Commentary

Breast cancer prevention

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The concept of using tamoxifen to prevent breast cancer is a good one. Experimental evidence [1] shows that this drug prevents the development of experimental oestrogen-dependent mammary tumours, and there is now clear evidence [2] that it will reduce the incidence of contralateral breast cancers by about 50%.

In 1986 we started a feasibility trial at the Royal Marsden Hospital to determine whether it is possible to use such an intervention in healthy women to prevent breast cancer. At that time, only women at high risk because of a strong family history could be considered eligible for such a trial. By 1989 we had clearly shown that tamoxifen had very selective anti-oestrogenic activity that conferred safety factors for cardiovascular disease and bone [3], which justified the start of multicentre trials. In 1992 the National Surgical Adjuvant Breast and Bowel Project (NSABP) started such at trial (P-1) in the USA, and a similar trial was started in Milan that was followed in 1993 by the UK International Breast Cancer Intervention Study (IBIS).

Following the publication of the results of an interim analysis of the NSABP P-1 trial [4], which showed a 49% reduction in the incidence of breast cancer, there has been much debate about the possible use of tamoxifen in healthy women. The debate has not been about the validity of these results, but rather about the magnitude of the overall clinical benefit from this observed reduction. This is especially important because the long-term effect on incidence and the overall health benefit from using tamoxifen in healthy women is not known at present. Furthermore, there is the possibility that significant groups of women at risk may not gain benefit and may even be harmed by tamoxifen.

There is no doubt that the result of the interim analysis of the P-1 trial showed a clear-cut, very significant ($P < 0.00001$) 49% reduction in the incidence of breast cancer over the 4 years of follow up in the 6681 women who were randomised to tamoxifen 20 mg/day compared with the 6707 women who were randomized to placebo [4]. The inclusion criteria for the P-1 trial was based on the model of risk of Gail *et al* [5], indicating a 5-year absolute risk of 1.66% or greater, or a previous history of lobular carcinoma *in situ* (LCIS). All categories of risk within the Gail model based on age, previous benign histology and family history of breast cancer appeared to gain benefit. Participants who had had previous benign histology with atypical hyperplasia appeared to gain most benefit (relative risk 0.14, LCIS relative risk 0.44). This means that the remaining group of participants defined by the Gail model (without atypical histology or LCIS) had a reduction in early incidence of breast cancer of only about 40%.

Concerns about the application of the benefits of tamoxifen from the P-1 results to all healthy women arose from the publication of the interim results of two smaller tamoxifen breast cancer chemoprevention trials (the Royal Marsden trial and the Italian trial) in healthy women [6,7]. Both of these trials showed no effect of tamoxifen on breast cancer incidence. Although the statistical powers of these trials were substantially less than that of the P-1 trial [4], it is unlikely that lack of power, low compliance or use of hormone replacement therapy contributed significantly to these negative results. This raised the possibility that the different population characteristics of the participants in the three trials could contribute to these different results [8]. In the Italian trial about 40% of the participants had had oophorectomy, which could have compromised

IBIS = International Breast Cancer Intervention Study; LCIS = lobular carcinoma *in situ*; MORE = Multiple Outcomes of Raloxifene Evaluation; NSABP = National Surgical Adjuvant Breast and Bowel Project; STAR = Study of Tamoxifen and Raloxifene.

any subsequent tamoxifen effect. In the Royal Marsden trial participants were more likely to have inherited a high-risk breast cancer gene that could predispose to tamoxifen resistance. These negative results could therefore indicate that there may be subgroups of healthy women who may be resistant to tamoxifen chemoprevention.

The encouraging results from the interim analysis of the P-1 trial [4] required that the trial should be stopped and unblinded before completion of the planned follow up. This meant that further follow up of P-1 to establish the longer term effect of tamoxifen on breast cancer incidence and mortality would not be possible. This is unfortunate, because the effects of tamoxifen may vary at different stages in breast cancer tumourigenesis. In the early development of breast cancer, tamoxifen could permanently disrupt the carcinogenic process and give rise to long-term prevention. Later in the natural history of the disease, before the clinical appearance of the cancer, tamoxifen may only treat occult but established cancers. This would reduce the early incidence of breast cancer, but may give rise to only temporary remissions. The later that tamoxifen is given before the presentation of clinical cancer, the less likely it is that it will be permanently effective. At this time it is not possible to extrapolate from the early incidence data from P-1 to the probable long-term effects of tamoxifen on breast cancer incidence in healthy women. This will only become possible from the long-term continued follow up of European trials such as IBIS, which has now enrolled over 7000 healthy women.

Another major concern about the P-1 results [4] relates to the assessment of overall clinical benefit from the reported reduction in early incidence of breast cancer. Of the 13 388 women in the P-1 trial there were 86 fewer patients who developed invasive breast cancers on tamoxifen compared with placebo, together with 26 fewer patients who developed 'osteoporotic' fractures. Rather surprisingly, no reduction was observed in the number of myocardial infarctions. As anticipated there were 21 extra endometrial cancers, 14 extra strokes, 12 extra pulmonary emboli, 13 extra deep vein thromboses, and 67 extra patients with cataracts.

It is clearly difficult to balance the relative gain and loss from these beneficial and harmful effects of tamoxifen at this time, and even more difficult to predict how these rates of clinical benefit and harm may change with longer follow up. This is particularly important because there is no evidence of a reduction in breast cancer mortality for women on tamoxifen. The 86 fewer breast cancers were all oestrogen-receptor positive, were mostly less than 2 cm in diameter, and were mostly axillary node negative, indicating an 80–90% curability. Therefore, the question of whether it would have been better to treat 86 extra patients with good prognosis breast cancer rather than 6466 healthy women remains unanswered.

Nonetheless, the P-1 results [4] are very encouraging, indicating that there is a real possibility that tamoxifen will prevent the long-term incidence of breast cancer, and that this will give rise to long-term overall clinical benefit that will justify its use in large numbers of healthy women. Clearly, the lack of data on breast cancer mortality, with no evidence of overall treatment benefit, and no adequate explanation for the negative Royal Marsden and Italian trials leave many questions unanswered. With the closure of the P-1 trial these questions can only be answered by the continued accrual and follow up of the European trials.

Because of the detrimental side effects of tamoxifen, particularly on the uterus, the search has been on for other agents that have a spectrum of oestrogenic and anti-oestrogenic activity on various tissues of the body that may be more attractive overall. One such agent is raloxifene, which has been shown experimentally to be anti-oestrogenic on breast and uterus, but oestrogenic on bone and lipids [1,9,10]. A large double-blind, placebo-controlled clinical trial of raloxifene involving 12 512 healthy postmenopausal women at increased risk of osteoporosis because of a reduced bone mineral density [Multiple Outcomes of Raloxifene Evaluation (MORE) trial] [11] has clearly shown that raloxifene will reduce the risk of osteoporotic fractures. Participants in this trial had annual mammography in order to evaluate a secondary end point of breast cancer incidence. An interim analysis of these data [12] clearly shows a substantial reduction in the incidence of breast cancer, with no evidence of an increase in the incidence of endometrial cancer. The NSABP has now started a new trial [the Study of Tamoxifen and Raloxifene (STAR)], which aims to recruit 22 000 healthy women to compare directly the effects of raloxifene versus tamoxifen on the incidence of breast cancer and toxicity.

So where do we go from here? I believe we should continue the follow up of the Royal Marsden trial and continue accrual and follow up of the IBIS trial. It may be possible to have an overview meta-analysis of all trials in 2005, in order to identify the long-term effects of tamoxifen on incidence and mortality, and which subgroups of healthy women at risk gain benefit. Continued follow up of the raloxifene MORE trial will be very important, as will accrual and follow up of the STAR trial directly comparing tamoxifen with raloxifene. Finally, it will be important to continue to pilot new initiatives, particularly new selective estrogen receptor modulators, as they become available. In low-risk healthy women we would like to evaluate dietary constituents such as isoflavonoids. In higher risk women, the role of endocrine agents that have no agonist effects on the breast, such as luteinizing hormone-releasing hormone agonists, aromatase inhibitors and pure anti-oestrogens, should be investigated as potential interventions.

With the encouraging results of the P-1 trial [4], the endocrine chemoprevention of breast cancer is a reality. We must never forget, however, that this involves treatment of very large numbers of healthy women in order to reduce the incidence of a few cancers. The level of acceptable toxicity is therefore very much lower than it is for treatment trials. It is therefore imperative that the outcomes for these trials should include factors other than early incidence, in order to be able to show long-term treatment benefit in healthy women.

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