Can Breast Cancer Be Prevented?

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Breast cancer is the most common invasive cancer in American women and is second only to carcinoma of the lung in cancer deaths. The results of the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial (BCPT) were released in April 1998. In the BCPT, 13,388 women at increased risk for the development of breast cancer were randomized to receive tamoxifen or placebo for 5 years, resulting in a 49% reduction in invasive breast cancer and a 50% reduction in noninvasive breast cancer. In May 1998, the preliminary results from the Multiple Outcomes of Raloxifene Evaluation (MORE) trial were reported to the American Society of Clinical Oncology. The MORE trial was evaluating the drug raloxifene for the prevention and treatment of osteoporosis; however, a secondary outcome was a reduction in breast cancer risk in raloxifene-treated women. Based upon the results of the BCPT and MORE trials, a second-generation breast cancer prevention trial has been initiated. The Study of Tamoxifen and Raloxifene (STAR) was initiated in June 1999. Ochsner Clinic and Alton Ochsner Medical Foundation, active participants in the BCPT, were named a clinical center for the STAR trial.

Kardinal CG, Cole JT. Can breast cancer be prevented? The Ochsner Journal 2000; 2:10-13.

In the year 2000 there will be approximately 180,000 new cases of breast cancer in the United States resulting in approximately 45,000 deaths. Between 1973 and 1991 the incidence of breast cancer increased 25% and has become a major public health threat. Though the very term "breast cancer" precipitates fear, anxiety, and unrest, awareness of the disease has been greatly increased by activist groups and numerous articles in the press. There have also been numerous advances in breast cancer therapy in the past 2 decades, including the introduction of postoperative adjuvant therapy for women with early stage breast cancer who have an increased risk of recurrence. Breast cancer conservation therapy has been introduced, and the majority of women with Stage I and Stage II disease are candidates for breast conservation. The widespread use of screening mammography has resulted in the detection of smaller and smaller lesions, increasing the patient's chances of a cure.

There are definite limits, however, to our diagnostic capabilities. Breast cancers of <3 mm and even <1 mm must exist, as well as sub-clinical phenotypic abnormalities in women destined to develop breast cancer. It is highly unlikely that a breast lesion of <1 cm in diameter will be detected on routine physical examination and equally unlikely that a breast lesion of <3 mm to 5 mm will be detected on mammogram. Can women at increased risk for the development of breast cancer or women with sub-clinical breast cancer be identified? If so, can anything be done to prevent or delay the development of the disease?

Two important breakthroughs led to the National Surgical Adjuvant Breast and Bowel Project's (NSABP) Breast Cancer Prevention Trial (BCPT):

1. The development of the Gail Model (1) to better define a woman's risk of developing breast cancer
2. The observation that women with Stage I breast cancer have a 50% reduction in the incidence of contralateral breast cancer if they have been treated with tamoxifen (2).

The Gail Model

In 1989, Gail and colleagues (1) at the National Cancer Institute developed a model of breast cancer risk based upon known risk factors (see Table 1). From these various factors, relative risk can be calculated and a high-risk group for the development of breast cancer can be identified. (A "Risk Disc" based upon the Gail Model, as well as a risk calculator, are available from Zeneca Pharmaceuticals 302 886-8000.)

The NSABP Breast Cancer Prevention Trial (BCPT)

On June 1, 1992, NSABP implemented a randomized clinical trial to evaluate the use of tamoxifen for the prevention of breast cancer in women at high-risk for the disease. The primary aim of the BCPT was to determine whether tamoxifen administered for at least 5 years prevented invasive breast cancer in women at increased risk for the disease (eligibility criteria are listed in Table 2). Secondary aims were to determine whether tamoxifen administration would lower the incidence of fatal and nonfatal myocardial infarctions or reduce the incidence of bone fractures. Additional objectives were to evaluate breast cancer mortality and tamoxifen's adverse effects in order to assess the benefits and potential risks of the drug. Information concerning tamoxifen's role in breast cancer prevention for women at increased genetic risk for the development of breast cancer will soon be available.

Tamoxifen was chosen to be evaluated because of its demonstrated benefits in the treatment of advanced breast cancer, when used alone as well as in combination with chemotherapy, and because of its efficacy in reducing tumor recurrence when administered as postoperative adjuvant therapy in Stages I and II of the disease. Of particular importance was that tamoxifen-treated patients have a statistically significant lower incidence of contralateral breast cancer. Most patients used tamoxifen safely, with good compliance and minimal side effects.

It was originally proposed that it would require 16,000 women to answer the primary objective of the BCPT protocol. However, by September 30, 1997, with 13,388 women age ≥35 randomized to the P-1 trial, the effect of breast cancer reduction was so striking that the trial was stopped early. The primary objective of the prevention of an invasive breast cancer had been established in the group of women taking tamoxifen compared with the placebo group.

Table 1. Known risk factors for the development of breast cancer.

- Breast cancer in one or more first-degree relatives (sister, mother, or daughter)
- Prior history of benign breast disease (especially atypical ductal or lobular hyperplasia)
- Chronologic age (risk increases with age alone)
- Age at first pregnancy or nulliparity
- Age at menarche
- Race (Caucasians have a greater incidence of breast cancer than either African-Americans or Orientals).

Table 2. Eligibility criteria for the Breast Cancer Prevention Trial.

- Age 60 or older with no additional risk factors
- Age 35 to 59 with increased risk factors (based on the Gail Model)
- A history of lobular carcinoma in situ
- A life expectancy of at least 10 years
- No hormone replacement therapy or oral contraceptives for at least 3 months
- No history of deep vein thrombosis or pulmonary embolism

Of the 13,388 women who were randomized, 6681 received tamoxifen and 6707 received a superficially identical placebo. The results of the trial were released in April 1998 with a median follow-up time on study of 54.6 months. The data were presented to the American Society of Clinical Oncology in May 1998, and were published in the *Journal of the National Cancer Institute* in September 1998 (3). Approximately one third of the women enrolled in the study were age 35 to 49 (pre-menopausal), one third were age 50 to 59, and one third were ≥60. Very few minorities participated in the trial despite extensive recruitment efforts, and 96.4% of the participants were Caucasian.

Ochsner's Role in the BCPT

The Ochsner Community Clinical Oncology Program (CCOP) was an active participant in the BCPT, submitting over 2000 risk assessment profiles to the NSABP, 907 of which were potentially

eligible for enrollment in the protocol. There was a very high drop-out rate between the number of women who initially expressed an interest in the BCPT and those who actually enrolled. Of the 907 women who were potentially eligible, only 132 actually entered the clinical trial. This high drop-out rate was also noted nationally: the NSABP performed almost 100,000 risk assessment profiles to enroll the 13,388 participants.

BCPT Results

A total of 368 invasive and noninvasive breast cancers developed during the 54.6-month observation period: 244 in the placebo group and 124 in the tamoxifen group. This represents a 49% reduction in invasive breast cancer ($P < .00001$). There was also a 50% ($P < .002$) reduction in noninvasive breast cancer; i.e. ductal carcinoma in situ and lobular carcinoma in situ (LCIS). Tamoxifen was equally effective in reducing the incidence of invasive and noninvasive breast cancer in all subgroups: women aged $\leq$49, 50 to 59, and $\geq$60; women with LCIS; and women with atypical hyperplasia.

Given tamoxifen's known mechanism of action in blocking estrogen receptor (ER), it is no surprise that tamoxifen markedly reduced the incidence of ER-positive tumors and had no effect on the development of ER-negative tumors. Tamoxifen had its greatest effect on reducing the development of tumors of $\leq$2 cm rather than larger tumors.

Secondary End Points and Adverse Reactions

Tamoxifen is not a pure anti-estrogen selective estrogen receptor modulator (SERM) and has what has been termed an "estrogenic tickle" that is both favorable and unfavorable. Tamoxifen is estrogenic with reference to postmenopausal bone and tends to prevent osteoporosis. In fact, there was a significant reduction in osteoporotic fractures of the vertebrae and hip in the women in the BCPT who were treated with tamoxifen. Tamoxifen is also estrogenic with reference to lipids with 10% to 20% reductions in low density lipid (LDL) cholesterol, but this did not translate to a reduction in cardiovascular deaths in women in the BCPT.

The unfavorable part of the "estrogenic tickle" of tamoxifen is its action on the uterus with an increased risk of endometrial hyperplasia and even endometrial carcinoma. BCPT participants who received tamoxifen had a 2.5 times greater risk of developing endometrial cancer (2.5/1000 per year) than women who received placebo (the normal 1/1000 per year). This increase was noted only in those participants aged $\geq$50 and the endometrial cancers observed were generally low-grade and low-stage and presented early with postmenopausal bleeding. The only endometrial cancer death that occurred in women in the BCPT occurred in the placebo group.

The other significant adverse event was an increased incidence of deep vein thromboses and pulmonary emboli in women taking tamoxifen. This increase in thromboembolic events is probably no greater than that associated with hormone replacement therapy and oral contraceptives.

The MORE Trial

The results of the Multiple Outcomes of Raloxifene Evaluation (MORE) trial were reported to the American Society of Clinical Oncology in May 1998 (4) and published in the *Journal of the American Medical Association* in June 1999 (5). It is important to emphasize that the MORE trial was not initially a breast cancer prevention trial; it was designed to detect a reduction of vertebral fracture risk in post-menopausal women with osteoporosis who were treated with raloxifene (6). A total of 7705 post-menopausal women with osteoporosis age <81 were randomized to receive raloxifene 120 mg daily or 60 mg daily versus an identical placebo. The main outcome measure of the protocol was the incidence of vertebral fractures. However, a significant reduction in the incidence of breast cancer in those women treated with raloxifene was noted.

Thirteen cases of breast cancer were confirmed in the 5129 women assigned to the two raloxifene groups versus 27 cases among the 2576 women assigned to the placebo group ($P < .001$). Raloxifene acts as an estrogen on bone; however, it does not have the estrogenic stimulation of tamoxifen on the uterus. Based upon the results of the MORE trial and the potential of decreased toxicity of on the uterus, raloxifene has been selected for the second-generation breast cancer prevention trial to be tested against tamoxifen.

The STAR Trial

The Ochsner CCOP has been selected to serve as a nucleus center for the Study of Tamoxifen and Raloxifene (STAR) trial, the second-generation breast cancer prevention trial initiated by the NSABP in June 1999. The trial is a randomized, double-blind study designed to evaluate 22,000 postmenopausal women who are at increased risk for developing breast cancer. Participants are randomly assigned to receive tamoxifen (20 mg daily) or raloxifene (60 mg daily) for a period of 5 years.

The STAR trial is based on the positive results of the BCPT and the possibility that raloxifene may be as effective as tamoxifen in breast cancer prevention but have fewer side effects. Whereas tamoxifen has proven activity in the treatment of all

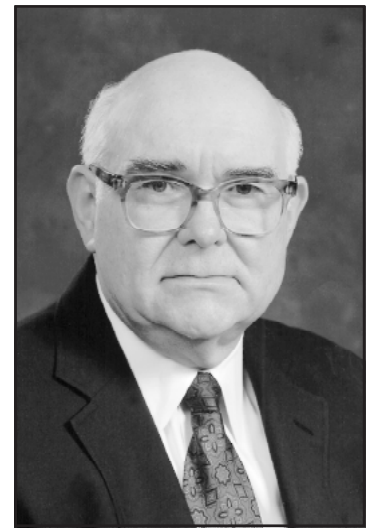
stages of breast cancer, raloxifene has been tested primarily for the treatment and prevention of osteoporosis. The preliminary data of the MORE trial are encouraging; however, it must be emphasized that this trial was designed to evaluate the treatment and prevention of osteoporosis and was not a breast cancer prevention trial.

Unanswered Questions

Results of the BCPT are a landmark breakthrough in cancer therapy. For the first time a major cancer can be prevented, or at least delayed, in high-risk groups. Several questions remain unanswered:

- Was breast cancer truly prevented or simply delayed by tamoxifen?
- What is the optimum duration of tamoxifen therapy?
- How long will the effects of tamoxifen last?
- Who in the general population should be treated with tamoxifen?
- Will raloxifene be as effective as tamoxifen in breast cancer risk reduction but have a lower incidence of side effects?

We hope to answer some of these questions in the STAR trial.



Dr. Kardinal is the Principal Investigator of the Ochsner Community Clinical Oncology Program (CCOP), a member of the Board of Directors of the National Surgical Adjuvant Breast and Bowel Project (NSABP), and a member of the The Ochsner Journal Editorial Board.

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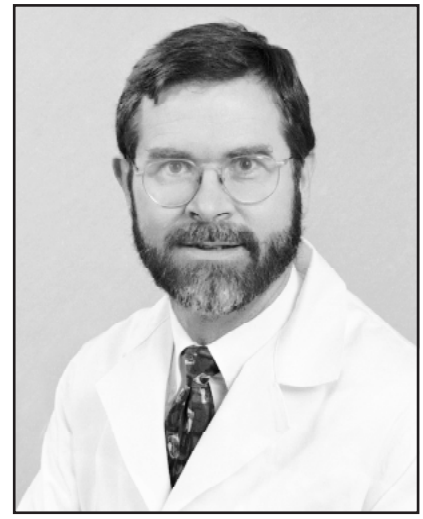

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