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Tamoxifen for the prevention of breast cancer

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In 1991, my National Surgical Adjuvant Breast and Bowel Project (NSABP) colleagues and I concluded that enough biological and clinical data were available to provide justification for conducting a clinical trial to evaluate the worth of tamoxifen for the prevention of invasive breast cancer in women at increased risk for that disease. Tamoxifen had been proven to be of value in treating advanced breast cancer [1,2] as well as stage I and II diseases [3,4]; it reduced the incidence of contralateral breast cancer [4–6] and interfered with the initiation, promotion and growth of tumours in experimental systems [7]; and it could be used in most patients with good compliance and few side-effects.

Our trial was based upon biostatistical and epidemiological considerations related to (1) each woman's estimated risk of breast cancer, which was determined before her enrolment in the study; (2) the estimated frequency of undesirable side-effects that women might experience from tamoxifen; (3) assessment of study benefits versus risks; (4) sample-size estimates; (5) interim end-point analyses; and (6) rules for stopping the study. In order to limit confounding factors that might influence the study findings, strict eligibility and ineligibility requirements were established. Women were considered to be at increased risk if they were 60 years of age or older, were 35–59 years of age and had a 5-year predicted risk for breast cancer of at least 1.66%, i.e. that of a 60-year-old woman free of other risk factors, or if they had a history of lobular carcinoma *in situ* (LCIS). An algorithm based on a multivariate logistic regression model that employed a combination of risk factors was used to estimate, for each participant, the probability (risk) of the occurrence of breast cancer over time [8]. The variables included in this model were age, number of first-degree relatives with breast cancer, nulliparity or age at first live birth, number of breast biopsies, history of a pathological diagnosis of atypical hyperplasia and age at menarche. The reader is referred to previous reports for additional information about the design and implementation of the trial, conditions for participant eligibility, breast cancer risk assessment, risk–benefit estimates, statistical methods, secondary aims, and the study findings [9,10].

In the NSABP breast cancer prevention trial (P-1), appropriate methodology was used to obtain data that could either support or reject the hypothesis that was being tested. Thus, the study should be viewed as more than merely a 'test' of tamoxifen or an estimate of the extent of certain putative undesirable side-effects of the drug. The role that science played in the conduct of the study and the clinical significance of the findings were often obscured by the political and social issues and unwarranted criticisms that plagued the trial before and after 3 July 1991, when the United States Food and Drug Administration (FDA) granted us permission to proceed with it. None the less, it was the credibility of the scientific process employed in its conduct that permitted the P-1 study to be completed despite the adverse reaction to it. For that reason, until critics can provide sound scientific justification (in the form of credible data from another study with boundaries similar to those that governed the P-1 trial) for challenging either the appropriateness of the scientific process used to

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obtain the results or the credibility of the data themselves, the P-1 findings must stand on their own merit. In this commentary, I will reiterate my response to several of the points of contention that have been raised with regard to that study [11]. Before doing so, however, I will present a brief overview of the P-1 findings [9].

Between 1 June 1992 and 30 September 1997, 13 388 women in P-1 were randomly assigned to receive either placebo or tamoxifen (20 mg/day) for 5 years. The effect from tamoxifen was consistent among various cohorts of the population, as is demonstrated by the rates of invasive cancer that occurred among the several subgroups evaluated. When age, history of LCIS, history of atypical hyperplasia, and levels of predicted risk of breast cancer were taken into consideration, tamoxifen was found to be effective in preventing breast cancer in all subgroups. Tamoxifen reduced the overall risk of invasive cancer by 49% (two-sided $P < 0.00001$). The cumulative incidence of invasive cancer throughout 69 months of follow-up was 43.4 versus 22.0 per 1000 women in the placebo and tamoxifen groups, respectively. The decreased risk occurred in women in all age groups and was 44% in women aged 49 years or younger, 51% in those aged 50–59 years, and 55% in women aged 60 years or older. Tamoxifen also reduced the risk of non-invasive cancer, i.e. ductal carcinoma *in situ* (DCIS) and LCIS, by 50% ($P < 0.002$). Particularly important was the observation that the drug reduced the incidence of oestrogen receptor (ER)-positive invasive tumours by 69%. There was, however, neither an increase nor a decrease in the incidence of oestrogen receptor-negative tumours amongst women in either the tamoxifen or placebo groups. In women with a history of LCIS or ductal or lobular atypical hyperplasia — lesions most often found to be ER-positive — the risk of invasive cancer after removal of such lesions was reduced by 56% and 86%, respectively. The risk was also reduced in women within any category of risk. In women with a risk of $\leqslant 2.00\%$, the reduction was 63%; it was 66% in those who had a risk of $\geqslant 5.0\%$. During each of the first 6 years of follow-up, tamoxifen administration resulted in a significant reduction in the risk of invasive cancer; the rates of decrease in years 1 to 6 were 35, 55, 39, 49, 69 and 55%, respectively. Those data, together with the finding that tamoxifen also resulted in a significant reduction in the rate of non-invasive breast cancer in P-1 study participants, prompted an appraisal of the magnitude of the adverse effects from tamoxifen with regard to decision-making about whether the benefit from the drug exceeded its undesirable side-effects to an extent that would warrant its use outside as well as within the clinical trial setting. The P-1 findings have failed to support concerns about quality-of-life issues and about the dangers of liver damage, hepatoma, colon cancer and retinal toxicity from tamoxifen administration. A disproportionate number of events occurred only in the breast and uterus (endometrium) in either the placebo or tamoxifen groups of P-1. No liver cancers were observed in either group, and there has been no increase in colon, rectal, ovarian or other genitourinary tumours. The excess risk of endometrial cancer and of vascular-related events observed in the tamoxifen group, as compared with those in the placebo group, has given rise to the most concern, expressed mainly by critics of the study. In P-1, approximately 7 of 1000 women, or less than one woman per 100 (0.7%), in the tamoxifen group developed endometrial cancer over a 5-year period. Of clinical significance were the findings that all invasive endometrial cancers were stage 1 and that no deaths from endometrial cancer were reported. When the undesirable vascular events attributable to tamoxifen were evaluated, the findings showed that, over a 5-year period, 0.2–0.3% of women experienced a stroke, approximately 0.2% had a pulmonary embolism, and between 0.2 and 0.3% exhibited deep-vein thrombosis. Those events occurred less frequently in women $\leqslant 49$ years of age but were somewhat more frequent in women aged $\geqslant 50$ years. In the latter group, the rate of endometrial cancer was approximately 1% over 5 years; for each of the vascular-related events, it was less than 1%. Because women who had had a hysterectomy were not at risk for endometrial cancer, the major undesirable side-effects in that population consisted only of vascular-related events, the rate of which was similar to those that occurred in women who had not had a hysterectomy. When participants were evaluated with regard to undesirable events from tamoxifen that could have an effect on their quality of life, the only differences noted between the placebo and tamoxifen groups were related to hot flushes and vaginal discharge. 12% more women in the tamoxifen group experienced some degree of hot flushes and 20% reported vaginal discharge. Of those women having hot flushes, only approximately 8% more women in the tamoxifen group than in the placebo group reported that their hot flushes were extremely bothersome; about 2% described their vaginal discharge in the same manner.

In view of the impressive benefits and low rates of adverse events experienced by women in the tamoxifen group, it is reasonable to consider the way in which the benefits and risks associated with the drug are related to each other. From a clinical perspective [9], it is inappropriate to make a decision about the net worth of tamoxifen by simply 'trading' one event for another, i.e. by subtracting one undesirable event from one cancer prevented. Although the net benefit from tamoxifen may be quantified statistically, clinical consideration must also be included in any risk–benefit determination.

The P-1 findings led us to conclude that certain women should take tamoxifen to decrease their risk of developing breast cancer. Women younger than 50

years of age who meet the entry requirements for P-1 are likely to be considered eligible because their risk of experiencing an adverse event is practically nil and because their risk of breast cancer would be reduced by almost 50%. Women of any age who have had a hysterectomy are also favourable candidates for taking tamoxifen if they meet the P-1 eligibility requirements. Women with a history of LCIS, DCIS and atypical hyperplasia should be considered in view of their increased risk of developing invasive breast cancer. Although information is not yet available to indicate with certainty whether women at increased risk because of *BRCA1* and *BRCA2* mutations should be considered candidates for tamoxifen, it would be prudent to offer them that option, particularly if they are contemplating bilateral mastectomy. The issue of whether women 50 years of age or older who have stopped menstruating, have not had a hysterectomy, and have no history of LCIS, DCIS or atypical hyperplasia should receive tamoxifen is less clear. The higher their risk for breast cancer, the less controversial the issue, as the greater the likelihood that the mortality and morbidity associated with breast cancer that might have been prevented by tamoxifen would exceed that resulting from the adverse events associated with the drug. The precise level of risk above and below which such women should be considered candidates for tamoxifen is likely to be difficult to determine.

Some individuals have expressed concern about the use of tamoxifen in women 50 years of age or older because of the increased incidence of side-effects in that group. Two situations occurred subsequent to publication of the P-1 findings that have made that concern less of an issue. The findings with regard to the side-effects observed in all age groups in P-1 were insufficiently significant to justify this concern. When the P-1 findings were made known, the data monitoring committee decided to unblind the study so that women who had been randomly assigned to placebo, regardless of their age, could justifiably receive tamoxifen. In addition to the actions of the data monitoring committee, the approval and funding by the National Cancer Institute (NCI) of the NSABP P-2 trial comparing tamoxifen with the selective oestrogen-receptor modulator (SERM) raloxifene indicates the acceptance of the use of tamoxifen in women 50 years of age or older. Moreover, the NCI's decision that the tamoxifen group should serve as the control, or standard, against which raloxifene will be compared in P-2 tacitly acknowledges that the use of tamoxifen is appropriate in that age group. Also, there has been no modification with regard to the use of tamoxifen in women aged 50 years or older in the British International Breast Cancer Intervention Study (IBIS) trial, which is currently evaluating the worth of the drug for breast cancer prevention. Thus, there seems to be substantial justification for administering tamoxifen to women in this age group who are at sufficiently increased risk for breast cancer and who meet the eligibility requirements for P-1.

Another set of concerns related to the P-1 study arose as a result of widely promulgated opinions that were detrimental to the way in which the study was received by physicians and the public. One such issue was related to the idea that the P-1 study had been terminated prematurely and that the findings were reported too early. That criticism has no basis in fact. The trial was stopped only when an independent monitoring committee charged with its oversight had concluded that the primary hypothesis being evaluated, i.e. that tamoxifen had decreased the incidence rate of invasive breast cancer ($P < 0.00001$) and that additional follow-up time would not result in improved estimates of treatment effects, had been confirmed beyond a reasonable doubt. The action of the data monitoring committee was based on stopping rules that had been established before the onset of the study, a procedure used in the conduct of most clinical trials. In view of the magnitude of benefit observed, it was considered that there was an ethical imperative for prompt disclosure of the findings, which did take place, particularly with regard to affording women who received placebo the opportunity to either take tamoxifen or to participate in the P-2 trial. When positive (or negative) findings occur in a clinical investigation, there may arise a tension between the "need to know" and the "need to know more". Obviously, keeping a control group intact has its virtues, as it allows for a more precise estimation of the effects of a longer follow-up time. However, to withhold information, such as that obtained in the P-1 study, for an additional 5–10 years to determine if survival differences occur is both unrealistic and unethical. Consequently, to deprecate the findings of P-1 because a survival difference has, as yet, not been demonstrated is inappropriate. In treatment trials conducted by the NSABP, the benefit in disease-free survival, survival, and the decrease in contralateral breast cancer resulting from the use of tamoxifen has been shown to persist beyond 10 years [12]. Although these issues cannot be resolved immediately, they do not diminish the significance of the P-1 findings themselves. Despite the uncertainties generated by the outcome of that study, the findings justify following a new pathway of investigation that addresses the ambiguities that have been created.

Another issue that resulted in criticism of the P-1 study arose as a consequence of findings reported from two European prevention trials [13,14], both of which failed to verify the findings from P-1. The simultaneous reports of those trials resulted in a misunderstanding amongst the public, the media and physicians, who failed to realise that the three studies were too dissimilar in design, population enrolled and other aspects to permit making valid comparisons between them. Although

an effort has been made to attempt to explain the reasons for the differences in the three studies, any conclusions reached in that regard must be viewed as speculative [15,16]. The findings from each of the trials relate to the boundaries of each being defined a priori and to how those boundaries were adhered to during the conduct of each study. Consequently, because the boundaries differed in many respects, to view the results of the two European studies as being "apparently contradictory" [17] to those of P-1 and to contend that the findings from one study either confirmed or rejected the findings of another is inappropriate. There were many differences between the studies; fewer breast cancer events occurred in the British and Italian studies than in P-1; the criteria for selecting participants were different in the three trials; study participants had different risks for breast cancer; there were some differences in protocol compliance amongst the trials; hormone replacement therapy was used in the two European studies but not in P-1. Thus, the judgement that the two European studies failed to confirm the P-1 study is unwarranted in light of the fact that, in actuality, there were too many differences for their comparison to be valid.

Just as occurred in the 1970s after the first reports of a benefit from the use of adjuvant chemotherapy for the treatment of breast cancer, it can be expected that a multitude of breast cancer prevention trials will be implemented in the near future. Those studies will, undoubtedly, elaborate upon the P-1 findings and will address many of the questions that have arisen from them. Women who meet the eligibility criteria outlined in the P-1 study must be encouraged to participate in the new trials. Despite the many unanswered questions that exist, women who do not participate in those studies but who meet the eligibility criteria of P-1 should be given the opportunity to reduce their risk of developing invasive breast cancer by taking tamoxifen. To withhold the drug from these women until it is known whether or not raloxifene, or another SERM, is more effective and/or is associated with fewer undesirable side-effects is to deny them that chance. Moreover, since thousands of women with invasive breast cancer die each year, despite receiving 'effective' treatments, we cannot afford to deny those women at increased risk for the disease who qualify for tamoxifen, a preventive agent of demonstrated efficacy, the opportunity of receiving the drug.

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