo to see if tamoxifen could prevent breast cancer in healthy women at increased risk for the disease. Dr. Richard Klausner, Director of NCI, ended the trial and declared that answer "an unequivocal yes," heralding results that showed there were "45% fewer cases of invasive breast cancer in women who took tamoxifen compared to women who took a placebo."

The tamoxifen trial was halted prematurely, 14 months before its scheduled conclusion, to allow women in the placebo group the option of taking tamoxifen. Because the BCPT failed to recruit enough women (the study design called for 16,000, but only 13,388 were recruited) and was stopped too soon, it did not show a difference in mortality, that is, whether taking tamoxifen actually saved lives. Nor did the brief trial determine long-term risks versus benefits, or the optimal length of time a "high risk" well woman should remain on tamoxifen.

Scientists from Britain and Milan criticized the NCI findings and decision to halt the BCPT early, citing their own large, longer-term studies that failed to show that tamoxifen prevented breast cancer in healthy women. The U.S. Food and Drug Administration also disagreed with NCI and refused to allow Zeneca (now AstraZeneca), the manufacturer of tamoxifen, to use the term prevention in advertising the drug. Nevertheless, many media reports still refer to tamoxifen as a preventive drug.

The Breast Cancer Fund, The National Breast Cancer Coalition and other leading breast cancer and women's health organizations are strongly opposed to the STAR trial not only because of its lack of ethics in failing to have a placebo arm, but also because its predecessor

trial (BCPT) left too many unresolved issues. Most importantly, during the BCPT approximately 96% of the women taking a placebo did not get breast cancer and 98% of the women taking tamoxifen did not get breast cancer. This means there was only a 2% absolute reduction in risk, which leads to the second major issue with STAR: whether tamoxifen's small reduction in the absolute risk of breast cancer outweighs the risks it poses to healthy women. The most serious of these risks include uterine cancer, blood clots in the legs and lungs, and strokes.

The third unresolved issue of STAR is the definition of "high risk." Women at greatest risk for breast cancer are those believed to have inherited defects in either of the two breast cancer susceptibility genes. However, experts agree that less than 10% of all women diagnosed with breast cancer carry these defects, and very few women have ever been tested for these genes. The reality is that the vast majority of women with breast cancer have no family history of the disease. Yet, NCI now offers a computer "risk disk" to women interested in taking tamoxifen even though there are fundamental questions about the criteria, including family history, used for determining an individual's risk. Using NCI's criteria would classify 29 million American women at increased risk of getting breast cancer, creating a $6 billion market for AstraZeneca.

The fourth serious issue with STAR is its zealous recruitment of ethnic women despite the fact that only 3% of the BCPT participants were African American. Again, undaunted by the inadequate information provided by its first tamoxifen trial, the STAR trial is targeting African American, Native American and other under-represented women, suggesting that it provides a long-awaited opportunity for women of color to take part in clinical trials. Is this truly an effort about women and breast cancer prevention, or is it about amassing numbers to satisfy research statistics and to market drugs? Once again, NCI is underestimating just how savvy many women have become about issues related to their health, perhaps as evidenced by the slow accrual of STARlets.

Despite these major unresolved issues about tamoxifen, NCI has hitched their wagon to STAR, hyping it as "the largest breast cancer prevention study in North America." It might also be called the largest wholesale exploitation of healthy women since DES and the Dalkon Shield. Without a placebo group, STAR will expose 22,000 women to one of two drugs with potentially life-threatening side effects.

The most serious risks of tamoxifen, outlined above, are most common in women over 50, the women at greatest risk for breast cancer and therefore most likely to take the drug as a preventive measure. Raloxifene, manufactured by Eli Lilly and marketed as Evista, is another story. Evista is a synthetic hormone with both estrogenic and anti-estrogenic effects, advertised as "a new way to prevent osteoporosis" (while admitting that "its effect on fractures is not yet known") and reduce the levels of LDL (the "bad" cholesterol).

The reported risks of Evista are similar to tamoxifen's risk but, according to a professor of environmental medicine at the University of Illinois School of Public Health, one unreported risk – ovarian cancer – could prove even more deadly. Writing in the *Chicago Tribune* (April 19, 1998), Dr. Samuel Epstein says: "Lilly's pre-market clearance study clearly shows that Evista induces ovarian cancer in both mice and rats...at dosages well below the recommended therapeutic level." While effects in rodents are not proof of human risk, there is strong scientific consensus that carcinogenic effects in two rodent species constitutes significant evidence of human risk.

Eli Lilly also claims that Evista poses no risks of breast and uterine cancers. However, the pre-market trials of Evista lasted less than four years, too short a time to measure such risks. Epstein called Lilly's suppression of its own evidence about ovarian cancer risk "reckless and threatening to women's health and life." He also termed the FDA's marketing approval of the drug without the ovarian cancer warning "equally reckless." The Breast Cancer Fund agrees.

The STAR trial could have been used to address many of the unanswered questions from the BCPT tamoxifen study. It could have tested each drug against a placebo to properly evaluate the risk/benefit ratio compared to nothing or to a vegetarian diet or to a diet containing soy products or to other factors. But instead of advancing research in the direction of breast cancer prevention, STAR is exposing healthy women to toxic drugs in a way that will ultimately provide no new information.

This trial, which gives a whole new meaning to "star quality," reminds us of one breast cancer activist's summary of the tamoxifen trial: "Bad drug. Bad science. Bad news for women."

"We Need to Know"

Ad Hoc Discussion Group

"Learning Together"

The BCERF Ad Hoc Discussion Group meeting on September 28 was held in the Faculty Commons in Martha Van Rennselaer Hall on the Cornell campus in Ithaca. The meeting drew over 30 people for updates and discussion on breast cancer-related services and activism in the Tompkins County area, and related research on the Cornell campus. It was the first Ad Hoc Discussion group meeting facilitated by BCERF's new director, Rod Dietert.

Rod provided the group with the Director's update on BCERF activity. He highlighted the following activities and events.

- Three Critical Evaluations were available for public comment: Alachlor, Phosmet, and Mancozeb.
- The five BCERF Education Tool Kit modules have entered the field testing phase; 28 sites around the state are participating.
- *Shape* magazine had an article highlighting BCERF's '4 E's' for breast cancer risk reduction concept (Eating, Exposure, Exercise, and Exams).

Rod told the group that he is active in spearheading a faculty appointment in environment and cancer: a high priority of his will be to have researchers "on the ground" to pursue timely research opportunities. He also mentioned that he has submitted a request for supplemental funding, for BCERF to pursue focused projects in new areas of logical expansion: non-pesticide chemicals and breast cancer risk, and childhood cancers. Rod welcomes input into the five-year plan that is currently being prepared.

The Ithaca Breast Cancer Alliance

Andi Gladstone and Bob Riter, Director and Associate Director of the Ithaca Breast Cancer Alliance, overviewed the history and current direction of their support, education and advocacy group. Andi gave an eloquent "thank you" to BCERF for its role in contributing to IBCA's educational program. She provided some historical information on the group, including early efforts to move toward a statewide network of breast cancer organizations. This eventually came about through the Albany-based New York State Breast Cancer Network, of which IBCA is an active participant. Andi remarked that this network is "going to be a powerful voice in the coming years," and outlined the major legislative issues that they are prioritizing. These issues include: good cancer mapping; improvements on the Pesticide Sales and Use Registry; placing more survivors on the Health Science Research Board, and; developing a state funding stream for services. Bob Riter, new to his position at IBCA and formerly a faculty member at Ithaca College, introduced himself, sharing his personal background of being a male breast cancer survivor. Welcome, Bob!

Comparative Cancer Program at Cornell University

Dr. Rodney Page, Director of the Comparative Cancer Program at Cornell, described the mission and priorities of this new undertaking at Cornell. He described to the group how the "10,000 years of shared intimacy" between people and their companion animals need to be drawn upon in answering cancer research questions. For example, many important known facts about environment and cancer in animals may enable the enhancement of cancer surveillance. The group was eager to discuss possibilities for improvement in both human and animal cancer surveillance, and the increase in knowledge about risk factors that may result. He pointed to the fact that breast cancer develops even more frequently in dogs than in women, and tends to behave in a similar way. This paves the way for a wealth of transferable knowledge. Dr. Page included BCERF as a major strength in its planned collaborative outreach component. For more information see *The Ribbon*, Volume 5, Number 2, Spring 2000 or contact Dr. Page at (607) 253-4368 or rlp24@cornell.edu

Phytochemicals

Dr. Ruihai Liu, of the Department of Food Science, described his research analyzing the antioxidant activity of fruits and vegetables when looked at synergistically, and when the whole fruit (with peel) is included, in his *in vitro* experiments. His hypothesis is that the benefits of a diet rich in fruits and vegetables

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FACT SHEETS

Single copies available at no cost. For multiple copies please contact BCERF (address below).

General Information on Breast Cancer

__*FS # 3*--Understanding Breast Cancer Rates
__*FS # 5*--The Biology of Breast Cancer
__*FS # 6*--Tumor Supressor Genes
__*FS # 9*--Estrogen - Relationship
__*FS #10*--Estrogen - Factors
__*FS #37*--Hormones in Food

Diet and Lifestyle

__*FS #1*--Phytoestrogens
__*FS # 8*--Childhood Life Events
__*FS #13*--Alcohol
__*FS #18*--Fruits and Vegetables
__*FS #19*--Exercise
__*FS #27*--Dietary Fat
__*FS #29*--Breast Feeding
__*FS #33*--Dairy Products
__*FS #36*--Grains and Fiber
__*FS #39*--Meat, Poultry & Fish

CRITICAL EVALUATIONS OF PESTICIDES AND BREAST CANCER

Critical Evaluations are available on the BCERF web page as portable document files (pdf), and can be accessed on the BCERF web site (see address below).

If you would like to order a hard copy please indicate below and send your check payable to Cornell University for **$3.00 each**, to cover the cost of reproduction and mailing.

__#1 2,4-D
__#2 Lindane
__#3 Heptachlor and Heptachlor Epoxide
__#4 Chlordane
__#5 Simazine
__#6 Cyanazine
__#7 Dichlorvos
__#8 Atrazine
__#9 Chlorpyrifos
__#10 Diazinon
__#11 Alachlor
__#12 Phosmet
__#13 Mancozeb

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Pesticides and Breast Cancer Risks

__*FS # 2*--DDT, DDE
__*FS #11*--Chlordane
__*FS #12*--Heptachlor
__*FS #14*--2,4-D
__*FS #15*--Lindane
__*FS #16*--Simazine
__*FS #17*--Cyanazine
__*FS #20*--Dichlorvos
__*FS #23*--Atrazine
__*FS #26*--Chlorpyrifos
__*FS #28*--Diazinon
__*FS #32*--Alachlor
__*FS #34*--Phosmet
__*FS #38*--Mancozeb

Pesticide-Related Issues

__*FS # 4*--Reducing Pesticide Exposure: Resource Sheet
__*FS #7A*--Drinking Water--*Part I: Contaminant Sources*
__*FS #7B*--Drinking Water--*Part II: Treatment Options*
__*FS #21*--Avoiding Exposure: Protective Clothing
__*FS #22*--Safe Use and Storage
__*FS #24*--Pesticides in Food
__*FS #25*--Pesticide Residue Monitoring and Food Safety
__*FS #30*--Health Effects of Pesticides; Response to Poisonings
__*FS #31*--IPM Around the Home and Garden
__*FS #35*--IPM: Talking to Your Customers

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are attributable to the complex mixtures of phytochemicals in those foods. Dr. Liu emphasized that his research results point to the importance of whole foods, and that pharmacological doses of vitamins may do more harm than good in risk reduction. He noted that, in his research, different fruits had different inhibitory impacts on the proliferation of, for example, colon cancer versus liver cancer cells. Dr. Liu said that these results also point to the need for a diet that includes a variety of fruits and vegetables.

Natural History of the Breast

Sandra Steingraber, Visiting Assistant Professor with BCERF, shared some of her explorative research on mammary gland biology, sharing much interesting information on "the natural history of the breast." Her research contributes to her work-in-progress on the ecology of pregnancy and childbirth. In this work, questions arise such as, if in the seventh week of pregnancy mammary gland development begins, then what is the potential impact of prenatal chemical exposures on the developing breast? Her work stimulates other questions such as, if the breasts continue to develop, as "a house with additions worked on one week per month" until approximately age 35, how does this influence susceptibility to exposures? We thank Sandra for engaging the group with this unique exploration.

MARK YOUR CALENDARS!

The next Ad Hoc Discussion Group meeting will take place on February 14, 2001 in Room 711A, Legislative Office Building Albany, NY

Ad Hoc Discussion Group meetings are open to any and all stakeholders to come together to discuss issues related to breast cancer and environmental risk factors.

The Ribbon is published by the Cornell Program on Breast Cancer and Environmental Risk Factors in New York State. Comments are welcome; contact the Editor

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