

# Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomised chemoprevention trial

Trevor Powles, Ros Eeles, Sue Ashley, Doug Easton, Jenny Chang, Mitch Dowsett, Alwynne Tidy, Jenny Viggers, Jane Davey

## Summary

**Background** Tamoxifen, a drug with antioestrogenic effects, is predicted to prevent the occurrence of breast cancer. We have undertaken a trial of tamoxifen in healthy women who are at increased risk of breast cancer because of family history. We report a planned interim analysis.

**Methods** Between October, 1986, and April, 1996, we accrued 2494 healthy women aged between 30 and 70 with a family history of breast cancer. They have been randomised (double blind) to receive tamoxifen 20 mg per day orally or placebo for up to 8 years. Follow-up included clinical assessment, annual mammography, and assessment of toxicity and compliance. The primary endpoint was the occurrence of breast cancer, which was analysed on an intention-to-treat basis with a survival curve.

**Findings** With a median follow-up of 70 months, 2471 women (tamoxifen 1238, placebo 1233) were suitable for analysis. The groups were evenly matched at baseline, and compliance was good. The overall frequency of breast cancer is the same for women on tamoxifen or placebo (tamoxifen 34, placebo 36, relative risk 1.06 [95% CI 0.7–1.7],  $p=0.8$ ). Participants who were already on hormone-replacement therapy when they entered the study had an increased risk of breast cancer compared with non-users. Those participants who started such therapy while on trial had a significantly reduced risk. The safety profile of tamoxifen was as expected.

**Interpretation** We have been unable to show any effect of tamoxifen on breast-cancer incidence in healthy women, contrary to the report from the NSABP-P1 study showing a 45% reduction in healthy women given tamoxifen versus placebo. Differences in the study populations for the two trials may underlie these conflicting findings: eligibility in our trial was based predominantly on a strong family history of breast cancer whereas in the NSABP trial was mostly based on non-genetic risk factors. The importance of oestrogen promotion may vary between such populations.

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Royal Marsden NHS Trust, London and Sutton, Surrey, SM2 5PT, UK (T Powles PhD, S Ashley PhD, J Chang MB, Prof M Dowsett PhD, A Tidy MB, J Viggers MB, J Davey MB); Cancer Genetics Team, Institute of Cancer Research, Sutton (R Eeles MB); and CRC Genetic Epidemiology Unit, Strangeways Laboratory, Cambridge (D Easton PhD)

**Correspondence to:** Dr Trevor Powles  
(e-mail: trevor.powles@rmh.nthames.nhs.uk)

## Introduction

Tamoxifen, a drug that has antioestrogenic effects, prevents the development of rat mammary tumours,<sup>1</sup> and in clinical adjuvant trials reduced the incidence of new contralateral breast cancers, with low symptomatic toxicity.<sup>2,4</sup> To assess whether tamoxifen would prevent breast cancer in healthy women, we started in 1986 a pilot randomised placebo-controlled chemoprevention trial with tamoxifen in healthy women at an increased risk of breast cancer because of family history of the disease. We found it possible to recruit healthy women to a chemoprevention trial and that toxicity was low, with good compliance.<sup>5</sup> Furthermore, tamoxifen reduced serum cholesterol<sup>5</sup> and prevented loss of bone-mineral density in postmenopausal women,<sup>6</sup> which encouraged the starting of multicentre national trials based in Italy in 1990, in the USA in 1992, and in the UK in 1993. Regulatory problems delayed the planned start of the UK trial in 1991, and it was agreed that accrual to our pilot trial should be extended to 2500 women for the trial to have the power to detect a significant chemoprevention effect of tamoxifen by 1998. We report the results of this planned interim analysis.

## Participants and methods

### Inclusion and exclusion criteria

Healthy volunteers were identified in our screening and symptomatic breast clinics. Women were eligible if aged between 30 and 70 years, with no clinical or screening evidence of breast cancer and with an increased risk of breast cancer because of family history. Each participant had at least one first-degree relative aged under 50 with breast cancer, or one first-degree relative with bilateral breast cancer, or one affected first-degree relative of any age plus another affected first-degree or second-degree relative. Women with a history of a benign breast biopsy who had a first-degree relative with breast cancer were also eligible.

Women with a history of any cancer or of deep-vein thrombosis or pulmonary embolism were excluded. Premenopausal women who were considering further pregnancies or who were taking oral contraception were not eligible. However, postmenopausal women taking hormone-replacement therapy were eligible without having to stop such therapy. Women in the trial were allowed to start hormone-replacement therapy if indicated.

Eligible women were counselled about the trial, were provided with written information, and gave written consent to enter. Women who agreed to participate were prescribed "Tamoplac", and then randomised by the hospital pharmacy to receive tamoxifen 20 mg per day by mouth for 8 years or identical placebo (Orion Pharma). Treatment allocation was concealed from all participants, clinicians, and data staff. The trial was approved by the Royal Marsden Hospital ethics committee.

Menopausal status at randomisation was defined as premenopausal if the woman had had a normal period within the previous 6 months, perimenopausal if the last period was 6 months to a year previously, and postmenopausal if longer than 12 months. Participants who had had a hysterectomy were considered postmenopausal if aged 50 or more. From 1992, blood samples were collected to enable future screening for breast-cancer genes.

### Follow-up

A data and safety monitoring committee periodically reviewed our data, with relevant reports from other tamoxifen trials.

	Tamoxifen (n=1250)	Placebo (n=1244)
<b>Age</b>		
Median (range)	47 (31-70)	47 (30-70)
<50	774	749
<b>Menopausal status</b>		
Pre/peri	822	812
Post	416	421
<b>Family history</b>		
First-degree relative <50	698	668
2 or more, any age	225	205
<b>Previous benign lump excised</b>	280	263
<b>On HRT at start</b>	187	202

HRT=hormone replacement therapy.

Table 1: Clinical characteristics

Follow-up every 6 months included clinical examination and assessment of acute toxicity with an oral checklist. Other diseases and medical problems including gynaecological evaluation, and any changes in the family history of breast cancer, were recorded at each visit. Mammography was repeated annually.

Compliance was assessed by direct questioning and checked against random blood testing of participants for tamoxifen.<sup>7</sup> Serum cholesterol was measured before treatment and then every 6 months.<sup>7</sup>

### Statistical analysis

Initial entry criteria allowed patients who had had ductal carcinoma-in-situ to be included. This disorder was later made an exclusion criterion and 22 such patients have been excluded from analysis. Administrative errors led to 11 participants being re-randomised by the pharmacy. The data for these women have been censored at the time of their second randomisation. All other women have been analysed by intention to treat.

Based on the accrual rate in 1993 and the relative risk of breast cancer in the study population, we estimated that we should be able to detect a 75% effect of tamoxifen in 1996 and a 50% effect in 1998 (two-sided  $\alpha=5\%$ , power=90%) and interim analyses were planned for these times. The results of the 1998 interim analysis are reported here.

The primary endpoint is the occurrence of breast cancer. Baseline characteristics were compared by  $\chi^2$  and *U* tests. Breast-cancer-free survival was analysed with Kaplan-Meier and logrank techniques. We adjusted for possible confounding variables (age, menopausal status, family history of breast and ovarian cancer, use of hormone-replacement therapy) with Cox's proportional hazards model.

Compliance was analysed by a survival (time to stopping treatment) analysis. The numbers of participants who stopped treatment prematurely were compared by the  $\chi^2$  test. To analyse the effectiveness of treatment, women were deemed compliant if they had taken at least 6 months' treatment.

Percentage changes from pretreatment values for cholesterol were calculated and analysed by *t* test.

## Results

### Accrual and non-breast-cancer events

Accrual started in October, 1986, and ended in April, 1996. The treatment and placebo groups were well matched for age, menopausal status, including use of hormone-replacement therapy, family history, and previous history of benign breast biopsy (table 1).

Of the 2494 women who consented to the trial, 23 were excluded from analysis (12 tamoxifen and ten placebo participants had evidence of pre-existing ductal carcinoma-in-situ and one placebo participant was found to have pre-existing invasive cancer), which leaves 2471 for this analysis (figure 1). The median follow-up is 70 months in both groups and 1033 (42%) participants are no longer taking the tablets (table 2). 156 have completed 8 years of

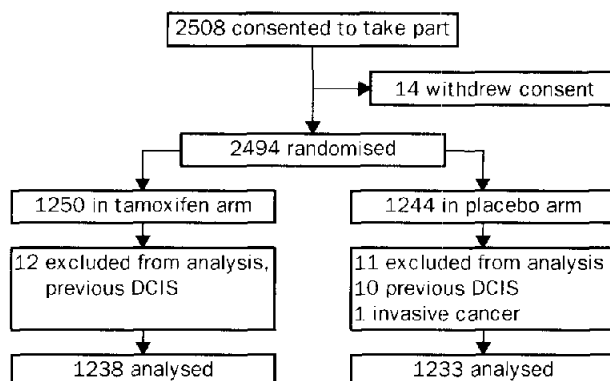


Figure 1: Trial profile

DCIS=ductal carcinoma-in-situ.

medication; 877 have prematurely stopped either for non-toxic reasons or because of side-effects (tamoxifen 320, placebo 176,  $p<0.0005$ ). The most frequent side-effects leading to discontinuation of tamoxifen were hot flushes and other vasomotor symptoms, gynaecological problems including period irregularities, vaginal discharge, and benign abnormalities found on transvaginal ultrasonography (table 2). During the trial 336 women on tamoxifen and 305 women on placebo required hormone-replacement therapy. Only 280 (11%) of the women in the trial have been lost to follow-up for over 18 months.

The occurrence of clinically significant adverse events, including other cancers, thromboembolisms, and non-breast-cancer deaths, remains low (table 3). There is no significant difference between tamoxifen and placebo, although there are four cases of endometrial cancer in the tamoxifen group compared with one in the placebo group.

### Breast cancer

The frequency of breast cancer in this trial is the same for women on tamoxifen or placebo (tamoxifen 34, placebo 36; relative risk=1.06 [95% CI 0.7-1.7], figure 2). Of these 70 cancers, eight were non-invasive ductal carcinomas-in-situ, four in each group.

Prognostic factors for breast-cancer-free survival are shown in table 4. Nulliparous women had a two-fold increase in risk of breast cancer compared with women with children. Participants who were already on hormone-replacement therapy when they entered the study had an increased risk of breast cancer compared with non-users. Those participants who started such therapy while on trial had a significantly reduced risk. After we adjusted for all confounding variables, the randomised treatment of

	Tamoxifen	Placebo	p
<b>Median follow-up (months)</b>	70	70	>0.9
<b>Stopped medication</b>	576	457	<0.0005
<b>Completed 8 years</b>	79	77	0.5
<b>Premature stop</b>	497	380	<0.0005
Non-toxic	177	204	0.2
Toxic	320	176	<0.0005
Nausea	12	6	0.2
Headaches	13	14	0.8
Hot flushes	51	13	<0.0005
Weight gain	6	12	0.2
Period abnormality	18	6	0.01
Gynaecological problems	69	18	<0.0005
Mood change	8	1	0.02
Other or not known	143	106	0.01
<b>HRT during trial</b>	336	305	0.2
<b>Lost to follow-up &gt;18 months</b>	141	139	0.9

Table 2: Follow-up and compliance

	Tamoxifen	Placebo
<b>Other cancers</b>	19	24
Endometrium	4	1
Ovarian	2	5
Gastrointestinal	3	3
Other	10	15
<b>Deep-vein thrombosis</b>	4	2
<b>Pulmonary embolism</b>	3	2
<b>Death</b>		
Cancer of breast	4	1
Other causes	5	5

Table 3: Other cancers and events

tamoxifen or placebo was not predictive of breast cancer. Furthermore, there appeared to be no interaction between the use of hormone-replacement therapy and any effect of tamoxifen on breast-cancer occurrence. There were 12 cancers in the 523 women who received hormone-replacement therapy on tamoxifen compared with 13 of 507 women on placebo ( $p=0.6$ ).

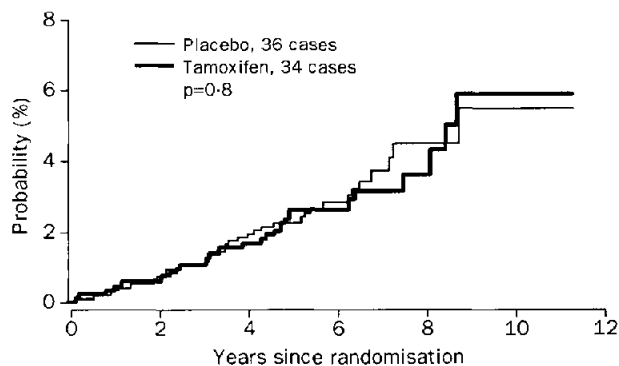
### Compliance

Compliance has been assessed by direct questioning at each visit. Tamoxifen and its metabolites were measured in 55 of the patients who developed cancer in this trial. Neither tamoxifen nor its metabolites were detected in 29 placebo patients and in ten tamoxifen patients who said they were not compliant at the time of blood testing. Tamoxifen and its metabolites were detected in 15 of 16 tamoxifen patients who claimed to be compliant at the time of blood sampling. Overall, this gives a 96% accuracy for volunteered history of compliance in relation to blood testing.

To test for biological activity of tamoxifen versus placebo in participants, we examined changes in cholesterol in a random subset. In 403 compliant non-breast-cancer participants on placebo, mean post-treatment cholesterol was 98.2% (95% CI 97.0–99.4) of the pretreatment level. In 390 compliant non-breast-cancer participants on tamoxifen the corresponding figures were 90.4% (88.8–91.9), indicating around a 10% fall. Measurement of sequential cholesterol levels in a random subset of 34 of the 70 breast-cancer participants in whom blood samples were available showed that the mean post-treatment level in 18 placebo patients was 100.7% (93.6–107.9) of the pretreatment level; for the 16 breast-cancer participants on tamoxifen the figures were 94.8% (86.1–103.5) and for the 12 compliant tamoxifen breast-cancer participants, 89.2% (80.8–97.6).

### Discussion

From the 47% reduction in the frequency of contralateral new breast cancers in women on adjuvant tamoxifen after



Variable	Relative risk of breast cancer	95% CI	p
<b>Age-group</b>			
<50	1.0		
≥50	1.1	0.7–1.8	0.6
<b>Menopausal status</b>			
Pre	1.0		
Peri	1.1	0.3–3.5	0.9
Post	1.0	0.6–1.6	
<b>Number of first-degree relatives with breast cancer</b>			
1	1.0		
2	1.2	0.8–1.8	0.3
3	1.5	0.7–3.3	
<b>Relatives aged &lt;50 with breast cancer</b>			
None	1.0		
1	1.1	0.7–1.5	0.7
2	1.2	0.6–2.3	
<b>Relatives with bilateral breast cancer</b>			
No	1.0		
Yes	1.2	0.5–3.0	0.7
<b>Previous benign lump</b>			
No	1.0		
Yes	0.8	0.1–6.9	0.8
<b>Nulliparous</b>			
No	1.0		
Yes	2.0	1.1–3.4	0.02
<b>On HRT at randomisation</b>			
No	1.0		
Yes	1.9	1.1–3.3	0.04
<b>Started HRT during trial</b>			
No	1.0		
Yes	0.4	0.2–0.7	0.01
<b>Randomised treatment</b>			
Tamoxifen	1.0		
Placebo	1.06	0.7–1.7	0.8

Table 4: Univariate analysis of prognostic factors for breast-cancer-free survival in all 2494 participants

treatment of primary breast cancer<sup>9</sup> we anticipated that giving tamoxifen to healthy high-risk women would produce at least an equivalent result. The early results of the NSABP-P1 prevention trial showing a reduction of 45% in breast-cancer frequency in healthy women receiving tamoxifen are in keeping with this anticipated effect.<sup>10</sup> We are therefore surprised to see no overall reduction in the occurrence of breast cancer in participants randomised in our trial to tamoxifen. With nearly 2500 women in this trial, an estimated 70% compliance at 5 years, a median follow-up of 70 months, and with a total of 70 cancers, the power to detect a significant 50% reduction in breast cancer frequency at the 5% level is about 90%.

There are several reasons why we have a negative effect at this time, including the possibility of a freak statistical result. With the size of the effect in NSABP-P1, there is only about a 10% chance that we would have failed to show a significant reduction in frequency for women on tamoxifen. It is therefore surprising that we did not even see a trend towards reduction.

It is unlikely that a lack of compliance in our trial could account for our negative result. We found adequate compliance, confirmed by random sampling and measurement of tamoxifen. We have also shown that tamoxifen is biologically active in our participants, including effects on bone,<sup>11</sup> the uterus,<sup>12</sup> and clotting factors and plasma lipids.<sup>3</sup> Furthermore, in the current report, tamoxifen lowered cholesterol in those on study drug who developed breast cancer.

One reason for the difference between our data and those of the NSABP-P1 trial could relate to the study populations. Our entry criteria for all ages were

predominantly based on a strong family history, with an associated increased risk of inheriting a high-risk breast-cancer-predisposing gene such as *BRCA1*. In our trial, using pedigree analysis,<sup>13</sup> we estimate that about 36% of all participants and over 60% of those who have developed breast cancer are in clusters that have a greater than 80% chance of being due to a breast-cancer-predisposition gene. In NSABP-P1, the entry criteria are based mostly on non-genetic risk factors. Oestrogen promotion, which we would be expecting tamoxifen (with its antioestrogenic effects) to oppose, may not be important in the genesis of clinical breast cancer in high-risk gene carriers. This is supported by the lack of progesterone receptors in *BRCA1* and *BRCA2* cancers, which indicates phenotypical hormone resistance.<sup>14</sup>

In NSABP-P1, by contrast with our trial, use of hormone-replacement therapy was not allowed at entry or during follow-up. However, we found no evidence that the use of such therapy by participants in our trial confounded any possible beneficial effect of tamoxifen.

Another reason for the difference between the NSABP-P1 and our results could relate to the duration of follow-up. The average follow-up for NSABP-P1 is only 3.5 years compared with our own median of nearly 6 years. The relatively early frequency data in the NSABP trial would largely reflect treatment of occult primary cancers, rather than prevention by blocking oestrogen promotion of a transformed cell into an active cancer. We do not know whether early endocrine treatment of occult cancers would prevent the long-term appearance of these cancers, and therefore confer clinical benefit, especially after cessation of treatment. Animal data indicate that tumour development could return after the end of treatment.<sup>15</sup> In our trial with longer follow-up, over 40% of participants have completed medication, and we see no evidence for a persistent preventive effect of tamoxifen.

The frequency of other events, including endometrial cancer, other cancers, thromboembolism, and deaths is relatively low but in keeping with reports from other trials.<sup>9,10,16</sup>

The long-term risks for healthy women taking tamoxifen are not clear.<sup>17</sup> The balance between adverse effects and any long-term clinical benefit from a reduction in breast-cancer frequency will need to be carefully evaluated in all risk groups of women. There is no evidence to justify advising high-risk women to take tamoxifen, outside of a clinical trial, until clear long-term benefit has been established. This is important because of the genotoxic potential of tamoxifen in women who may have inherited a mutation in *BRCA1* or *BRCA2* which could impair DNA repair.<sup>18</sup> The possibility of a reduction by the use of tamoxifen in the occurrence of breast cancer in *BRCA1* or *BRCA2* gene-mutation carriers in the long term will need to be carefully evaluated.

We conclude that there remains doubt about what the reported early reduction in the incidence of breast cancer in the NSABP-P1 trial means in terms of prevention of breast cancer, and we should continue blinded follow-up of tamoxifen chemoprevention trials to identify which women may benefit. Larger numbers of women and longer duration of follow-up will be required to evaluate fully the long-term benefits from tamoxifen for chemoprevention of breast cancer, in relation to adverse effects, and to identify for which groups of women the balance of benefit and risk will justify using tamoxifen. A meta-analysis of all tamoxifen chemoprevention trials over the next few years

may better define any clinical benefits in healthy women. We therefore decided that we should continue treatment and follow-up in our trial to contribute our high-risk population of women to such an overview.

#### Contributors

Trevor Powles initiated the study, is principal investigator, and supervised the running of the trial. Ros Eccles and Doug Easton are responsible for pedigree analysis and genetic testing. Sue Ashley is principal statistician. Jenny Chang, Jenny Viggers, and Jane Davey were responsible for clinical care of the participants. Mitch Dowsett is responsible for biochemical and endocrine testing. Alwynne Tidy was the senior data coordinator. Trevor Powles was the main author of the paper, and all the other investigators contributed to completion of the paper.

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