"Breast Cancer Prevention Trial"

Department of Health & Human Services
National Institutes of Health

Statement of Leslie Ford, M.D.
Associate Director for Early Detection and Community Oncology
National Cancer Institute
Before the Congressional Caucus for Women's Issues
April 30, 1998

Good morning, Members of the Caucus. I am Leslie Ford M.D., Associate Director of the Early Detection and Community Oncology Program at the National Cancer Institute (NCI). I am pleased to testify before you today about the Breast Cancer Prevention Trial.

For the past six years, the National Surgical Adjuvant Breast and Bowel Project (NSABP), an NCI funded national clinical trials organization, has been carrying out an historic clinical trial - called the Breast Cancer Prevention Trial or BCPT- to determine whether women at increased risk of developing breast cancer can prevent the development of that cancer by taking the drug tamoxifen.

The BCPT enrolled 13,388 women at increased risk for developing breast cancer. These included women 60 years of age and older who qualified to participate based on age alone, and women between the ages of 35-59 with an increased risk of breast cancer equivalent to or greater than that of a 60 year old woman.

Of the 13,388 women on the trial, about 40 percent were ages 35-49, about 30 percent were ages 50 to 59, and about 30 percent were age 60 or older. About 3 percent of the participants were minorities, including African American, Asian American, Hispanic, and other groups.

Participants in the BCPT were randomized to receive either tamoxifen or a placebo. The trial was "double blinded" so that neither the participant nor the researcher knew which pill she was on. Setting up the study in this way allowed the researchers to clearly see what the true benefits and side effects of tamoxifen are without the influence of other factors.

As with all of our clinical trials, an independent Endpoint Review, Safety Monitoring and Advisory Committee met regularly to examine the data to monitor whether unacceptable or unexpected toxicities had arisen or whether the trial had succeeded in answering the questions it had been designed to answer. When this committee last met on March 24, it was concluded that tamoxifen can significantly reduce the incidence of breast cancer in women at increased risk. Nevertheless, there were, as you have heard, adverse effects of tamoxifen which may make the very personal decision about taking tamoxifen complex. For all of these reasons, the committee recommended that the participants of the study be

notified of these important results. It has been our commitment to the participants from the very start to notify them as soon as clear results had been achieved.

On March 26, the NSABP leadership presented these recommendations and the data behind them to the NCI and we -- NCI and NSABP -- agreed to accept the recommendations of the independent advisory committee. This morning, I will share this information with you, describing the study, its results, and its implications, and very importantly, place this study in the context of what we know and don=t know about breast cancer prevention.

Study Results

- Results show 45 percent fewer diagnoses of invasive breast cancer in women who were randomized to take tamoxifen compared to women who were randomized to take the placebo (85 cases in the tamoxifen group versus 154 cases in the placebo group).
- Women on tamoxifen also had fewer diagnoses of noninvasive breast cancer, such as ductal carcinoma in situ (31 cases in the tamoxifen group versus 59 cases in the placebo group).
- The reduction in the incidence of breast cancer was seen across all age groups.
- Women in the tamoxifen group had fewer bone fractures of the hip, wrist and spine than women in the placebo group (47 cases in the tamoxifen group versus 71 cases in the placebo group).
- The use of tamoxifen was also associated with infrequent but potentially life-threatening adverse events. Although these adverse events were no greater than had been predicted prior to the initiation of the study, they must be given careful consideration in determining the propriety and utility of tamoxifen in reducing breast cancer risk.
- The risk of tamoxifen-associated adverse events was predominant in women older than 49 years of age. In this age group, there were 26 endometrial cancers (cancer of the uterus) in the tamoxifen treated participants compared with 6 in the placebo group.
- There was also an excess of Avascular events@ (thromboembolic phenomena, stoke and transient ischemic attacks), 81 in the tamoxifen group versus 53 in the placebo group. The increased risk of Avascular events@ was similar to that noted in postmenopausal women taking hormonal replacement therapy. There was no increased incidence of ischemic heart disease including myocardial infarction.

Risk Determination for Participants

The risk factors for the trial were determined using a computerized model that was developed by Dr. Mitchell Gail of the National Cancer Institute. This model took into account such factors as the number of first degree relatives that had breast cancer, --that's mothers, sisters, and daughters--the number of biopsies that the woman might have had for suspicious lesions herself; whether any of these biopsies had a diagnosis of atypical hyperplasia , or a pre-invasive cancer called lobular carcinoma in situ; her age when she

started her periods, whether she had any children, and how old she was when those children were born.

A woman was eligible for the BCPT if her risk was at least as great as that of the average 60 year old woman. For example:

- For the youngest women in the trial, they needed not only to have two first degree relatives that had breast cancer, but in addition, another risk factor, such as a personal history of biopsies.
- As the woman reached age 40, two first degree relatives and no live births would have given her sufficient risk to be eligible for the trial. And by age 45, she could have two first degree relatives or one affected first degree relative and a personal history.

The important message here is twofold: First, that the number of additional risk factors needed for eligibility decrease as age increases, and second, there are thousands of combinations of these risk factors that put a woman at increased risk of breast cancer.

Risk in the General Population

A very important point to consider is that women, especially in the younger age groups, tend to vastly overestimate their risk of developing breast cancer. For this reason and other reasons already mentioned, it is important to take all of these factors into consideration when making a decision about using tamoxifen.

We estimate that overall in the United States, approximately 29 million women, or 21 percent of the population, might fit these risk criteria. A large number of those, 26 million, would come from just being over 60. This would also include women who had the diagnosis of lobular carcinoma in situ, and approximately 3 million women between the ages of 35 and 59 who would have additional risk factors that put them into the high risk group.

In the 35-39 year old group, only 3 out of 1,000 women would have met the eligibility requirement. As a woman ages, that number gets bigger, to about 27 out of 1,000 (age 40-44), 71 out of 1,000 (age 45-49) and about 10 percent of women ages 50-59 would have met the criteria.

We are now in a position to give women an option. We can now intervene prior to the detection of breast cancer, and really reduce a woman's chance of developing the disease. But as with any medication, the decision to began tamoxifen therapy is a very complex one. There are no simple answers. Not all women are at increased risk for breast cancer, and the balance of benefits and risk varies with age and hysterectomy status. Even for women at high risk for developing breast cancer, tamoxifen may not be an appropriate choice.

Making a Choice: Risks and Benefits

To put these numbers into some context, imagine 1,000 women between the ages of 35 and 49 who might meet the criteria for this trial: what could we expect over a five year period based on these results? Without tamoxifen, we would expect 31 cases of breast cancer to develop; and with tamoxifen 14 (or 45 percent) of these could be prevented. Also, with respect to non-invasive breast cancers, about 11 of the 15 cases could be prevented. In this age group, we see no difference in the rate of endometrial or vascular events that have occurred.

However, in women 50 years old and over, it is more complex. If all 1,000 of these women have a uterus, then they would all be at risk for endometrial cancer. In that situation, we might prevent 17 out of the 33 expected cases of breast cancer, and 3 out of the 10 expected cases of noninvasive breast cancer. But there could be as many as 12 more cases of endometrial cancer.

We are looking at ways to help us better define who is at risk of breast cancer and who is at risk for some of the unwanted side effects that come with tamoxifen therapy, as well as with other hormone replacement therapies. Great interest has been generated about genetic predisposition to breast cancer, and we know that some breast cancer is linked to certain mutations. It is likely that some of the women in this study, especially those with very strong family histories of breast cancer, carry such a genetic predisposition. While it is reasonable that such women would also experience a decreased risk of breast cancer with tamoxifen, no specific gene testing has been done. As further analyses of the data from this clinical trial are done, we hope to be able to provide more information over the next 6-12 months as to whether women with alterations in BRCA1 & 2, the two known genes whose alterations predispose to breast cancer, were protected from cancer in this trial. I would like to emphasize, however, that there are many important considerations as to how new knowledge about genetics can and should be made a part of medical decision-making that further complicate this process.

The choice to take tamoxifen has to be a personal one, a decision between a woman and her health care provider. We are feverishly working to analyze this data so we can better define who is at increased risk for breast cancer. For women whose risks of developing breast cancer fall within the range of this study, tamoxifen can provide, for the first time, an option to reduce that risk, much as new cholesterol-lowering medication can reduce the risk of heart attacks. But that option must be weighed carefully and on an individual basis.

This emphasis on individual risk is extremely important. Our ability to identify individuals at risk for disease and to begin to rationally intervene, based upon our knowledge of the disease process, is what medicine will become.

The NCI is committed to communicating the importance of research findings to all women and their physicians in a clear and understandable manner. NCI has solicited feedback about the impact the Breast Cancer Prevention Trial announcement has had on those who counsel women regarding their decision to take tamoxifen for the prevention of breast cancer. The preliminary findings from a survey of Cancer Center Directors,

NCI=s Cancer Information Service, Principal Investigators of the NSABP, and the advocacy community indicate that it has been possible for them to respond to most inquiries and counseling requests using information already provided by NCI and NSABP. This information was disseminated through existing NCI and NSABP communication mechanisms before or at the time of the public announcement of the trial=s early results. A new mechanism was also used. NCI launched on the day of the announcement a new clinical trials web site, which included information about the benefits and risks of tamoxifen.

The feedback concerning the handling of the announcement and the materials provided to date has been very positive. This feedback is being used to assist NCI and the NSABP to develop tools to help each woman, and her health care provider, when making a decision about whether use of tamoxifen is appropriate for her.

Minority Recruitment

Throughout the trial, several strategies were used to increase participation of women from racial and ethnic minority groups. These strategies included placing study-related recruitment materials in businesses and churches located in minority communities; collaborating with a minority-owned public relations firm to develop a structured media campaign targeting racial and ethnic minorities; developing and broadly disseminating a Public Service Announcement that featured singer Nancy Wilson; and communicating information to study sites about how other sites successfully reached racial and ethnic minorities.

When the early strategies did not attract sufficient numbers of minority participants, the NSABP launched the Pilot Minority Recruitment Program in August 1996. The goal of the program was to increase participation by increasing awareness and educating minority populations about the trial. A multidimensional approach was used: Community Outreach Coordinators employed at five BCPT sites offered personalized presentations on breast cancer risk factors, incidence, and survival rates, and on clinical trial research at African-American churches, community hospitals and health clinics, health fairs, public housing sites, businesses, and local chapters of sororities, the Urban League, and minority medical societies. In less than a year, these strategies enabled the coordinators to establish many relationships in their communities. As a result of these efforts, the number of Risk Assessment Forms submitted by minority groups increased, and during this period, the BCPT experienced the highest level of randomizations from racial and ethnic minority groups since the trial began. The Pilot Minority Recruitment Program has been the most effective strategy to date and will serve as the model for minority recruitment for future prevention trials.

Conclusion

This study is not an end. It is rather a very propitious beginning. But it tells us that it is possible to prevent breast cancer. Tamoxifen is far from ideal. Its efficacy is only partial and it has significant risks. To move forward will require new agents and new clinical

trials. Newer selective estrogen receptor modifiers are being developed and will be tested. The NCI hopes to be able to follow this study soon with additional clinical trials to find answers to the many questions that remain.

Thank you for the opportunity to address the caucus. I will be happy to answer any questions you may have.