Re: Tamoxifen for the Prevention of Breast Cancer: Current Status of the National Surgical Adjuvant Breast and Bowel Project P-1 Study

We read with great interest the recent report of Fisher et al. (1) on the longer-term follow-up of the P-1 trial. This article underlines the importance of determining the effect of tamoxifen prophylaxis in the 5-year period following treatment. Unfortunately, interpretation of the data for P-1 is very difficult because the reduced difference in the breast cancer rates after treatment cessation appears to be due to a lower incidence of breast cancer in the control group in years 6 and 7 of follow-up [Fig. 3 of (1)]. An important question is whether this reduced incidence in control subjects is a result of tamoxifen use in the control subjects after unblinding or whether some other mechanism is involved, possibly related to increased dropout in the control subjects.

The Fisher et al. article raises the issue of the conditions under which prevention trials should be stopped prematurely. The authors make several references to the International Breast Cancer Intervention Study (IBIS) studies, particularly in relation to the early stopping of prevention trials. A more complete representation of our views on this issue has recently been published (2). We would like to emphasize that the reporting of statistically significant early results, which is an obligation to the patients in the trial, should not always entail enforced unblinding and early termination of the trial. In the IBIS-I trial, which was very similar to P-1, patients were informed of our early published results (3) and those of P-1 (4), but neither the Independent Data Monitoring Committee nor the Steering Committee felt that the results were sufficient to change clinical practice. Accordingly, the women were told these results, and blinded continuation was recommended by the Steering Committee after written re-consent. Because of the level of communication we maintained with the participants, all but a handful of women agreed to continue in their original trial arm, and the trial remains blinded at this stage, with excellent compliance. We plan an updated analysis of IBIS I next year, with an 8-year median follow-up, and at that time we will review again whether blinded continuation is recommended.

It has been suggested that such an open policy is not possible in the United States. However, the Anastrozole, Tamoxifen, Alone or in Combination (ATAC) trial also continued blinded despite positive initial results (5), and again unblinding has been rare even in the United States, where more than 2000 patients were entered in this trial.

The starting point for tamoxifen prevention trials was the Royal Marsden study, which commenced in 1986 under the direction of Trevor Powles (6), following a proposal of Cuzick et al. (7). We have yet to reach a definitive conclusion on its use for prevention.

In summary, we feel that early stopping for a successful outcome requires a clear indication of clinical benefit and that important information has been lost from P-1 because of its early termination. A new approach to early termination is needed in which data monitoring committees exercise judgment about clinical impact.

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REFERENCES


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RESPONSE

Cuzick et al. contend that it was inappropriate both to announce the results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) prevention trial (P-1) (1,2) and to unblind the participants. They argue that those actions make it difficult to interpret the data from P-1 and that important information has been lost. We disagree.

We question some key points in the authors’ comments. 1) They are uncertain about the reason for the lower incidence of breast cancer in the control group in years 6 and 7. We demonstrated in our update (2) that this finding was the result of the fact that about one-third of women in the placebo group had switched to tamoxifen, providing further evidence that tamoxifen is effective for chemoprevention of breast cancer. In any case, the speculation that another mechanism might have been involved is irrelevant because the rate of breast cancer in the tamoxifen group remained consistently low through 7 years of follow-up. 2) It is not surprising that the British International Breast Cancer Intervention Study (IBIS-I) prevention trial participants agreed to remain blinded in light of the fact that they had been told by their physicians that “neither the Independent Data Monitoring Committee (DMC) nor the Steering Committee felt that the results were sufficient to change clinical practice” and that “blinded continuation was recommended.” We could not tell our participants the same thing because our data indicated otherwise. 3) Although Cuzick et al. state that their “open policy (allowing participants to remain blinded) is not possible in the United States,” our policy of openness required us to inform women about our findings.
In every aspect of the planning, implementation, and reporting of the P-1 trial, which was conducted with intensive oversight, it was clear that reduction in the incidence of breast cancer was to be the primary endpoint of the study. Because definitive information about mortality was likely to take 15 to 20 years of follow-up, we considered it unrealistic to use mortality as the primary endpoint. The presence of breast cancer is a medical outcome in and of itself, not a surrogate endpoint for death from breast cancer. Only when the DMC had concluded, based on the data, that the primary endpoint of the trial—i.e., an almost 50% reduction in the risk of breast cancer ($P = .0000006$)—had been attained was it recommended that the findings be disclosed and the study be unblinded so that each woman who received placebo could decide for herself whether or not to take tamoxifen. That action was in keeping with what was in the consent form that each participant had signed before she entered the study.

The decision to unblind the P-1 trial was made judiciously. Unblinding of the participants was not recommended on the first occasion that the interim monitoring boundary was crossed. It was only after the boundary was crossed on three successive interim analyses over 2 years of monitoring that the DMC recommended such an action. At that time, there were sufficient data to provide an understanding of not only the effects of tamoxifen on invasive breast cancer but also of its effects on the other non–breast cancer-related benefits and risks of treating healthy women with the drug (3). Therefore, when the trial was unblinded, a spectrum of benefits and risks from tamoxifen was available to help women make informed decisions about using the drug to lower their risk. In view of these facts, we fail to comprehend why Cuzick et al. would imply that the P-1 DMC did not exercise good judgment.

The P-1 trial was a scientific inquiry aimed at testing the hypothesis that occult pathologic aberrations could be altered so that they failed to become clinically detectable. The evidence obtained via the scientific method that tamoxifen has important health benefits in many women at high risk for breast cancer established proof of that hypothesis.

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REFERENCES


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