Twenty-Year Follow-up of the Royal Marsden Randomized, Double-Blinded Tamoxifen Breast Cancer Prevention Trial

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Background Several clinical trials have reported an early reduction in breast cancer incidence in healthy women using tamoxifen to reduce their risk of breast cancer but have not reported longer follow-up data for the evaluation of breast cancer prevention. We report the blinded 20-year follow-up (median follow-up = 13 years) of the Royal Marsden trial to identify any long-term prevention of breast cancer associated with tamoxifen treatment.

Methods We randomly assigned 2494 healthy women to oral tamoxifen (20 mg/day) or placebo for 8 years. The primary outcome was occurrence of invasive breast cancer. A secondary planned analysis of estrogen receptor (ER)–positive invasive breast cancer was also done. Survival was assessed by use of a Cox proportional hazards model in both univariate and multivariable analyses. The durability of the treatment effect was assessed by use of a Cox regression analysis. All statistical tests were two-sided.

Results Among the 2471 eligible participants (1238 participants in the tamoxifen arm and 1233 participants in the placebo arm), 186 developed invasive breast cancer (82 on tamoxifen and 104 on placebo; hazard ratio [HR] = 0.78, 95% confidence interval [CI] = 0.58 to 1.04; $P = .1$). Of these 186 cancers, 139 were ER positive (53 on tamoxifen and 86 on placebo; HR = 0.61, 95% CI = 0.43 to 0.86; $P = .005$). The risk of ER-positive breast cancer was not statistically significantly lower in the tamoxifen arm than in the placebo arm during the 8-year treatment period (30 cancers in the tamoxifen arm and 39 in the placebo arm; HR = 0.77, 95% CI = 0.48 to 1.23; $P = .3$) but was statistically significantly lower in the posttreatment period (23 in the tamoxifen arm and 47 in the placebo arm; HR = 0.48, 95% CI = 0.29 to 0.79; $P = .004$). Fifty-four participants in each arm have died from any cause (HR = 0.99, 95% CI = 0.68 to 1.44; $P = .95$). The adverse event profiles for both arms were similar to those previously reported and occurred predominantly during the treatment period.

Conclusions A statistically significant reduction in the incidence of ER-positive breast cancer was observed in the tamoxifen arm that occurred predominantly during the post treatment follow-up, indicating long-term prevention of estrogen-dependent breast cancer by tamoxifen.

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After reports of laboratory data indicating that tamoxifen might prevent breast cancer (1) and clinical data indicating a reduction in contralateral breast cancer incidence associated with tamoxifen treatment (2), four randomized placebo-controlled tamoxifen prevention trials with more than 25 000 healthy women were started between 1986 and 1992 (3–8). The results were variable. The National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 trial reported a highly statistically significant 49% reduction in the incidence of invasive breast carcinoma after a median follow-up of 54 months ($P<.001$); this reduction was confined to estrogen receptor (ER)–positive cancers (3). The NSABP P-1 trial was unblinded at the time of the initial report, and participants in the placebo arm were offered tamoxifen. Analysis of further follow-up showed a 43% reduction in incidence of invasive breast cancer in the tamoxifen group, although the unblinding may have compromised this result (4). The International Breast Intervention Study (IBIS) 1 trial, after a median follow-up of 50 months, showed a risk reduction of 32% in the incidence of all breast cancers; however, this reduction was not statistically significant for invasive cancers (5). Finally, the Italian national trial, after a median follow-up of 81.2 months, showed no effect (6).

On the basis of the NSABP P-1 trial result, tamoxifen was approved by the US Food and Drug Administration for risk reduction of breast cancer in healthy women in the United States. However, the use of tamoxifen by women for breast cancer

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See "Notes" following "References."

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CONTEXT AND CAVEATS

Prior knowledge

Four randomized, placebo-controlled trials, including the Royal Marsden trial, tested tamoxifen against placebo in healthy women for the prevention of breast cancer. Initial reports from these trials were inconsistent. Early results of the Royal Marsden trial found no reduction in breast cancer between tamoxifen and placebo groups.

Study design

Placebo-controlled, double-blinded, randomized trial.

Contribution

At the median follow-up, the risk of invasive breast cancer was lower in the tamoxifen group than in the placebo group but not statistically significantly so. However, during the posttreatment period, the risk of ER-positive breast cancer was statistically significantly lower in the tamoxifen group than in the placebo group.

Implications

Tamoxifen treatment for 8 years appears to have a long-term preventative effect against ER-positive breast cancer.

Limitations

This study was a small, single-institution study. Participants were younger and had a stronger family history of breast cancer than those in other trials.

prevention has been less than expected, in part because of the variability of the results from the trials and in part because of the toxicity of tamoxifen, particularly on the uterus, in healthy women. Furthermore, there was uncertainty about the durability of the beneficial effect after the relatively short follow-up period before unblinding in the NSABP P-1 trial.

The Royal Marsden trial started 20 years ago, in 1986, and has remained blinded. Its original purpose was to be a pilot trial to evaluate the feasibility of using tamoxifen in a placebo-controlled trial in healthy women at high risk of breast cancer. Satisfactory accrual, compliance, and toxicity allowed the trial to develop into a single-center trial that accrued 2500 women by 1996. Participants were randomly assigned to tamoxifen or placebo for 8 years and have been followed since treatment was discontinued. The first efficacy analysis of this trial in 1998, after 70 breast cancers had been diagnosed among participants, found no reduction in breast cancer incidence when the tamoxifen arm was compared with the placebo arm (7,8). There have now been more than 200 breast cancer events during the 20 years since the beginning of the trial, with a median follow-up of more than 13 years. The purpose of this second analysis of breast cancer incidence in this trial, in particular the long-term incidence of ER-positive breast cancer, was to identify any long-term prevention of breast cancer associated with tamoxifen treatment.

Participants and Methods

Study Population

From October 1, 1986, through April 30, 1996, healthy women between 30 and 70 years old, with no clinical or screening evidence of breast cancer and with an increased risk of breast cancer because of their family history of breast cancer, were identified in our screening and symptomatic breast clinics. They were considered eligible for the trial if they had 1) at least one first-degree relative who was younger than 50 years when diagnosed with breast cancer, 2) one first-degree relative with bilateral breast cancer, or 3) one first-degree relative with breast cancer who was diagnosed at any age plus at least one other affected first- or second-degree relative with breast cancer. 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, deep-vein thrombosis, or pulmonary embolism; with a risk of pregnancy; or who were using oral contraceptives were not eligible. However, women taking hormone replacement therapy were eligible without having to stop such therapy, and women in the trial were allowed to start any form of hormone replacement therapy if indicated. This therapy was either estrogen combined with a progestin or estrogen alone, if the women had previously had a hysterectomy.

Study Design

Eligible women were provided with verbal and written information about the design of the trial and the known toxic effects of tamoxifen. Those who volunteered to take part in our trial gave written consent to enter and were prescribed "Tamoplac" on their pharmacy card, which was adequate for a legal prescription of either tamoxifen or placebo. They were then randomly assigned by the hospital pharmacy to receive tamoxifen (20 mg/day) or placebo (both from Orion Pharma, Espoo, Finland) by mouth for 8 years. Participants, clinicians, and data-processing staff have remained blinded to the treatment options throughout follow-up. The trial was approved by the Royal Marsden Hospital Ethics Committee. The trial is registered with controlled-trials.com as ISRCTN07027313.

The menopausal status of participants at randomization or at any time during follow-up was defined as premenopausal, if her last normal period was within the previous 6 months; perimenopausal, if her last normal period was from 6 months to 1 year ago; or postmenopausal, if her last normal period was more than 1 year

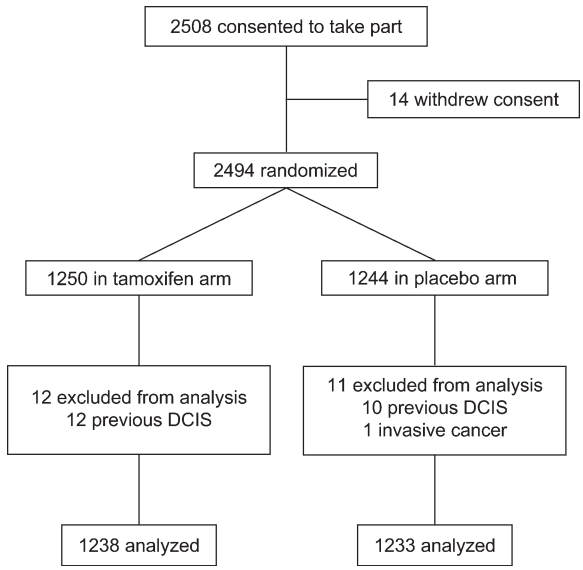

Fig. 1. CONSORT trial flow diagram.

Table 1. Possible prognostic factors*

Factor	Tamoxifen arm	Placebo arm	*P*	Test
No. of patients	1238	1233		
Age, No.				
<50 y	774	749	.5	MW
50–59 y	367	374		
≥60 y	974	110		
Median age, y (range)	7 (31–70)	47 (30–70)		
Menopausal status, No.				
Premenopausal	801	798	.9	χ^2
Perimenopausal	49	43		
Postmenopausal	388	392		
No. of first-degree relatives with breast cancer				
0/nk	43	58	.1	χ^2_{trend}
1	959	959		
2	210	201		
≥3	26	15		
No. of first-degree relatives aged <50 y				
0	531	555	.2	χ^2_{trend}
1	631	612		
≥2	76	66		
No. of first-degree relatives with bilateral breast cancer				
0	1161	1156	1.0	χ^2_{trend}
1	75	73		
≥2	2	4		
No. of first- or second-degree relatives with breast cancer				
0/nk	8	10	.6	χ^2_{trend}
1	373	372		
2	476	496		
3	257	228		
4	81	82		
≥5	43	45		
Previous benign lump, No.	280	267	.6	Fisher
Previous breast surgery, No.	336	323	.6	Fisher
Benign breast disease, No.	96	93	.9	Fisher
Previous atypical hyperplasia/LCIS, No.	4	5	.8	Fisher
Nulliparous, No.	159	172	.4	Fisher
On HRT at randomization, No.				
Estrogen alone	87	102	.5	χ^2
Combined	102	103		
Menopausal status at last follow-up†, No. (%)	1009 (81.5)	1000 (81.1)	.8	Fisher
HRT on treatment, No.				
Estrogen alone	195	192	.7	χ^2
Combined	255	272		
HRT after treatment, No.				
Estrogen alone	218	180	.1	χ^2
Combined	245	245		

* MW = Mann–Whitney *U* test; nk = not known; LCIS = lobular carcinoma in situ; HRT = hormone replacement therapy.

† Postmenopausal (or age >50 years if no data on status at last follow-up).

ago. Participants who had had a hysterectomy were considered postmenopausal if they were aged 50 years or older.

Follow-up

A data and safety monitoring committee periodically reviewed the data and compared data from this trial with relevant reports from other tamoxifen trials. Follow-up visits occurred every 6 months and included a clinical breast examination and assessment of acute toxicity. Data forms were completed at each visit and continuously updated on the computer database at the Royal Marsden. This procedure continued after the treatment period throughout follow-up. Other diseases and medical problems, including gynecologic problems, and any changes in the family history of breast cancer were recorded at each visit. A mammographic examination occurred annually.

Statistical Analysis

The efficacy analysis was performed after 209 breast cancer events had been documented. The cutoff for data collection and the commencement of this analysis occurred on September 1, 2006, and follow-up data received since this date have not been analyzed. In this study, a total of 2494 women were randomly assigned to tamoxifen or placebo (Fig. 1). Participants who had had ductal carcinoma in situ were eligible initially, but a protocol amendment later excluded such participants. Twenty-two patients with ductal carcinoma in situ and one patient with invasive breast cancer were

Table 2. Breast cancer events and deaths*

Event	Tamoxifen arm		Placebo arm		HR (95% CI)	*P*‡	$P_{interaction}$§
	No.	Rate†	No.	Rate†			
Breast cancer–related event							
Any breast cancer	96	5.6	113	6.6	0.84 (0.64 to 1.10)	.2	
DCIS	14	0.8	9	0.5			
Invasive cancer‖	82	4.8	104	6.1	0.78 (0.58 to 1.04)	.1	
During treatment	44	4.5	48	5.0	0.91 (0.61 to 1.37)	.7	
Posttreatment	38	5.1	56	7.6	0.67 (0.44 to 1.01)	.05	
ER-negative	24	1.4	17	1.0	1.4 (0.7 to 2.6)	.3	
ER-positive¶	53	3.1	86	5.1	0.61 (0.43 to 0.86)	.005	
Treatment	30	3.1	39	4.0	0.77 (0.48 to 1.23)	.3	
Posttreatment	23	3.1	47	6.4	0.48 (0.29 to 0.79)	.004	
Menopausal status#							
Premenopausal	14	2.8	28	5.6	0.50 (0.26 to 0.95)	.03	.004
Postmenopausal	9	3.7	19	8.1	0.46 (0.21 to 1.02)	.06	
HRT use during treatment#							
Yes	12	3.6	25	7.9	0.46 (0.23 to 0.91)	.03	.004
No	11	2.7	22	5.3	0.51 (0.25 to 1.05)	.07	
Family history#							
0–2	14	2.7	28	5.3	0.51 (0.27 to 0.96)	.04	.004
≥3	9	3.9	19	9.1	0.43 (0.19 to 0.95)	.04	
Deaths							
Total	54		54		0.99 (0.68 to 1.44)	.95	
Breast cancer	12		9				
Other cancer	30		24				
Stroke	1		2				
Heart condition	6		2				
Other causes or nk	5		17				

* HR = hazard ratio; CI = confidence interval; DCIS = ductal carcinoma in situ; ER = estrogen receptor; HRT = hormone replacement therapy; nk = not known.

† Rate = number of events per 1000 woman-years.

‡ Statistical significance of the difference between the tamoxifen arm and the placebo arm was determined with a two-sided likelihood ratio test.

§ *P* for interaction is the statistical significance of the interaction between tamoxifen and placebo, after adjusting for menopausal status at randomization, HRT use during treatment, and the number of relatives with breast cancer. Statistical significance was assessed by use of the likelihood ratio test.

‖ Six cancers are of unknown invasive status and are assumed to be invasive in the above analysis.

¶ Six invasive cancers of unknown ER status were excluded.

Analysis was restricted to patients with ER-positive tumors diagnosed after treatment. Menopausal status at randomization is presented. Family history refers to the number of first- or second-degree relatives with breast cancer.

excluded from analysis, leaving 2471 women (1238 in the tamoxifen arm and 1233 in the placebo arm) eligible for this analysis. Eleven participants were randomly reassigned to a treatment group by the pharmacy in error. Data for these women were censored at the time of their second randomization. All other women have been analyzed by the intention-to-treat procedure.

From the accrual rate in 1993 and the relative risk of breast cancer in the study population, it was estimated that a 50% effect (i.e., reduction of breast cancer incidence in the tamoxifen arm) could be detected in 1998 (two-sided statistical test, $\alpha = 5\%$ and power = 80%), and an interim analysis was published in 1998 that reported no difference in breast cancer incidence between the two arms. A further analysis was then planned after 200 events had occurred to detect possible late effects of tamoxifen on invasive breast cancer. Consequently, a plan for this second analysis was triggered in August 2006, after a total of 209 breast cancer events had occurred, and was completed by September 2006.

The primary endpoint was the occurrence of invasive breast cancer. Baseline characteristics were compared by two-sided chi-square and Mann–Whitney *U* tests. Breast cancer–free survival was analyzed by Cox proportional hazards model in both univariate and multivariable analyses. The proportionality assumption was checked by means of log-minus-log plots. A step-up procedure was used in the multivariable analysis, and variables that were statistically significant at the 5% level were entered into the analysis. Finally, treatment was added to the model, and its effect was reported as a hazard ratio (HR). Variables investigated in the analysis included age (continuous variable), menopausal status (pre-, peri-, or post-menopausal), parity (nulliparous or not), family history of breast cancer (number of first-degree relatives with breast cancer, number of first- or second-degree relatives with breast cancer, number of first-degree relatives with bilateral breast cancer—all continuous variables), previous benign breast disease (yes or no), and use of hormone replacement therapy (none, estrogen only, or combined estrogen and progestin). These variables were determined while the data were still blinded. When evidence of nonproportionality was identified, time-dependent variables were used. Survival was analyzed by the Kaplan–Meier method. Six cancers were not clearly defined as invasive or noninvasive, and a robustness test showed that inclusion or noninclusion in the invasive group made no difference to the results. A secondary planned analysis of ER-positive invasive breast cancer was also done. Six cancers were of unknown

ER status, and a robustness test showed that their inclusion in the ER-positive or -negative groups made no difference to the results.

A time-dependent Cox regression analysis addressed the durability of the treatment effect and posttreatment effect by use of a cut point for treatment at 8 years, the planned duration of treatment. Compliance was determined by a survival (time to stopping treatment) analysis. All statistical tests were two-sided.

Results

For this analysis, 1238 participants in the tamoxifen arm and 1233 participants in the placebo arm were eligible. Distribution of risk characteristics of participants in both treatment groups was the same (Table 1). Participant compliance, as assessed by self-reporting, was approximately 8% less in the tamoxifen arm than in the placebo arm (P = .002). This difference was evident at 1 year after the start of treatment and remained constant over the treatment period.

After a median follow-up of 13 years and 2 months (maximum = 19 years and 10 months), 209 women had developed breast cancer (96 on tamoxifen and 113 on placebo; HR = 0.84, 95% confidence interval [CI] = 0.64 to 1.10; P = .2) (Table 2 and Fig. 2). Invasive breast cancer was diagnosed in 82 women in the tamoxifen arm and 104 women in the placebo arm (HR = 0.78, 95% CI = 0.58 to 1.04; P = .1). After multivariable adjustment for prognostic factors at the time of entry, the result was still similar (HR = 0.77, 95% CI = 0.57 to 1.02; P = .07). To estimate any confounding effect of hormone replacement therapy on the reduction in the risk of invasive breast cancer by tamoxifen, we censored the follow-up of participants on hormone replacement therapy at the time that hormone replacement therapy was begun. Among participants who did not use hormone replacement therapy, invasive breast cancer was diagnosed in 58 in the tamoxifen arm and 64 in the placebo arm (HR = 0.93, 95% CI = 0.65 to 1.33; P<.7).

Information on the ER status was available for 180 (97%) of the 186 invasive cancers. Of the 180 cancers, 139 were ER positive—53 (69%) of the 77 cancers in the tamoxifen arm and 86 (83%) of the 103 cancers in the placebo arm. The incidence of ER-positive invasive breast cancers in the tamoxifen arm was 39% less (HR = 0.61, 95% CI = 0.43 to 0.86; P = .005) than that in the placebo arm. Multivariable adjustment for prognostic factors at the time of entry produced a similar result (HR = 0.60, 95% CI = 0.43 to 0.85; P = .004).

Evidence for nonproportionality of the effect of tamoxifen on the risk of invasive breast cancer was found, in which the effect was greater in the posttreatment period (38 cancers in the tamoxifen arm and 56 in the placebo arm; HR = 0.67, 95% CI = 0.44 to 1.01; P = .05) than in the 8-year treatment period (44 in the tamoxifen arm and 48 in the placebo arm; HR = 0.91, 95% CI = 0.61 to 1.37; P = .7) (Table 2). We found similar patterns when we compared the incidence of ER-positive cancers that were diagnosed during the 8-year treatment period (30 in the tamoxifen arm and 39 in the placebo arm; HR = 0.77, 95% CI = 0.48 to 1.23; P = .3) with the incidence of ER-positive cancers that were diagnosed in the posttreatment period (23 in the tamoxifen arm and 47 in the placebo arm; HR = 0.48, 95% CI = 0.29 to 0.79; P = .004) (Table 2 and Fig. 3). Similar levels of posttreatment reduction in the risk of ER-positive invasive breast cancer, comparing the tamoxifen arm with the placebo arm, were observed among premenopausal participants, postmenopausal participants, those using hormone replacement therapy, those not using it, and those with a family history of no more than two relatives with breast cancer or three relatives or more with breast cancer. Fifty-four deaths from all causes occurred in each arm (HR = 0.99, 95% CI = 0.68 to 1.44; P = .95).

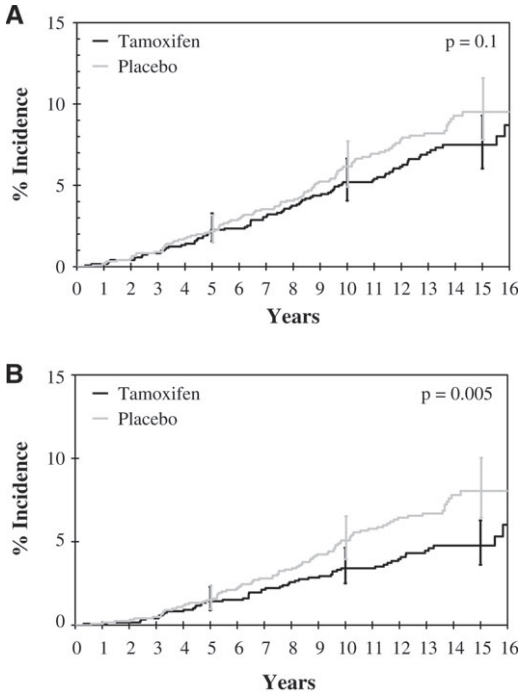

Fig. 2. Kaplan–Meier analysis for breast cancer incidence. **A**) Incidence of all invasive breast cancers. **B**) Incidence of estrogen receptor–positive breast cancer. At 5, 10, and 15 years, 95% confidence intervals for the percentage incidence have been inserted. At 5, 10, and 15 years, the numbers of participants at risk in the tamoxifen arm were 1144, 1013, and 243, respectively, and in the placebo arm were 1151, 993, and 241, respectively.

The profile of adverse events reported in the tamoxifen arm and the placebo arm was similar to that reported previously for this trial (8), with gynecologic toxicity being the most clinically important (Table 3). We found no evidence of any increase in the incidence of nonbreast and nonendometrial cancers.

Discussion

We found that, in spite of a null effect of tamoxifen on the early risk reduction of invasive breast cancer in this trial, after the 8-year treatment period, a highly statistically significant risk reduction was found that could be attributed principally to a reduction in the risk of ER-positive breast cancers. This reduced risk appears to be increasing with longer follow-up.

The first interim analysis of this phase III, randomized, double-blinded, placebo-controlled trial of tamoxifen in more than 2500 healthy women at increased risk of breast cancer was reported (8) in 1998, after the occurrence of 70 breast cancers and a median follow-up of nearly 6 years. It found no difference in the incidence of invasive breast cancer between the two arms. In that first analysis, we reported that 753 (60%) of 1250 participants in

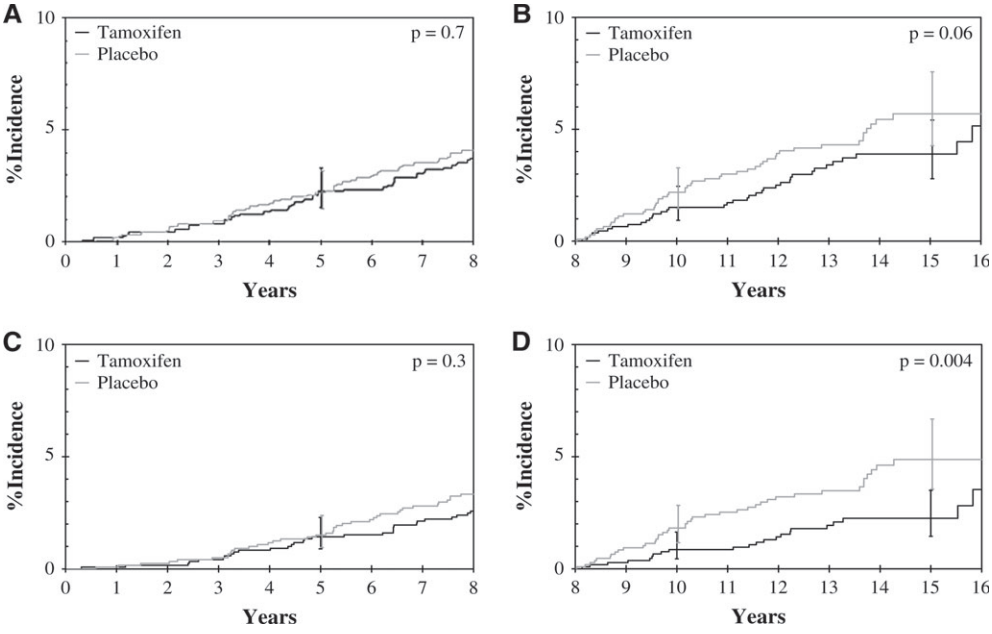

Fig. 3. Kaplan–Meier analysis for breast cancer incidence. **A**) Incidence of all invasive breast cancer during the 8-year treatment period. **B**) Incidence of all invasive breast cancer during the posttreatment period. **C**) Incidence of estrogen receptor (ER)–positive invasive breast cancer during the 8-year treatment period. **D**) Incidence of ER-positive invasive breast cancer during the posttreatment period. At 5, 10, and 15 years, 95% confidence intervals for the percentage incidence have been inserted. At 5, 10, and 15 years, the numbers of participants at risk were 1144, 1013, and 243, respectively, in the tamoxifen arm and 1151, 993, and 241, respectively, in the placebo arm.

the tamoxifen arm and 864 (69%) of 1244 participants in the placebo arm were compliant at 70 months, as determined by direct questioning and confirmed by blood tests in a subset of participants in both arms of the trial for tamoxifen and its metabolites. In that first report, even an analysis that was restricted to compliant patients found that tamoxifen did not reduce the incidence of breast cancer compared with placebo, in spite of the levels of serum lipids, clotting factors, and bone density and endometrium effects being similar to those reported by other tamoxifen trials (8).

In this second analysis, after a median follow-up of more than 13 years and the occurrence of nearly 200 breast cancer events, tamoxifen still fails to statistically significantly reduce the overall incidence of breast cancer. However, we did find a nonstatistically significant trend for a 22% reduced risk of invasive breast cancer in the tamoxifen arm compared with the placebo arm ($P = .1$). This result is similar to the values reported by the IBIS1 trial (5), which found a nonstatistically significant reduced risk of 32% after a median follow-up of more than 4 years, and the NSABP P-1 trial (3), which found a highly statistically significant 49% reduced risk for invasive breast cancers ($P<.001$) after a median follow-up of only 4.5 years. The Italian national trial reported that tamoxifen had no effect after a median follow-up of approximately 7 years (6). A meta-analysis of all these trials found a 38% reduction in breast cancer incidence in the tamoxifen arm compared with the placebo arm (9). Results of these trials are all probably statistically compatible, and differences in invasive breast cancer incidence may relate, in part, to the different risk factor profile for the populations in the studies. NSABP P-1 participants were selected on the basis of their risk of breast cancer by use of the Gail model. In the Marsden trial, participants were younger and had a higher relative risk that was based on their family history of breast cancer. Participants in the IBIS-1 were similar to those in the Marsden trial, but they were at lower risk. Participants in the Italian national trial were not at increased risk, all had had a hysterectomy, and most had had an ovariectomy; the latter of which may have compromised the prevention effect of tamoxifen in that trial.

Our study has several limitations. It is a small study compared with the NSABP P-1 trial, although it does have a much longer blinded follow-up. This trial did allow hormone replacement therapy, which the NSABP P-1 trial did not, but we have not observed any evidence that our results were confounded by such use. Participants in the Marsden trial were younger and had a stronger risk from a family history of breast cancer than participants in the NSABP P-1 trial. This difference in selection may give rise to a breast cancer risk that is biologically different from that of the NSABP P-1 population.

Analyses of clinical trials testing another selective estrogen receptor modulator, raloxifene, primarily as an antiosteoporotic agent have found statistically significant reductions in the incidence of breast cancer, which was reduced by 72% at 4 years (10) and by 66% at 8 years (11). Also, in a cardioprotective trial of raloxifene, after a median follow-up of 5.6 years, no effect on the incidence of heart events was observed, but a statistically significantly 44% reduced risk of invasive breast cancer and a statistically significantly 55% reduced risk of ER-positive breast cancer were reported (12). In these trials, a statistically significantly reduced rate of vertebral fractures was found that was similar to that reported by the NSABP P-1 trial for tamoxifen (3,13,14). The results of these trials led the NSABP to conduct their P-2 trial, which was designed as a head-to-head comparison of tamoxifen with raloxifene, but with no placebo arm. Analysis of the P-2 trial found an almost identical incidence of invasive breast cancer in the tamoxifen and raloxifene arms, indicating that both are equally effective at reducing breast cancer risk. There were, however, fewer toxic gynecologic events with raloxifene than with tamoxifen (15).

A common feature of all these trials is that tamoxifen and raloxifene do not appear to reduce the incidence of ER-negative breast cancer, even after the long follow-up in the Marsden trial, indicating that ER-negative cancers may not initially arise from ER-positive breast cancer cells. However, a statistically significant

Table 3. Adverse events in the two treatment groups during and after treatment*

Adverse event	No. on treatment or for whole follow-up†			No. after treatment		
	Tamoxifen arm	Placebo arm	*P*	Tamoxifen arm	Placebo arm	*P*
Nausea	131	147	.3	8	4	.3
Vomiting	17	26	.2	2	2	1.0
Headaches	227	244	.4	18	14	.5
Hot flushes	598	394	<.001	73	47	.001
Weight gain	275	319	.03	26	12	.02
Period abnormality	496	439	.02	119	87	.008
Breast symptoms	65	60	.7	10	14	.5
Mood change	112	119	.6	13	14	1.0
Vaginal discharge	321	167	<.001	41	17	.001
Eye problems	94	86	.6	10	2	.02
Fluid retention	60	68	.5	2	0	.3
Hair or nail problems	92	79	.3	3	0	.1
Skin rash	103	107	.8	8	3	.1
Sleep disturbance	41	40	.7	5	1	.1
Indigestion	13	16	.6	3	1	.4
Other abdominal problems	70	55	.2	8	3	.1
Aches in joints	67	57	.4	4	4	1.0
Dizzy	54	57	.8	4	3	.7
Bowel, constipation, or diarrhea	42	45	.7	2	2	1.0
Bladder symptoms	27	25	.9	3	1	.4
Vasomotor symptoms	162	96	<.001	19	10	.1
Weight loss or appetite change	23	28	.5	3	7	.3
Lethargy	77	79	.9	7	7	1.0
Hypertension	26	30	.6	3	0	.1
Vaginal symptoms	37	17	.008	1	0	.5
Muscular cramps	32	19	.09	2	1	.5
General malaise	34	25	.3	0	3	.3
Loss of libido	23	26	.7	1	2	1.0
Voice change	12	19	.2	0	0	–
Gynecologic problems	37	13	.001	1	1	1.0
Cardiovascular problems	10	12	.7	11	14	.7
Venous thromboembolic events	8	3	.2	5	6	1.0
Stroke	7	9	.6	3	7	.3
Cataracts	9	1	.02	3	2	1.0
Fractures	19	22	.6	9	11	.8
Hysterectomy†	177	96	<.001			
Endometrial cancer†	13	5	.06			
Cancers other than endometrial or breast cancer†	64	70	.8			

* Events were reported from at least 3 months after treatment was stopped until the end of follow-up. Data were available for 1079 participants in the tamoxifen arm and 1034 participants in the placebo arm. Statistical significance between tamoxifen and placebo was assessed by Fisher's exact test. All statistical tests were two-sided.

† These events are reported for the entire follow-up period; other events are reported during treatment only.

69% reduced risk in ER-positive cancers was observed in the NSABP P-1 trial (4) and a statistically significant 48% reduced risk was observed in the meta-analysis of all tamoxifen trials (9). In the Marsden trial, the incidence of ER-positive breast cancer was statistically significantly reduced by 35% ($P = .005$). However, this reduced incidence was not statistically significant during the 8-year treatment period ($P = .3$) but occurred, for the most part, in the posttreatment period when a statistically significant 51% reduced risk was observed ($P = .004$). This effect on ER-positive breast cancers was sufficient to cause a 33% reduction in the incidence of all invasive cancers in the posttreatment period ($P = .05$). The reason for the weak effect during the early years of the Marsden trial is not clear. Tamoxifen, however, does appear to reduce the risk of developing ER-positive breast cancer for at least 15 years after treatment ends.

The profile of adverse events associated with tamoxifen treatment over this 20-year study period was similar to that previously reported. Gynecologic problems made up the primary adverse events, and these events occurred predominantly during the treatment period. There were concerns that tamoxifen had been shown to be genotoxic in the laboratory (16). It is therefore reassuring that the incidence of endometrial cancer did not continue to increase with longer follow-up and that there was no observed increase in the incidence of other cancers.

In conclusion, because this trial was initially negative, unlike the NSABP P-1 trial, a much longer double-blinded follow-up

was allowed, with a median follow-up of more than 13 years. Although, with this long follow-up, we still could not demonstrate a statistically significant advantage of tamoxifen over placebo in prevention of invasive cancer, we did demonstrate a reduction in the incidence of ER-positive invasive cancers that was similar to values reported for other primary prevention trials. This overall risk reduction for ER-positive cancers occurred for the most part after the treatment period, indicating a preventative rather than a treatment action by tamoxifen on estrogen-dependent disease.

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Notes

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