Editorial

The National Surgical Adjuvant Breast Project (NSABP) Breast Cancer Prevention Trial Revisited[1]

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The challenges in evaluation of a cancer prevention intervention are multiple and significantly greater than the challenges in evaluating a treatment for malignancy. In treatment studies, benefit is the focus because the assumption is made that if benefit is demonstrated it must (or is very likely to) outweigh the usually serious and often lethal cost of no intervention. In prevention studies, however, benefit is a focus, but because only a small minority of study subjects will be affected, the total "costs" to the unbenefitted majority are much more important. The current status of estrogen replacement therapy as a public health intervention pointedly dramatizes the difficulties when costs are incompletely defined. Estrogen replacement therapy (alone, not combination therapy) is hypothesized to decrease risk of cardiovascular disease, demonstrably preserves bone density and prevents osteoporotic fractures, and has important symptomatic and psychological benefits for users. The incompletely defined risk for breast cancer, however, plays a major role in the limited long-term application of this preventive intervention. The lesson is that we must be concerned in prevention studies with defining comprehensively the costs as well as the benefits if we hope to reach the public health goals of decreasing incidence and/or mortality of serious diseases in the population.

An examination of the objectives and study participant profiles of the NSABP[3] P1 1 year after its beginning prompts the following questions. What is the likelihood that this study, as currently conducted, will answer as many questions as would be ideal? Will it allow attainment of an important public health goal, that of decreasing the incidence of breast cancer, should breast cancer prevention benefits from tamoxifen be demonstrated? Briefly, there are four stated objectives of NSABP P1: to assess in 16,000 women at risk for breast cancer whether long-term tamoxifen therapy (*a*) decreases the incidence of and mortality from invasive breast cancer; (*b*) reduces mortality from cardiovascular disease; (*c*) affects incidence of bone fractures; and (*d*) has significant toxicity and/or side effects. The protocol text, however, indicates that the focus of analysis and interim monitoring will be on breast cancer incidence and fatal and nonfatal myocardial infarction (1).

As of February 1, 1993, 44% of more than 6000 women entering the study were aged 35–49 years and the representation of members of higher socioeconomic groups was great.[4] In summary, approximately one-half of trial subjects are premenopausal at entry and a healthy volunteer effect is likely; *i.e.*, women entering the trial are likely to be healthier and therefore may have fewer adverse cardiovascular and bone events than women from the general population.

Postmenopausal Subjects: Rationale and Toxicities

The available data that provide the rationale for and predict the toxicity or costs of tamoxifen treatment are significantly different in quantity and quality for premenopausal and postmenopausal women. Consider first the situation for postmenopausal women where both rationale and data are compelling in providing support for the trial. While a rationale based on the suppression of contralateral second primary breast cancers in adjuvant tamoxifen trials is not ideal, it is nevertheless strong. The meta-analysis of 41 worldwide adjuvant tamoxifen trials in 31,000 women, mostly postmenopausal, with both short (1–2-year) and longer treatment times, has demonstrated a statistically significant 39% reduction in occurrence of contralateral breast cancers (2) and several individual trials have demonstrated benefits of similar magnitude (3). It has been suggested that tamoxifen given prior to development of clinical breast cancers may foster the appearance of more aggressive breast cancers with poorer prognoses (4, 5). While this may be true, the adjuvant tamoxifen therapy experience in women with both hormone receptor-positive and -negative primary tumors is reassuring: overall survival is clearly improved with tamoxifen (2). It is difficult to understand why this would not also be true if tamoxifen were given earlier in the natural history of the disease.

The data in postmenopausal women suggest that tamoxifen therapy benefits the cardiovascular and skeletal systems, those in which by far the most common causes of morbidity and mortality develop in older women. While not as comprehensive and extensive as might be ideal, these data are very supportive and reassuring. Our own randomized toxicity study, the Wisconsin Tamoxifen Study, has now developed data in subsets of postmenopausal women treated or not treated for 5 years. These show that the 2-year findings with respect to total and low density lipoprotein

Received 5/13/93; revised 6/28/93; accepted 6/28/93.

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[3] The abbreviations used are: NSABP P1, National Surgical Adjuvant Breast Project Breast Cancer Prevention Trial; CRC, Cancer Research Campaign.

[4] C. Redmond. Design and conduct of the NSABP Breast Cancer Prevention Trial. Presentation at the 17th Annual Meeting of The American Society of Preventive Oncology (ASPO), Tucson, AZ, March 20–23, 1993.

cholesterol (6), fibrinogen (7), and lumbar spine bone mineral density (8) are sustained at 5 years (9).[5] Total cholesterol was reduced by 12%, low density lipoprotein cholesterol was reduced by 20%, and fibrinogen was reduced by 15%, and lumbar spine bone mineral density was preserved and may increase, while in the absence of tamoxifen a decrease is seen. The meta-analysis data suggest a 25% reduction in odds of death from vascular causes (2), and retrospectively one trial has found a significant reduction in myocardial infarction in tamoxifen-treated subjects (10). Again, both of these latter observations apply mostly [meta-analysis (2)] or only to postmenopausal women (10).

Other possible benefits in postmenopausal women treated with tamoxifen are reductions in incidence of cancer of the ovary and hematopoietic malignancies (3). These merely suggested benefits are biologically plausible because of decreased gonadotropin and decreased growth factor levels seen with tamoxifen therapy in postmenopausal women (11, 12). The possible costs or serious toxic effects of tamoxifen that have evoked concern are pulmonary embolism, endometrial cancer, liver cancer, and eye changes. The liver cancer concern appears to have been overstated. Certainly any cancer caused by the intervention in a prevention study is serious, however, the threshold beyond which a hepatocellular cancer hormonal promoter such as tamoxifen acts may not be exceeded by this agent in humans (14, 15). The rarity of primary liver cancer and the observations to date suggest that if this ever occurs (*i.e.*, if tamoxifen causes liver cancer), it must be immeasurably rare (3). Some investigators have suggested that the appearance of lesions in the liver in women with breast cancer treated with tamoxifen has been accepted too frequently as evidence of metastatic breast cancer without evidence from a biopsy.

Endometrial cancer from tamoxifen is a biologically plausible and greater numerical concern (1, 3). In the NSABP protocol it has been suggested that the endometrial cancers that develop with tamoxifen treatment (which confers an increased relative risk of 2–3) are low stage and curable (1), but a recent retrospective study reached an opposite conclusion (15). Hysterectomy in as many as 40% of postmenopausal American women lessens the numerical concern.

Pulmonary embolism and death are serious concerns. The NSABP P1 protocol summarizes the NSABP B14 experience: 8 cases of pulmonary embolism with 2 deaths with tamoxifen; and 1 case of pulmonary embolism in the placebo group (1). The excess rate of pulmonary embolism is approximately 1/1000 women years in B14; a similar rate was reported in the Stockholm study (16). While it is not known with certainty that tamoxifen contributes to risk of thromboembolism (the excess rates in the forementioned studies are too low to be statistically significant), there is a consistent suggestion of an excess but low rate of this complication from these and other studies and from clinical experience.

Finally, lens changes, retinal opacities, and most significantly macular edema have been observed with the usual 20-mg doses of tamoxifen (17). The macular edema, which occurred in 4 of 63 women in this report, was reversible on cessation of the medication. An earlier cross-sectional study did not find an excess of significant ophthalmological changes in tamoxifen-treated women (18).

[5] R. R. Love, H. S. Barden, R. B. Mazess, *et al.*, unpublished data.

The study of tamoxifen in healthy postmenopausal women is adequately supported by current available data. The scientific benefits from the trial may be significantly increased with provisions for (*a*) further studies of intermediate endpoints, particularly cardiovascular (high density lipoprotein cholesterol, lipoprotein (a), blood pressure) and bone (femoral head) as ancillary studies; (*b*) specific toxicity and possibly risk-lowering studies of risk factors for pulmonary embolism, uterine changes, and ophthalmological changes; (*c*) with studies of recruitment strategies for women of all socioeconomic groups; (*d*) continuing careful monitoring of various relevant endpoints in B14; and (*e*) a clear commitment to provision of resources to ensure long-term follow-up of study participants.

The NSABP P1 trial in postmenopausal women should be supported if the study conduct is such that the four stated major objectives are likely to be addressed successfully. Given the current age and socioeconomic profile of study participants, objectives concerned with breast cancer mortality, cardiovascular mortality, and fractures may not be addressed at all. This point leads to the major concern about the entire trial and that is its inclusion of premenopausal women (19).

Premenopausal Subjects: Rationale and Toxicity

The rationale for the hypothesis that tamoxifen may suppress preclinical breast cancers is incomplete and weak in premenopausal women. As Kiang (20) has pointed out, questions of timing and duration of intervention may be more salient in younger women. In postmenopausal women the accepted position is that (late) preclinical lesions are treated in this "prevention" trial. The different pharmacology of tamoxifen in premenopausal women, however, offers significant challenges. In contrast to the absence of endogenous hormonal changes with tamoxifen therapy in postmenopausal women, in younger women total estrogens, estradiol, and progesterone blood levels increase significantly. In one of several studies which have documented these increases, peak levels of total estrogens of 3300 pg/ml and of estradiol of 1250 pg/ml have been measured in premenopausal subjects (21). In 2 of 8 carefully monitored women, estrogen levels in these ranges were measured, accompanied by steady state tamoxifen levels of 28 and 39 ng/ml (21). When MCF 7 cell xenografts are implanted under the skin of athymic mice, tumor growth is observed under similar conditions (22). The consequences of long-term ovarian stimulation and increased peak levels of estrogens and progesterone for breast and other tissues bear careful consideration (23).

Data on occurrence of contralateral breast cancers in premenopausal women are sparse. The recent updated meta-analysis of adjuvant tamoxifen trials does not specifically report on this subject (2). In NSABP B14 with 5 years continuous tamoxifen therapy in women with estrogen receptor-positive primary tumors, the most recent report is that 23 contralateral breast cancers have occurred in the women under 50 years of age treated with placebo, and 6 contralateral breast cancers have occurred in the tamoxifen-treated women; the corresponding numbers of contralateral breast cancers for women over 50 years of age are 24 in placebo-treated women and 20 in tamoxifen-treated women.[4] In the CRC trial, with 2 years of tamoxifen treatment in women with all types of primary breast cancers, the contralateral breast cancer incidence curves for premenopausal tamoxifen and control groups are superimposed for 4 years

Table 1 Ten thousand premenopausal women aged 35–49 years at increased risk for breast cancer; incidence and numbers of selected health events with and without tamoxifen with 5 years of treatment

	Incidence/ 10,000 women/year	Cases without tamoxifen	Cases with tamoxifen	Difference in cases (tamoxifen *vs.* no tamoxifen)
Benefits				
Invasive breast cancer[a]	35	175	117	58
Sudden death, fatal and nonfatal myocardial infarction	10	50	40	10
Total				68
Costs				
Pulmonary emboli[b]	1.4	7	57	50
Endometrial cancer[c]	3.6 (1.2)[d]	18 (6)[d]	45 (15)[d]	27 (9)[d]
Liver cancer[c]	<0.1	<1	3	2
Ovarian cancer[c]	3.6 (1.2)[d]	18 (16)[d]	45 (15)[d]	27 (9)[d]
Depression	20	100	200	100
Macular edema	2	10	100	90
Total				296 (260)[d]

[a] Relative risk with tamoxifen, 0.67.
[b] In NSABP B14, 1 woman in 1440 had a pulmonary embolism in 5 years (placebo) and 8 women in 1422 had a pulmonary embolism with tamoxifen.
[c] Surveillance, Epidemiology and End Results data 1984—1988 for women aged 40–44 years incidence/100,000 (31): endometrial cancer, 12.3; liver, 0.7: ovary, 11.6. By extrapolation from multiple primary cancer data the relative risk to women at high risk for breast cancer for uterine cancer is 3.0, and for ovarian cancer it is 3.0, and thus the expected incidence for these cancers in 10,000 high risk women is estimated to be 12.3 or 11.6 (the incidence/100,000) divided by 10 = 1.2 × 3.0 = 3.6/10,000 women (endometrial and ovarian cancers).
[d] Numbers in parentheses, numbers of cases expected assuming that the trial women (regardless of tamoxifen effects) are not at increased risk for malignancies of the endometrium or ovary.

after which there is an increase in these tumors in tamoxifen-treated subjects to total 50% more cancers for several years (24). In this trial there is a decrease in contralateral cancers in the postmenopausal subjects (24).

In the meta-analysis data there is a smaller effect of tamoxifen as adjuvant therapy in premenopausal than postmenopausal women (2). If the data and trends indicated above for B14 and the CRC trial (24) were both to be accepted as generalizable, then tamoxifen: (*a*) will not suppress preclinical breast cancer on average in premenopausal women likely to have unselected tumors of all hormonal receptor types (CRC trial); (*b*) will suppress preclinical cancers in premenopausal women with (a tendency to) hormone receptor-positive tumors (B14), but will have a weak effect in suppressing those tumors in similarly selected postmenopausal women, a conclusion from B14 data which is not consistent with the data from other trials; and (*c*) will be associated with increases in rates of clinical breast cancers in premenopausal women who are treated and then have the therapy stopped (CRC). In premenopausal women it seems premature to reach any conclusions about the efficacy of tamoxifen in suppressing contralateral breast cancers, and therefore, about the possible efficacy of tamoxifen in suppressing preclinical breast cancers generally.

The extent of tamoxifen toxicity data in premenopausal women is limited. The likelihoods and risks for major adverse health events in premenopausal women are lower and poorly defined. The preponderance of data on effects of tamoxifen on risk factors for cardiovascular disease is for postmenopausal women. High-quality, prospectively obtained and controlled data on lipids, lipoproteins, glucose metabolism, and blood pressure have not been reported. Furthermore, the important risk factors for cardiovascular disease in younger women are not sufficiently defined to allow interpretation of the available data. Good data on bone effects are also not available. One animal study suggests that the estrogenic bone-preserving effect of tamoxifen in castrated animals is not seen at all with normal levels of estrogens (25). The hormonal perturbations seen with tamoxifen in premenopausal women suggest that a different profile of long-term consequences to coagulation, and many organs and tissues might be seen in premenopausal compared with postmenopausal women. In summary, the long-term consequences of tamoxifen treatment in premenopausal women cannot be easily predicted from effects in postmenopausal women or from pharmacological data. Specific information is almost nonexistent.

The Risk (Costs) Benefit Balance for Tamoxifen in Premenopausal Healthy Women

In presenting the argument justifying the NSABP P1 trial the investigators developed an analysis of expected numbers of invasive breast cancers and myocardial infarctions prevented (benefits) and expected endometrial cancers, liver cancers, and pulmonary emboli deaths (costs) (1). By their analysis, under circumstances of 3 different participant populations (of different percentages of combined premenopausal and postmenopausal women), net benefits in cases would be expected to exceed net costs in cases by 46–93 of these events for 8000 tamoxifen-treated women in the trial (1).

The first and major question to be asked about the NSABP analysis concerns the justification for a combined analysis of premenopausal and postmenopausal women in light of the rationale and toxicity data summarized above. On the benefits side the entire case in suppressing premenopausal breast cancers is weaker. Furthermore, if only a premenopausal population is considered, the likely number of myocardial infarction cases prevented (particularly in the high socioeconomic status population currently entering the study) becomes very small. [This healthy volunteer effect for cardiac events was dramatically demonstrated in the Physician's Health Study (26).] Table 1 presents a benefits and costs analysis for an imaginary cohort of 10,000 premenopausal women, aged 35–49 years, at increased risk for breast cancer, treated for 5 years with tamoxifen (*i.e.*, high-risk women such as those entering the NSABP trial). (The size of

10,000 has been chosen to make review of the numbers easier for the reader.) This analysis differs from the NSABP analysis in concluding that the costs are very likely to exceed benefits in this population (net benefit cases, 68; net cost cases, 260–296). This analysis is similar to that of NSABP in that it:

1. Assumes a relative risk for breast cancer with tamoxifen treatment of 0.67;
2. Assumes benefit for major cardiovascular events (relative risk, 0.8); and
3. Concludes that the net costs of tamoxifen treatment in cases of endometrial and liver cancers are likely to be low. Increased risk of endometrial cancer from tamoxifen in premenopausal women is biologically plausible given increased levels of estrogens seen with this treatment (21), and fibroid tumor promotion has been observed with tamoxifen.

This analysis differs specifically from the NSABP analysis and thus leads to an opposite conclusion about premenopausal women in the following ways:

1. It considers both "life threatening" pulmonary emboli and pulmonary embolic deaths as important adverse case events (only deaths were considered in the NSABP analysis). As noted earlier in NSABP B14, there were 8 cases of pulmonary emboli with 2 deaths in 1422 tamoxifen-treated women in 5 years, while there was 1 case with 0 deaths in 1440 placebo subjects. A health condition with a 25% chance of causing immediate death is worthy of being counted as a "cost." Predisposing conditions for pulmonary emboli consequent to tamoxifen therapy are undefined and this complication occurs in both premenopausal and postmenopausal women.[6] There is no defined basis for arguing that the subjects in B14 are more likely to suffer this complication than are healthy women.
2. This analysis considers it likely that there will be an excess of ovarian epithelial cancers consequent to tamoxifen treatment. This effect, opposite to that hypothesized earlier for postmenopausal women, is biologically plausible based on the hypothesis that ovarian cancer is an epithelial disruption disease (23) and on observations that excess cyst formation occurs in premenopausal women treated with tamoxifen. A modest (2.5) level of increased risk has been assumed.
3. This analysis considers it likely that serious, life-altering depression will occur in 1% of women because of tamoxifen treatment. Hormonal change-precipitated depression is described in the postpartum period and with menopause, and reversible, temporally convincing tamoxifen-associated serious depression has been seen clinically (27). A recent retrospective study in axillary node-negative patients showed a 12% excess of depression in both premenopausal and postmenopausal breast cancer patients treated with tamoxifen; 4.5% of treated women stopped therapy (28).
4. This analysis considers it possible that drug induced macular edema or retinopathy will develop from tamoxifen in 1% of women (17). This is one-third the rate at which this complication developed from chloroquine, a similar retinal-affecting drug, in one study (29). In this study and in another case report in a younger individual progression of maculopathy was seen after cessation of the chloroquine (29, 30).

This analysis suggests that even if major breast cancer "prevention" benefits are assumed for premenopausal women, the costs are likely to be equivalent to or exceed these benefits; this re-emphasizes the need to define costs carefully. Refinements of this analysis considering how the case numbers might differ with healthy volunteers—without histories of thrombophlebitis, for example, and which include lag times before different adverse (or favorable) effects of tamoxifen might begin to be seen—would seem more appropriate when more data are available to put the entire analysis on firmer ground.

Some Conclusions

This review and analysis have suggested several activities and possible actions that should be carefully considered.

1. The appropriate review committees for the NSABP P1 trial should review the trial objectives and reconsider the appropriateness of continuing a study which addresses two significantly different populations. The projected benefits and costs of tamoxifen to these two populations are different both specifically and quantitatively, as well as in the degrees of confidence that characterize the projections. In these circumstances an analysis of mixed premenopausal and postmenopausal populations provides conclusions which are in fact applicable to neither population, at least quantitatively.
2. The critical roles and conduct of ancillary tamoxifen studies of toxic effects on cardiovascular risk factors, bone, eye, coagulation, and central nervous systems need to be reexamined. Additionally, treatment studies to minimize costs need to be developed.
3. Cessation of accrual of premenopausal women to NSABP P1 should be seriously considered. The 2600 women in this category already entered can be treated as a vanguard group and, together with the premenopausal women in NSABP B14, carefully studied to develop firmer data for a comprehensive analysis of benefits and costs. Justification of further accrual would depend on this analysis. Exposing more premenopausal women to both the risks of tamoxifen treatment as well as the possible risks on withdrawal of tamoxifen suggested by the CRC trial (24) cannot be justified based on currently available data. According to the analysis presented here, the overall risks are likely to significantly exceed the benefits.
4. A broad review of recruitment resources and plans should be initiated to address the need to include women of all socioeconomic and ethnic groups in this study.

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