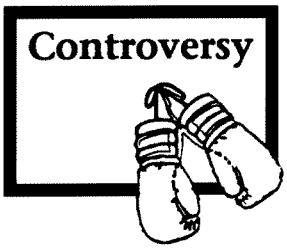

Tamoxifen: A caveat on the pro side of the debate

Virginia M Pressler MD*

Thank you for the opportunity to respond to Dr. Steven Moser's extensive letter-to-the-editor regarding the National Surgical Adjuvant Breast Project Breast Cancer Prevention Trial (NSABP Protocol P-1), also know as BCPT.

Dr. Moser's letter is obviously written out of concern for the safety of participants in this trial and his concerns are deserving of a response. The NSABP P-1 (BCPT) study has been under discussion and development since 1984. All of the concerns mentioned by Dr. Moser have been fully evaluated by the FDA, the National Institutes of Health (NIH), the NSABP and many other groups. At a recent congressional hearing, the Director of the NIH, Dr. Bernadine Healy, described this study as one of the most thoroughly reviewed protocols ever at the National Cancer Institute (NC1)[1].

Let me address each of Dr. Moser's individual concerns about this trial.

1. **Level of Risk of the Participants:** Contrary to the comment that premenopausal women eligible for this study "have a nil to slightly increased risk of breast cancer," women age 35 to 40 are required to have at least a 9-fold increased risk of breast cancer compared to a population of women without these risk factors before they can be considered for this trial. Most of these women are at an even higher than 9-fold increased risk, and many live in fear of dying from breast cancer. Most of these younger women have had at least 2 first-degree relatives (mother or sisters) diagnosed with breast cancer and some have seriously considered having bilateral prophylactic mastectomies in an attempt to prevent this dread disease. This is not a low-risk population and the fear of developing breast cancer is not a trivial concern in these young women's daily lives.

The NSABP already has randomized more than 5,200 women to tamoxifen or placebo in this trial as of December 1992. Only 4% of the women so far randomized have a risk of developing breast cancer equal to that of a 60-year-old woman. Over 70% of the women of all ages randomized to date have at least a 5-fold increased risk compared to that of a 60-year old woman and those who are premenopausal on the trial have much higher risks than this.

2. **Level of Reduction in Incidence of Contralateral Breast Cancers:** Contrary to Dr. Moser's claim that this effect may be overestimated, more recent publications than those referenced by Dr. Moser representing 41,000 woman-years of tamoxifen treatment unequivocally demonstrate tamoxifen's ability to reduce the incidence of recurrent ipsilateral and new contralateral breast cancer[2,3,4].

Furthermore, Peto's recent meta-analysis of all randomized studies demonstrated a 39% odds reduction in contralateral breast tumors in patients taking tamoxifen[4].

3. **Uterine Cancer Risk:** It is not surprising that tamoxifen might increase the risk of uterine cancer due to its estrogen-agonist effect. The BCPT consent form states:

> "An increased risk of uterine cancer has been reported with the use of tamoxifen. Existing data from several large controlled clinical trials using 20mg tamoxifen shows that 9 out of 3,097 women on tamoxifen developed uterine cancer (0.3%) versus 4 out of 3,091 women not treated with tamoxifen (0.1%)."

Seven randomized trials of tamoxifen all show the same relative rates of uterine cancer. It should be noted that 35% of the more than 5,000 women randomized so far on the BCPT have had hysterectomies. Thirty percent of the women under age 50 who are on the BCPT already have had hysterectomies for benign uterine changes. For those who haven't had hysterectomy, uterine cancer is rare under age 50.

All women on the study are required to have a complete pelvic exam before entry on the trial and at least annually thereafter. The patients and their gynecologists are advised to immediately evaluate any abnormal uterine bleeding and endometrial biopsies are recommended for irregular bleeding.

In the NSABP B-14 study, all of the uterine cancers that developed were diagnosed at Stage 0-I.

4. **Hepatic Cancer Risk:** The 2 liver cancers mentioned by Dr. Moser are the only 2 documented cases of liver cancer in the world in spite of 20 years of tamoxifen use in women with breast cancer. These 2 cases were from a Swedish trial using 40mg a day of tamoxifen (twice the currently used dose). Both of these cases occurred within 15 months of starting tamoxifen therapy. No other cases have been documented in spite of tracking thousands of women by the National Cancer Institute and the FDA.

Although liver cancers have been produced in rats given tamoxifen, this has not been reproducible in any other species. A recent paper by Mani and Kupfer[5] examining activation of tamoxifen to reactive metabolites in microsomes, implied that the human liver is apparently much less active than the livers of rats in activating tamoxifen to reactive intermediates.

A recent publication by Han and Liehr [6] cited by Dr. Moser describes the formation of covalent DNA adducts in Sprague-Dawley rat livers after high doses of tamoxifen. These adducts do not necessarily equate with DNA damage, which was not the subject of the investigation and no mutations were reported since

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rats were sacrificed 4 hours after 1 to 6 daily doses of tamoxifen (intraperitoneal tamoxifen 20mg/kg/day on days 1, 3, and 6). The significance of this phenomenon has been the subject of research by Liehr et al since 1985[7,8].

In several experimental animal systems, estrogen exposure previously has been observed to result in the formation of DNA adducts. A wide range of estrogens can participate in the process, including natural endogenous estrogens. Adduct formation occurs between DNA and an unknown estrogen-induced DNA reactive compound. The experimental process is observed in liver and kidney. The details and significance of the reaction process remain a research issue. It is thought that these adducts can be stripped from DNA by normal repair processes.

Two thousand women in 7 major adjuvant randomized clinical trials using 20mg of tamoxifen have an overall median follow-up of 80 months, extending as long as 135 months for some groups. There have been no reported cases of liver cancer. A small group of 43 patients at the University of Wisconsin continued receiving tamoxifen indefinitely following completion of adjuvant chemotherapy for early stage breast cancer. Follow-up currently exceeds 11 years with no reported cases of primary liver cancer[9].

Dr. Moser claims the tamoxifen breast cancer prevention trial does not call for specific liver function testing. This is not true. Liver function tests must be drawn on each patient before initiation of the trial and then at 3 months, 6 months, and then every 6 months for the duration of the study.

Dr. Richard Love at the University of Wisconsin has studied adverse effects of tamoxifen for many years and believes that "the much discussed possibility of human primary liver neoplasia consequent to long-term tamoxifen treatment does not deserve listing" as an adverse effect[10].

The potential risk of hepatic cancer is mentioned in the BCPT consent form and is discussed with every patient.

5. **Risk of Pregnancy:** All women on the trial are advised of the possibility of teratogenic risks of tamoxifen to the fetus. All women are told they must avoid

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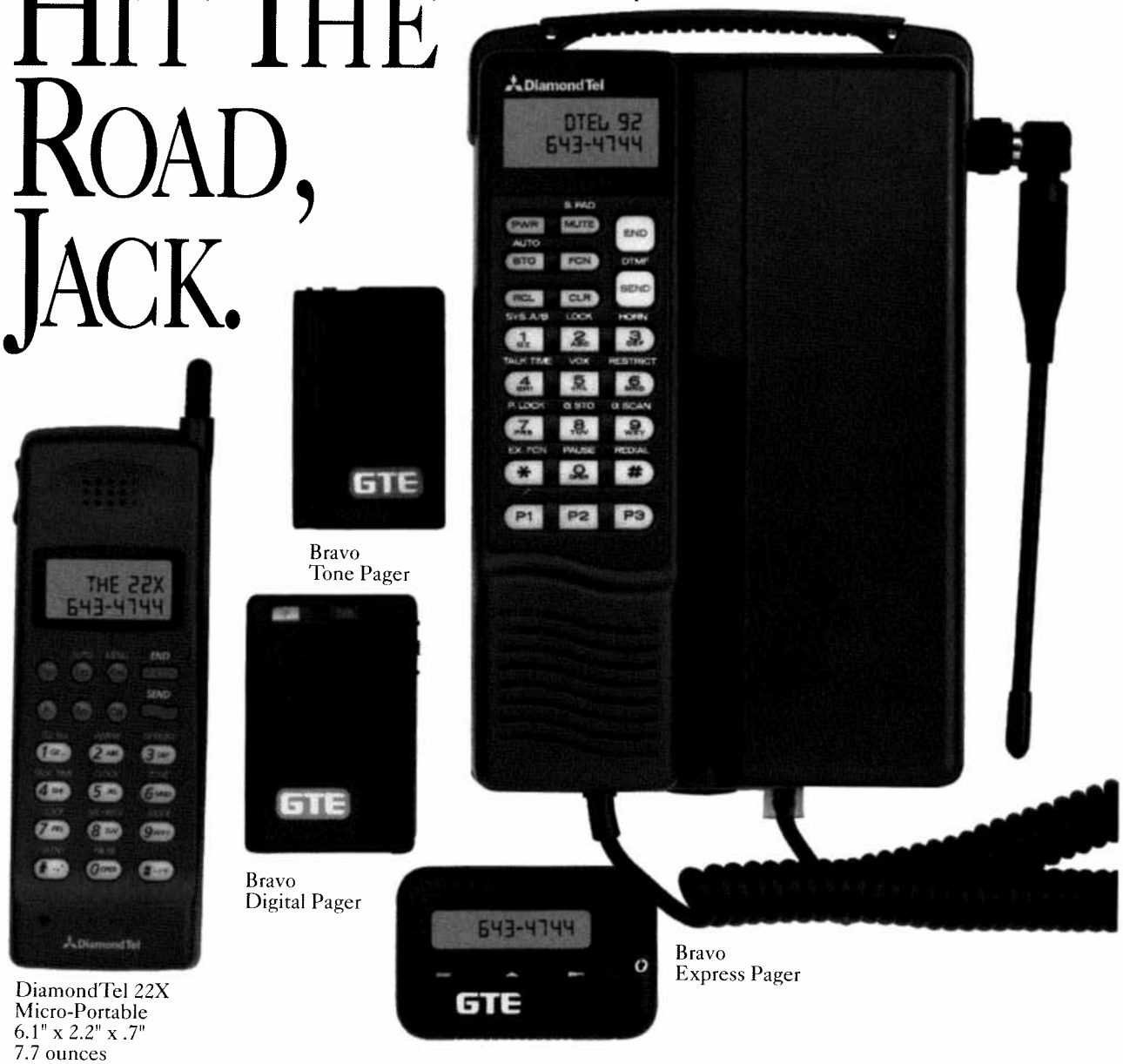
HIT THE ROAD, JACK.



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Beyond the call

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pregnancy. Furthermore, new policies will require that all premenopausal women who could become pregnant must either have a negative pregnancy test at the time of initiating the trial or start the trial during their menstrual period. They are advised that tamoxifen can increase fertility and that adequate barrier contraceptives must be used. Again, it should be noted that 30% of the premenopausal women in this study have already had hysterectomies.

If any woman should become pregnant while on the study, her medication will be immediately stopped and the code broken so that she will know if she was taking tamoxifen.

Premenopausal women have been denied participation in clinical trials for many years because they might become pregnant. If they are denied participation in this trial, we will never know whether or not tamoxifen may benefit this large group of women at risk for breast cancer. The National Cancer Institute agrees that to exclude premenopausal women is discriminatory. Furthermore, it is demeaning to assume they cannot responsibly avoid pregnancy when they have been advised of the risks.

NSABP B-14 data suggests that tamoxifen may actually be more effective in preventing second breast cancers in premenopausal than in postmenopausal women. Furthermore the risks of deep venous thrombosis and endometrial cancer as an adverse effect of tamoxifen are rare in premenopausal patients. It would be wrong to exclude these women from the opportunity to participate.

6. **Risk of Promoting Hormone-Independent Tumors:** The NSABP is aware of the data in rats showing development of rapidly growing hormone-independent tumors. In humans, we do not know if the breast cancers that are prevented are the hormone-dependent tumors, but we do know that multiple, large, randomized trials have shown benefit in disease-free survival and overall survival in patients with hormone receptor-negative, as well as hormone receptor-positive tumors, treated with tamoxifen. The role of tamoxifen in hormone-independent tumors currently is being evaluated in NSABP Protocol B-23 and other studies.

Dr. Moser also comments that tamoxifen may simply delay the onset of hormone-sensitive tumors. This does not seem to be the case since continued follow-up of disease-free survival and overall survival in patients with breast cancer treated with tamoxifen shows the curves to continue to widen over time, showing prolonged benefit of tamoxifen even many years after it has been discontinued.

7. **Thrombophlebitis and Ocular Toxicity:** Contrary to Dr. Moser's claim that these potential toxicities are not mentioned to patients, they both are included in the consent form.

Thrombophlebitis very clearly is described as an adverse effect of tamoxifen. Women with a prior history of deep venous thrombosis or embolism and women taking coumadin or heparin are not eligible for the study.

In the NSABP B-14 study, 3 of 1,414 women receiving placebo (0.2%) versus 18 of 1,403 women receiving tamoxifen (1.3%) developed deep venous thrombosis or embolism and 2 deaths occurred. This is clearly stated in the consent. Most of the thromboembolic events were in women over age 60 and most of the affected women had a history of thromboembolic problems. These women are excluded from this study. Also it should be noted that these data are from women who all had cancer and are known to be at increased risk of thrombosis.

Rare ocular side-effects have been reported in patients receiving tamoxifen for breast cancer. These usually consist of retinopathy with fine, white, refractile opacities located superficially in the retina and concentrated especially in the macular region. Cases of optic neuritis also have been reported[11].

Because of the rarity of the event, the true incidence of retinopathy has not yet been estimated accurately. The NSABP currently is planning a cross-sectional investigation of a subset of patients from protocol B-14 in order to determine the prevalence of retinal and other ocular toxicities associated with long-term, low-dose tamoxifen administration. As of August 1992, women with a history of macular degeneration of the retina are excluded from the BCPT. Tamoxifen is not known to accelerate pre-existing macular degeneration; however, the natural history of the disease is unpredictable.[11]

Participants are questioned on initiation of the study and at 3 months, 6 months, and then at six-month intervals regarding subtle visual changes. More than a simple ophthalmoscopic exam is necessary to identify this rare ocular toxicity and, therefore, would be prohibitive to screen in every participant. Participants who do note any visual changes are referred for ophthalmologic exam. In the meantime, the cross-sectional study of the subset of NSABP B-14 patients will be forthcoming to identify the true risk level.[11]

8. **Benefits of the Study:** What Dr. Moser fails to note in his letter is the potential beneficial impact of this study which far outweighs any potential risks. All medications have some side effects. Cholesterol-reducing drugs and aspirin are other examples of medications that are widely used to treat patients prophylactically to reduce their risk of disease. According to personal comunication by Dr. Leslie Ford of NCI, tamoxifen has been considered by the National Cancer Institute to be at least as safe as these drugs and as safe as routine vaccinations.

It is hoped that tamoxifen in this prevention trial will be shown to reduce the incidence of invasive breast cancer by at least 33% and the incidence of myocardial infarction by 20%. Studies also suggest that tamoxifen may delay or prevent bone density loss in postmenopausal women.

I personally know of physicians already prescribing tamoxifen to healthy women at increased risk of breast cancer outside of a clinical trial. This is the real risk, and if this practice becomes more prevalent, we will never know the true relative risks and benefits of tamoxifen. Only through a well-controlled prospective study such as the BCPT can we address the risks Dr. Moser is concerned about. Only through such a trial can we identify those groups of women who have the greatest net benefit from tamoxifen therapy.

The National Coalition for Cancer Research (NCCR) supports the BCPT and states "The NCCR believes" that the bad press about tamoxifen is "sensationalistic...and represents a disservice to the women of this country... There is ample scientific evidence to support the conduct of the study. Women deserve the right to choose whether or not to participate"[12].

Tamoxifen is a relatively safe medication that potentially could make an enormous impact in saving women's lives. No medication is without side effects but the safest way to determine the relative benefits and risks is through a well-designed, controlled, clinical trial. To exclude women under age 50 from this trial, or to prescribe tamoxifen off protocol, will eliminate the

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possibility of ever determining the real relative risks and benefits in this age group. These are the women who may have the most to gain in absolute reduction of incidence of breast cancer. The known risks are well explained in the consent. How can we *not* do this study? If we do not complete this study, women will be treated with tamoxifen empirically and the risks never will be really known. Also, they may not be followed as carefully as they are on the BCPT.

The facts speak for themselves, and it must be concluded that the tamoxifen breast cancer prevention trial is one of the most important, well designed and safest studies ever conducted.

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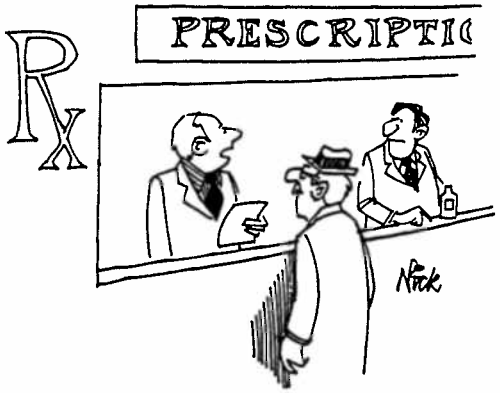

"Fred, do we have any [illegible] left?"