Contra:

T.J. Powles*

Royal Marsden Hospital, Downs Road, Sutton, Surrey SM2 5PT, UK

1. Introduction

Clinical trials of tamoxifen to prevent breast cancer in healthy women started in 1986 at the Royal Marsden Hospital, followed by larger trials in the USA (NSABP P-1 trial), in Italy (The National Cancer Institute, Milan) and in the UK (The International Breast Intervention Study, IBIS).

Since the publication and presentation of the results of an interim analysis of the NSABP P-1 tamoxifen chemoprevention trial in 1998 there has been much debate about the significance of the results. There is no dispute about the actual result, that giving tamoxifen 20 mg/day for up to 5 years to healthy women at a 5-year projected risk of breast cancer of $\geqslant 1.66\%$ as defined by the Gail model [1] will reduce the early incidence of breast cancer by approximately 50%. The doubts are about the interpretations of this observed reduction in early incidence of breast cancer in the contexts of the long-term prevention of breast cancer, the long-term risks and other benefits of tamoxifen, the overall health benefits including mortality from breast cancer and other causes, and the likelihood that some risk groups are tamoxifen resistant.

2. The long-term prevention of breast cancer

Epidemiological studies of breast cancer incidence following radiation exposure indicate that breast cancer takes from 13 to more than 30 years to develop as a clinical cancer from a single transformed cell [2]. Oestrogen promotion is likely to be needed especially in the early stages and the presentation of a clinical cancer is a fairly late event in this process. Progressive loss of oestrogen receptor occurs in the natural history of breast cancer development. In the early stages of development of breast cancer, tamoxifen could permanently interrupt the carcinogenic process giving rise to long-term prevention of the disease. At later stages, the use of tamoxifen would be as treatment of occult cancers which may give rise to only temporary remissions. The later in this process, the less likely it is that tamoxifen will be permanently effective. Thus, the observed reduction in early incidence, may not necessarily mean that breast cancer has been prevented.

* Fax: +44 (0) 181 770 7313.
E-mail address: trevor.powles@rmh.nthames.nhs.uk (T.J. Powles).

However, the results of the adjuvant trials of tamoxifen are very encouraging, showing an ongoing benefit out to 15 years on relapse and mortality for women who received only 2–5 years tamoxifen [3]. It is very likely that a similar ongoing cumulative benefit will be seen in the prevention setting and that the 50% reduction seen in the early incidence will improve with longer follow-up. Unfortunately, at this time we do not know this, and the unblinded NSABP P-1 study will never be able to provide long-term prevention data, which will only become available from the long-term follow-up of other placebo controlled trials, such as IBIS and the Royal Marsden trials.

3. The overall health benefit

At the time of reporting of the NSABP P-1 trial there was a balance of risks and benefits. The trial clearly shows a significant increase in thromboembolism, other vascular events and in endometrial cancer, but a reduction in fractures which may relate to a reduction in loss of bone mineral density. Rather surprisingly, there was no apparent early beneficial effect on coronary heart disease, in spite of the previous reports of a favourable effect of tamoxifen on lipid profile [4]. There was an increase in the incidence of cataracts and cataract surgery and in the incidence of vasomotor symptoms. As has been stressed by the investigators, it is difficult to summate these adverse and beneficial effects of tamoxifen at this time, and impossible to predict how this balance might change with longer follow-up. It is likely that there is an overall health benefit at this time but no evidence that this will be maintained long-term. Although many healthy women, especially in North America, will consider this reduction in early incidence worth the risk of taking tamoxifen, there is no evidence at this time that there is an overall health benefit [5] nor that any benefit would be maintained with longer follow-up.

4. Mortality

There is no evidence at this time to conclude that tamoxifen will reduce the risk of dying of breast cancer for women who do not have breast cancer [5]. It will not be possible to detect the effect of tamoxifen on mortality from NSABP P-1 because of the unblinding and allowed crossover to tamoxifen. Although it is likely

that a maintained substantial reduction in incidence would be followed by a reduction in breast cancer mortality, this is not known and will only become available from the continued follow-up of other placebo controlled tamoxifen chemoprevention trials.

In conclusion, evaluation of all of the effects of tamoxifen in the NSABP P-1 trial suggests there are currently insufficient data to determine whether tamoxifen provides an overall health benefit and increased chance for survival for women at increased risk of breast cancer [5].

5. Identification of risk groups for whom tamoxifen may be of benefit

The rather surprising negative result for the Royal Marsden trial indicated the possibility that tamoxifen may be less likely to reduce the early incidence of breast cancer in some risk groups other than those defined by the Gail model [6]. In the Royal Marsden trial there was a high proportion of participants (approximately 30%) likely to have inherited a high-risk breast cancer gene mutation with associated dysfunctional or absent oestrogen receptors in their cancers, whereas, in the NSABP P-1 trial most of the risk factors, as defined by the Gail model, were based on non-genetic factors. Some of these risk groups such as DCIS and AIH are very likely to be endocrine sensitive. In the development of genetically inherited breast cancers the loss or aberration of function of the oestrogen receptor may occur earlier in the carcinogenic process [7] than in the sporadic cancers giving rise to tamoxifen resistance or even tamoxifen-stimulated proliferation [6].

Although this acquired resistance is likely to be more manifest earlier in the development of inherited gene cancers, this would not mean that tamoxifen may not prevent the development of these cancers if given early enough in the carcinogenic process. This would mean that, although the Royal Marsden trial is negative at the present time, longer follow-up could show a difference in long-term incidence, indicating true prevention.

It is encouraging to note in the NSABP P-1 trial that the beneficial effect of tamoxifen on early incidence was similar in participants with 1, 2 or more relatives with breast cancer. It is not possible, however, to determine the likelihood of carrying high-risk breast cancer predisposing genes in these groups without a full pedigree analysis which is not available from the NSABP P-1 participants.

Therefore, at the present time it is not possible to define which groups within the Gail model may not gain benefit from tamoxifen chemoprevention, especially the younger high-risk women who may be gene carriers for breast cancer, for whom it is tempting to offer tamoxifen rather than prophylactic mastectomy.

6. Conclusions

The striking results of the NSABP P-1 trial, which clearly show a substantial and very significant reduction in the early incidence of breast cancer in healthy women given tamoxifen, is very encouraging. It is likely that this effect would increase with longer follow-up, with a corresponding overall health benefit and improvement in survival, although there are no data at this time to confirm this. The negative results of the Royal Marsden trial may be related to the population characteristics for entry into this trial, particularly the risk of inheriting a high-risk breast cancer predisposing gene.

In the USA, tamoxifen has now been licensed for use in healthy women, at a risk of developing breast cancer of at least 1.66% over 5 years, to reduce the early incidence of breast cancer. In Europe, the general consensus at the present time is that healthy women at any risk should not be offered tamoxifen outside of a clinical trial, until a clear overall health benefit or survival advantage has been shown.

The placebo controlled trials, such as IBIS and the Royal Marsden trial will, therefore, continue in order to clearly show the effects of tamoxifen on long-term incidence of breast cancer in well defined risk groups including gene carriers, and to show the impact of this on overall long-term health benefit and survival.

References

1. Gail M, Brintom L, Byar D, *et al*. Projecting individualised probabilities of developing breast cancer for white females who are examined annually. *J Natl Cancer Inst* 1989, **81**, 1879–1886.
2. Tokunago M, Norman J, Asano M, *et al*. Malignant breast tumours among atomic bomb survivors. *J Natl Cancer Inst* 1979, **62**, 1347–1359.
3. Early Breast Cancer Triallists' Collaborative Group E. Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet* 1998, **351**, 1451–1467.
4. Love R, Newcomb P, Wiebe D, *et al*. Effects of tamoxifen therapy on lipid and lipoprotein levels in postmenopausal patients with node-negative breast cancer. *J Natl Cancer Inst* 1990, **82**, 1327–1332.
5. Chlebowski R, Collyar D, Somerfield M, Pfister D. American Society of Clinical Oncology: technology assessment on breast cancer risk reduction strategies: tamoxifen and raloxifene. *J Clin Oncol* 1999, **17**, 1939–1955.
6. Powles T. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst* 1999, **91**(8), 730.
7. Osin P, Crook T, Powles T, Gusterson B. Hormone status of *in situ* cancer in *BRCA1*/*BRCA2* mutation carriers. *Lancet* 1998, **351**, 1487.

PII: S0959-8049(99)00270-1