

# THE FUTURE OF WOMEN OF MINORITY RACE/ETHNICITY IN BREAST CANCER CHEMOPREVENTION THERAPY

Women of minority race/ethnicity have been underrepresented in United States-based breast cancer chemoprevention trials. Searches of Medline between 1966 and 2004 were done with priority given to recent reports (1996–2004), and references from bibliographies of relevant articles. Large chemoprevention trials have reported significant breast cancer risk reduction and increased risk of serious adverse events in tamoxifen-treated, high-risk women, which illustrates the need to carefully assess the risk/benefits of this therapy. The mathematical model used for this purpose in the United States-based trials has resulted in the inclusion of very few women of minority racial/ethnic backgrounds. The continued use of this risk assessment that has not been adequately validated for its usefulness in non-Caucasian populations, should be reviewed, especially given that adequate alternative nonmathematical models exist. Current and future chemoprevention trials should also use nonmathematical selection criteria to ensure that eligible underrepresented minorities are adequately included in these trials. (*Ethn Dis.* 2006;16:216–222)

**Key Words:** Breast Cancer Chemoprevention, Selective Estrogen Receptor Modulators

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## INTRODUCTION

Breast cancer is the most common cancer among women. In 2004, an estimated 215,990 American women will be diagnosed with breast cancer, and 40,110 will die from it.<sup>1</sup> Breast cancer incidence and mortality are not evenly distributed among American women and differ according to racial/ethnic background as well as socioeconomic status. Between 1996 and 2000, the age-adjusted incidence of breast cancer among Caucasian women was 140.8 per 100,000 women compared to 121.7 per 100,000 for African-American women.<sup>1</sup> The incidence of breast cancer in the highest quintile of social class was 50% higher than that of the lowest quintile of social class.<sup>2</sup> Meanwhile, the mortality rate from breast cancer is higher in African Americans (35.9 per 100,000 women) when compared with Caucasian women (27.2 per 100,000 women), and this trend has been maintained for more than three decades.<sup>1</sup> The five-year breast cancer survival rate for Caucasians increased from 75% in 1974–1976 to 88% by 1992–1999, while the five-year survival rate for African Americans improved from 63% to 74% in the same period.<sup>1</sup> This lower survival rate in African Americans has been associated with poorer participation in screening activities, presentation at a more advanced stage of the disease, and poorer access to health care.<sup>3,4</sup> Between 1989 and 1993, the age-adjusted breast cancer mortality rate for Caucasian-American women decreased sharply by 6.8%.<sup>5,6</sup> This improvement has been attributed to early detection and increased use of adjuvant therapy such as tamoxifen.<sup>5,6</sup> Current efforts to prevent breast cancer include the use of selective estrogen receptor modulators (SERMs) such as

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tamoxifen, which has been approved by the US Food and Drug Administration for breast cancer chemoprevention, as well as related compounds being tested in chemoprevention trials. In order to assess the status of and the potential solutions to the poor participation of women of minority race/ethnicity in breast cancer chemoprevention therapy, searches of Medline between 1966 and 2004 were done with priority given to recent reports (1996–2004) and references from bibliographies of relevant articles. Terms like breast cancer, risk assessment, and selective estrogen receptor modulators were searched in combination with chemoprevention trials.

## THE RATIONALE FOR BREAST CANCER CHEMOPREVENTION THERAPY

Cancer chemoprevention is defined as treatment with either naturally occurring or synthetic chemical agents to prevent, reverse, or arrest the progression of preneoplastic lesions to invasive cancers.<sup>7</sup> The main strategy of chemoprevention is to block the effect of both epithelial mutagens and mitogens on neoplastic progression. This blockage is achieved by modulating specific steps in carcinogenesis, such as preventing DNA damage by free radicals, suppressing

epithelial cell proliferation, or increasing epithelial cell differentiation.<sup>8</sup> As their name suggests, SERMs exhibit target-specific effects on the estrogen receptors. Tamoxifen, a derivative of the triphenylethylene class of compounds, has both agonist and antagonist actions on estrogen receptors and competitively inhibits estradiol binding to those receptors.<sup>7-9</sup> Other agents with similar properties include raloxifene, toremifene, and droloxifene.<sup>9,10</sup>

The rationale for using tamoxifen to prevent breast cancer is provided by the findings of the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 study. This randomized clinical trial of tamoxifen for the prevention of breast cancer showed a 49% reduction in the risk of invasive breast cancer in high-risk women who received tamoxifen as compared with the control group who received a placebo.<sup>11,12</sup> However, this finding was in contrast to the results of two similar studies conducted in Britain and Italy that did not show any significant reduction in the risk of breast cancer in women in the tamoxifen arms as compared with women in the control arms.<sup>13,14</sup> Subjects in the three studies were different. The British study consisted of high-risk participants with a strong family history of breast cancer, whereas most of the participants in the NSABP P-1 trial had nongenetic risk factors.<sup>13</sup> The Italian group used a low-powered interim analysis to evaluate women with a lower median age than those in the NSABP P-1 trial and with no specific risk factors for breast cancer.<sup>14</sup> Another major breast cancer chemoprevention trial, the International Breast Cancer Chemoprevention Intervention Study (IBIS), conducted in the United Kingdom, Australia, New Zealand, and other European countries, reported a 32% reduction in the risk of developing breast cancer in women treated with tamoxifen when compared with those who received placebo.<sup>15</sup> The investigators followed up 7158 women at increased risk for breast cancer who

were between 35 and 70 years old for a median period of 50 months. Sixty-nine cases of breast cancer were diagnosed in the tamoxifen ( $n=3578$ ) arm while 101 cases were diagnosed in the placebo arm ( $n=3560$ ).<sup>15</sup> These findings provided further evidence of the efficacy of tamoxifen in reducing the risk of breast cancer. The efficacy of breast cancer chemoprevention therapy has been established by an analysis conducted by Cuzick et al in 2003.<sup>17</sup> They combined data from the NSABP P-1 trial, the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, the IBIS, and the Italian and the Royal Marsden Hospital trials.<sup>11,14-16</sup> Combined data from previous adjuvant trials were also included in the analyses.<sup>17</sup> In all, for the chemoprevention trials with tamoxifen,  $70 \times 10^3$  woman-years of follow up were available for the tamoxifen and the placebo arms. Tamoxifen prevention trials showed a 38% reduction in breast cancer incidence, and estrogen receptor (ER)-positive breast cancer incidence was reduced by 48%.<sup>16</sup> Further, with a longer follow-up period of participants in the Italian study (median period of 81.2 months), among tamoxifen-treated women at high risk for ER-positive breast cancer based on reproductive and hormonal factors, a significantly lower incidence of breast cancer was seen when compared with women of lower risk.<sup>18</sup> Therefore, given the proven benefits of SERMs, the need to use breast cancer chemoprevention as a viable preventive option for breast cancer in high-risk women is incontrovertible. However, careful ascertainment of risk versus benefit of therapy is pertinent.

### RISK AND BENEFIT OF BREAST CANCER CHEMOPREVENTION THERAPY

Beyond breast cancer risk reduction, tamoxifen-treated women showed re-

ductions of 15%–20% in low-density lipoproteins with little or no change in high-density lipoprotein levels,<sup>19</sup> 26% in the median C-reactive protein, 22% in the median fibrinogen, and 9% in cholesterol levels, which suggests that tamoxifen may lower the risk of cardiovascular disease.<sup>19,20</sup> However, such a benefit was not demonstrated in the NSABP P-1 trial.<sup>11</sup>

Raloxifene, another antiestrogen agent currently used to treat osteoporosis that has been reported to have potential advantages over tamoxifen as a chemopreventive agent for breast cancer, is also being studied for its usefulness in breast cancer chemoprevention in the ongoing Study of Tamoxifen and Raloxifene (STAR).<sup>17,21</sup> Current reports indicate that raloxifene is not associated with the endometrial side effects observed in tamoxifen-treated women, as described below.<sup>17</sup> Other promising agents include selective ER down-regulators, which act as antiestrogens on all tissues, and aromatase inhibitors such as anastrozole. Their usefulness as therapeutic and chemopreventive agents for breast cancer is currently being investigated.<sup>21,22</sup>

Findings from the IBIS-1 indicated that recipients of tamoxifen had a significantly higher incidence of adverse effects such as vasomotor symptoms, vaginal discharges, abnormal bleeding, endometrial polyps, amenorrhea, vaginal thrush, and ovarian cysts.<sup>15</sup> Further analyses of the combined data from the major chemoprevention and adjuvant trials showed that the rates of endometrial cancers were increased in all chemoprevention (relative risk [RR] = 2.4) and adjuvant trials (RR = 3.4), but so far not in the raloxifene trial. Meanwhile, thromboembolic events increased in both tamoxifen and raloxifene trials.<sup>16</sup> The side effects of tamoxifen are more severe for postmenopausal women.<sup>11,19,23</sup> Specifically, the NSABP P-1 trial showed an excess risk for vascular events among participants who were  $\geq 50$  years.<sup>11</sup> The risk for

**Table 1. The International Breast Cancer Intervention Study selection criteria**

Categories of Risk Factors	Eligibility for Inclusion*
<b>Family history of breast cancer</b>	
One FDR with breast cancer	Eligible if FDR was diagnosed with breast cancer at 50 years of age or less
One FDR with bilateral breast cancer	Eligible at age 35 if FDR had breast cancer before 40 years of age; eligible at age 40 if FDR had breast cancer before 50 years of age
Two or more FDRs with breast cancer	Eligible at age 35 if both relatives had breast cancer before 50 years of age
Two or more second degree relatives with breast cancer	Eligible at age 40 if both relatives had breast cancer before 50 years of age
<b>Premalignant lesions</b>	
Lobular carcinoma <i>in situ</i>	Eligible at age 35
Atypical hyperplasia	Eligible at age 40
<b>Combination of risk factors</b>	
Nulliparous plus an FDR with breast cancer	Eligible
Benign breast biopsy plus an FDR with breast cancer	Eligible
<b>Risk equivalent</b>	
Women with strong family history of breast cancer who did not fit into above categories	Eligible if judged to be at higher risk than the minimum eligibility category

FDR=first-degree relative.  
 \* Permitted age of entry was 45 years for all criteria.

endometrial cancer was also higher in older participants.<sup>11,19,23</sup> Further assessments of the effect of tamoxifen therapy on psychosocial functioning (including anxiety, psychosocial distress, and sexual functioning) of women at increased risk for breast cancer showed no evidence of treatment-related side effects when compared with women receiving placebo.<sup>24,25</sup> To assess the risk-benefit index of tamoxifen chemoprevention by using the risk model they developed, Gail et al<sup>27</sup> in 1999 reviewed the results of the NSABP P-1. They reported that tamoxifen was most beneficial for younger women, and the benefits were greatest in younger Caucasian women.<sup>26-28</sup> For example, Caucasian women of ages 40-49 with an estimated five-year risk of breast cancer of 3% who had no hysterectomy had a net benefit-risk index from chemoprevention therapy of +135 compared to +76 for African-American women with similar characteristics. This figure was determined based on the projected number of life-threatening events, such as invasive breast cancer, endometrial cancer, pulmonary embolism, stroke, and hip fractures plus half of the projected

number of severe events, such as non-invasive breast cancer and deep vein thrombosis, in 10,000 women who received tamoxifen therapy.<sup>26-28</sup> A further report by Freedman et al<sup>29</sup> in 2003, which was also based on the model by Gail et al, showed that of the 65,826,074 women aged 35-79 years whose data were derived from the National Health Interview Survey Cancer Control module, Caucasian women would account for 18.7% of those eligible to receive tamoxifen, African Americans for 5.7%, and Hispanics for 2%. While 4.9% of these eligible Caucasian women would have a positive benefit-risk index, only 0.6% (not significant) of African-American women would benefit from the therapy.<sup>29</sup> Based on the model by Gail et al, eligible Black women would at best have little benefit from breast cancer chemoprevention therapy. However, these assessments are limited by the breast cancer risk assessment tool used,<sup>27</sup> which was shown to have a low predictive accuracy of 58% for breast cancer incidence in a five-year period.<sup>30</sup> Further, women of ethnic minority groups were underrepresented in both arms of the trial on

which these analyses were based.<sup>11</sup> Consequently, the net risk-benefit index for women of minority race/ethnicity has not been properly assessed. This fact places some doubt on the adequacy of the selection process for the inclusion of these women into chemoprevention trials.

## SELECTION CRITERIA FOR ENROLLMENT INTO CHEMOPREVENTION TRIALS

In view of the significant risk of adverse effects, the need for careful selection of women with high risk of developing breast cancer and lower risk of adverse effects becomes paramount. Currently, the methods used for risk-benefit assessment include the use of mathematical models such as the risk model developed by Gail et al<sup>26</sup> in 1989. A modified version of this risk assessment model was used in the NSABP P-1 trial and is used for other chemoprevention trials conducted by the NSABP such as the STAR. The tool was developed by using multivariate logistic models that comprise a combination of risk factors such as age, number of first-degree relatives (FDRs) with breast cancer, nulliparity or age at first birth, and number of breast biopsies.<sup>26,27</sup> It has been used to estimate the probability of the occurrence of breast cancer over time.<sup>26,27</sup> To be eligible for the NSABP P-1 trial, a woman had to have a five-year predicted risk of developing breast cancer of at least 1.67%.<sup>11</sup> Other non-mathematical methods included the criteria used for the IBIS-1 investigators where eligible women had risk factors for breast cancer that conferred a RR of at least two-fold for ages 45-70 years, four-fold RR for ages 40-44 years and approximately 10-fold RR for ages 35-39 years (Table 1).<sup>16</sup> A similar but less robust criterion was used for the Royal Marsden Hospital trial.<sup>13</sup> The Italian chemoprevention trial included women

who had hysterectomies with no specific risk factors for breast cancer.<sup>14</sup>

Associated with these methods of subject selection are specific problems, such as the tendency to include women with average or less-than-average risk for breast cancer who were then exposed to considerable risk of adverse effects of tamoxifen therapy, as in the case of the Italian and the Royal Marsden Hospital trials. Further, the inclusion of participants with less-than-average risk for developing breast cancer may have accounted for the initial null results reported in these studies.<sup>13,14</sup> Another problem is the rigorous use of a mathematical model such as the Gail model, which was developed from data obtained from a population of Caucasian women who were also breast cancer screening participants. Use of this model may have led to underestimation of the breast cancer risk of women of minority race/ethnicity in the United States and subsequently the tendency to exclude these women from future breast cancer chemoprevention trials.<sup>31-36</sup> The risk factors for breast cancer in African-American women has not been adequately studied, and even where the model was modified to improve its applicability to African-American women, the risk factors used and the final scores were unchanged.<sup>26,27</sup> Further, the results of the recent validation of the Gail model by Rockhill et al indicated that the model underpredicted the five-year risk for developing breast cancer in younger women.<sup>30</sup> Consequently, since African-American women have a higher risk of early onset (<45 years) breast cancer,<sup>37</sup> their risk would be underestimated with this model.

## PARTICIPATION OF ETHNIC MINORITY WOMEN IN CHEMOPREVENTION TRIALS

African-American women bear a greater burden of the death toll due to breast cancer in the United States,<sup>1</sup>

yet a negligible proportion of these women are enrolled into chemoprevention trials.<sup>36</sup> A detailed review of the racial/ethnic distribution of the participants in previous chemoprevention trials show limited inclusion of women of minority racial/ethnic backgrounds. For instance, of the 13,388 participants randomized into the treatment groups of the NSABP P-1 study, 96% were Caucasian, 3.4% were African American, and 3.8% were of other racial/ethnic groups.<sup>11</sup> Further, the ongoing STAR designed to compare the efficacy of tamoxifen with raloxifene also has the same problem in that at the point where 16,300 of the targeted 19,000 participants have been enrolled, 94% of the participants are Caucasian.<sup>38</sup> Studies conducted in other countries have not reported the distribution of the racial/ethnic backgrounds of their participants.<sup>13,14,16</sup> However, these are European countries where women of minority race/ethnicity constitute a small part of the general population.<sup>39</sup> Consequently, not only are these women excluded from United States-based breast cancer chemoprevention trials, but this fact may become the trend as new agents such as anastrozole, currently being tested in adjuvant trials (eg, the NSABP B-35 adjuvant trial), become available for future primary chemoprevention trials.<sup>22</sup> We must review the continued use of the Gail model in its current form to assess the risk and benefits of chemoprevention therapy for women of minority race/ethnicity. Other chemoprevention trials that used alternative selection criteria have reported significant benefits and tolerable adverse effects of tamoxifen therapy.

Beyond the problem of enrollment of women of minority race/ethnicity into breast cancer chemoprevention trials is the acceptance and use of this therapy by these women. Recent reports on the correlates of acceptance of breast cancer chemoprevention are few and are based on small, conveniently sampled study populations.<sup>40-43</sup> Further, women

of low socioeconomic status and minority racial/ethnic backgrounds were grossly underrepresented or totally excluded (Table 2).<sup>41-46</sup> Consequently, no information on the distribution and characteristics of these women who would accept chemoprevention therapy is available, and as such no clear basis for targeted interventions exists to empower these women to make informed decisions about this preventive option.

The overall consequence of poor participation in chemoprevention therapy in light of the demonstrated benefits and in the absence of adequate evidence of a poor risk-benefit index for African-American women is that the higher mortality due to breast cancer will continue in this subpopulation of women. The added cost of medical care, the loss of employment, the lowered general productivity, and the personal years of life lost to the disease will lead to further disenfranchisement of this subpopulation.<sup>47</sup> The result of this disenfranchisement will be further poor participation, and the cycle will continue unless definitive changes are made to the selection process (see Figure 1).

## RECOMMENDATIONS

To ensure adequate enrollment of underrepresented minorities, ongoing chemoprevention trials, such as the STAR should adopt available, peer-reviewed alternatives such as the IBIS-1 selection criteria.<sup>16</sup> Where necessary, the targeted number of subjects to be enrolled may be increased and the enrollment deadline extended. The potential biases that the differences in the selection criteria may introduce can be eliminated by stratifying the predictors of specific endpoints by the selection criteria used. This approach is not only feasible but is relatively cheaper and faster than instituting a new chemoprevention trial just for women of



Table 2. Summary of determinants of acceptance of breast cancer chemoprevention with tamoxifen

Study	Main objectives	Study population	Results	Limitations
Kinney et al, 1998a <sup>44</sup>	To evaluate the effect of physician recommendation on acceptance or refusal to enroll in a chemoprevention trial	Participants in BCPT (N=175)	Predictors of acceptance were physician recommendation and absence of concern about HRT use	Small sample size, small proportion of minorities and women of low SES
Lovegrove et al, 2000 <sup>42</sup>	To compare women who accept with those who refuse to enroll in a chemoprevention trial	Clinical trial-based population (53 in each group)	Women who refused to enroll were more knowledgeable of lifestyle risk factors, had less comprehension of information on chemoprevention treatment, were more apprehensive, and were younger	Small sample size, impact of beliefs on subsequent health behaviors was not assessed
Kinney et al, 1998b <sup>45</sup>	To evaluate a regression model predicting enrollment status in a chemoprevention trial	Participants in BCPT (N=89)	Predictors of nonenrollment were age ≥50 years, not being able to take HRT, concerns of significant other, and concerns about out-of-pocket expenses	Non-White women were excluded; women of low SES were under-represented
Bastian et al, 2001 <sup>46</sup>	To determine the interest of women in breast cancer chemoprevention	A community sample enrolled in a randomized trial (N=1273)	Women interested in chemoprevention therapy were younger, had greater perception of personal risk, were more worried about having breast cancer, and had symptoms of depression	Interest was not assessed behaviorally; limited to women between ages of 40 and 50 years; data collected were not specific for the correlates of tamoxifen use

BCPT=Breast Cancer Prevention Trial; HRT=hormone replacement therapy; SES=socioeconomic status.

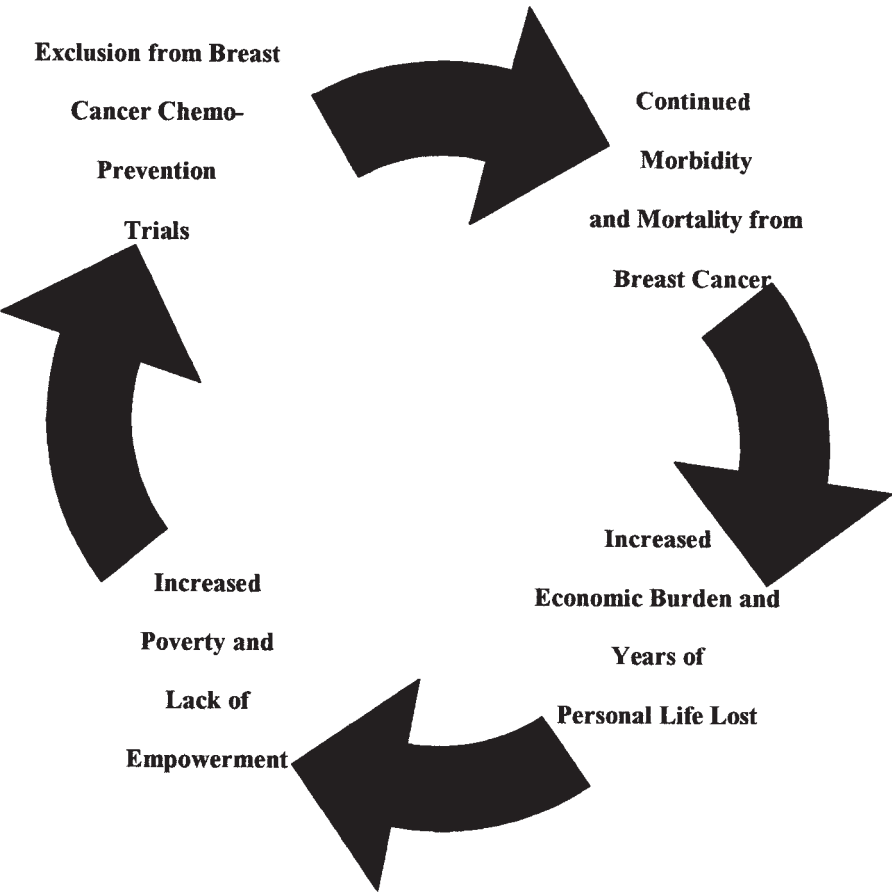


Fig 1. A schematic representation of the cycle associated with non-participation in breast cancer chemoprevention trials

minority race/ethnicity. Another advantage of the suggested approach is that future chemoprevention trials that may result from the findings of current adjuvant trials (for example, NSABP B-35) need not be repeated for underrepresented minorities since the IBIS-1 selection criteria can also be easily adopted. The long-term goals should include the development and conduct of prospective cohort studies with adequate numbers of women of minority race/ethnicity to provide much-needed information about risk factors for breast cancer and determinants of recurrence and mortality due to this disease in these women. Such data would provide adequate bases for the development of algorithms with high predictive accuracy for clinical decision-making in the care of these women.

SUMMARY

A concerted effort should be made to assess the health-seeking behavior of women of minority race/ethnicity with respect to the use of breast cancer chemoprevention therapy to determine potential modifiable factors for targeted

interventions that would enhance informed decisions about their health.

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## BREAST CANCER CHEMOPREVENTION IN ETHNIC MINORITIES - Cyrus-David

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### AUTHOR CONTRIBUTIONS

*Design and concept of study:* Cyrus-David

*Acquisition of data:* Cyrus-David

*Data analysis and interpretation:* Cyrus-David

*Manuscript draft:* Cyrus-David