Arbiter:

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In 1998 results became available from three randomised trials of tamoxifen versus placebo for the prevention of breast cancer [1–3]. At first glance, published results from these trials seemed contradictory. The results of the NSABP P-1 (National Surgical Adjuvant Breast and Bowel Project Prevention-1) study, first released in April of 1998 to investigators and to the public [4], showed that at a median follow-up of 69 months, 20 mg/day of tamoxifen given for up to 5 years, in women at a moderately increased risk of developing breast cancer, was associated with a reduction in the incidence of invasive breast cancer of 49% (two-sided $P < 0.00001$). Tamoxifen also reduced the risk of non-invasive cancers (ductal carcinoma *in situ*, DCIS and lobular carcinoma *in situ*, LCIS) by approximately the same amount (50% ($P < 0.002$)). This risk reduction was seen in women of all ages, and in those with a family history of breast cancer as their only risk factor, as well as in those with a history of LCIS, or ductal or lobular atypical hyperplasia. Somewhat surprisingly, the subsequently published Italian and British studies [2,3] did not show any such reduction. Aside from a significantly reduced incidence within a subset [those receiving hormone replacement therapy (HRT)], the Italian study showed virtually no risk reduction. The British study showed almost no difference between the two treatment groups overall, or within any subset. Whilst the populations studied in the British and Italian trials were somewhat different than those studied in the North American trial (women in the British and Italian trials were allowed to take HRT whilst on study, women in the Italian trial were at considerably lower risk of developing breast cancer, women in the British trial were selected almost entirely on the basis of family history, etc.), almost certainly, the lack of significant benefit seen in the British and Italian trials related to the much lower number of events seen in those studies [5]. The consistency of the results across the NSABP P-1 study, as well as their remarkable concordance with the effects seen on the development of contralateral breast cancer in the Early Breast Cancer Trialists Collaborative Group (EBCTCG) [6] meta-analysis of randomised trials of adjuvant tamoxifen, suggest that the results quoted in P-1 are indeed accurate and reliable. Thus, it seems clear: tamoxifen given for 5 years in this population of women will result in an approximately 50% reduction in the incidence of breast cancer, at least over a 5–6-year follow-up period.

But was the NSABP P-1 trial stopped too soon? The NSABP P-1 study was designed to detect a decrease in the incidence of invasive breast cancer. An independent data monitoring committee was in place, as designed by the NSABP in conjunction with their funding, ethical and regulatory bodies, and was actively reviewing data as it accrued. A set of stopping rules had been prospectively established, and were used to disclose the findings of the trial, as had been planned. Thus, according to its design, the trial was not "closed prematurely". "But", critics ask, "was the original study design optimal or should the study have been planned to detect a survival difference?" With close monitoring and presumably relatively early detection of breast cancers in both arms of the study, and considering the long natural history of breast cancer and the increasingly effective therapies in the adjuvant and metastatic setting, women might have been followed for many years before any survival difference was detected. In the meantime, had the effects on incidence not been disclosed, no patient or physician could have taken clinical advantage of this information, nor have used this information for subsequent study planning. As B. Fisher himself recently commented "In every clinical trial with a positive result, there eventually arises a conflict between the need to know and the need to know more". Thus, although one might have wished to leave the P-1 trial blinded longer in order to obtain more information, it seems that the study was unblinded according to its original design, and that the design was a reasonable one. Unfortunately, however, women and their physicians are left without results concerning all of the outcome measures one would like to have assessed. Interestingly, the situation is similar to that in the mid-1970s, when it had been clearly demonstrated that chemotherapy in the adjuvant setting delayed recurrence, but it was not yet so clear that it prolonged overall survival. That 'half result' was due mainly to the small size and hence relative underpowering of most studies carried out at that time. Survival outcome was clearly demonstrated when the techniques of meta-analysis were applied to all of the available results [7]. At present, however, there are not enough events related to overall survival in all of the prevention studies combined to provide these sort of data.

And so, in the meantime, what can we learn from further follow-up of the studies that have already been

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completed? In the unblinded studies, even though many patients have discontinued their assigned therapies, further follow-up to assess whether the effects of tamoxifen persist, in the case of the P-1 study, or become more apparent, in the case of the Italian or British studies will be important. When one carefully examines the effects on the incidence of contralateral breast cancer seen in the EBCTCG meta-analysis of adjuvant tamoxifen studies, it is apparent that the 'preventive' effects of tamoxifen in that setting persist beyond 5 years, out to 10 and 15 years of follow-up. It will be crucial to see whether this effect is duplicated in trials such as the NSABP P-1. It would seem likely that this will be the case.

But, will further follow-up of the already unblinded trials teach us more about survival related to the use of tamoxifen as a preventive? It is possible that the reduced incidence of breast cancer seen to date in a trial such as NSABP P-1 could result in survival differences, as women in this study are followed over future years, but because there is little effect, at least as yet, on the incidence of breast cancer in the British or Italian trials, it seems unlikely that these will contribute to any positive survival effect. Here, as in confirming the effects on breast cancer incidence, the results of ongoing, as yet unblinded, studies such as the International Breast Cancer Intervention Study (IBIS) remain crucial. Those studies should be continued. Of course, the EBCTCG Overview cannot provide survival data specifically relevant to tamoxifen use as a preventive, since all women in these trials have had a previous breast cancer, and are therefore at considerably greater risk of death from the original breast cancer than from any new breast cancer which might arise.

We also need additional data, which can perhaps be drawn from the NSABP P-1 study, on the specific effects of tamoxifen on women carrying *BRCA1* and *2* mutations. Data from the British study suggest that women selected totally on the basis of family history, a population which may contain a higher proportion of women with *BRCA1* and *2* mutations, may not benefit from tamoxifen, but as discussed earlier, the negative effects in this study may also relate to the smaller number of events seen. Investigators are now looking at genetic data from women in the P-1 study, as well as in other trials, to determine whether tamoxifen reduces the incidence of breast cancer in the specific population of women carrying these mutations.

It is of interest that 18 months after the original publication [4] of data showing that tamoxifen reduces the incidence of breast cancer, the use of tamoxifen as a preventive is still relatively limited in Europe, and in North America. The reasons for this are unclear. Certainly many women and their physicians have an intuitive resistance to the concept of the long-term administration of any pill in a population of healthy women. Both also remain concerned about the known adverse effects of tamoxifen, as well as other possible long-term adverse effects, which may not, as yet, be clearly delineated. It is known that tamoxifen in the P-1 study was associated with an increased incidence of thromboembolic disease and of endometrial cancer. A possible increase in cerebrovascular disease has also been described. Moreover, it is difficult to place the use of tamoxifen to reduce the incidence of breast cancer in the setting of other lifestyle and health risk affecting manoeuvres. For example, should a 60-year-old woman with no other risk factors for breast cancer continue her oestrogen/hormone replacement therapy (ERT/HRT) or switch to tamoxifen? Should she take both? If she has concerns about osteoporosis, should she take tamoxifen and a bisphosphonate, or raloxifene, or simply stick to 'natural' measures such as diet and exercise and perhaps some calcium and vitamin D? Results from the Women's Health Initiative will eventually provide randomised data comparing cardiovascular, breast cancer and bone outcomes in women randomised to receive or not receive ERT/HRT, but the once proposed third arm in which tamoxifen would be given was never instituted in that study. Thus, long-term comparisons concerning this broad variety of health outcomes in women randomised to receive tamoxifen, oestrogen, or both given together, are unlikely to become available in the near future.

In the meantime, it seems clear that for women at increased risk of breast cancer, tamoxifen can reduce the incidence of this disease, at least over a 5–6-year follow-up period and at the cost of a moderately increased risk of deep-vein thrombosis (DVT), pulmonary emboli and endometrial cancer. However, the long-term effects of tamoxifen on survival in relation to breast cancer and/or to other disease outcomes remain unclear. Perhaps, more to the point, the relative placement of tamoxifen as a health improving manoeuvre in comparison, in particular, to ERT/HRT remains to be established. Thus, women and their physicians must continue to make decisions regarding the use of tamoxifen for breast cancer risk reduction on the basis of incomplete information until the results of ongoing and future trials become available.

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