Five Versus More Than Five Years of Tamoxifen for Lymph Node-Negative Breast Cancer: Updated Findings From the National Surgical Adjuvant Breast and Bowel Project B-14 Randomized Trial

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Background: **Previously reported information from B-14, a National Surgical Adjuvant Breast and Bowel Project (NSABP) randomized, placebo-controlled clinical trial, demonstrated that patients with estrogen receptor (ER)-positive breast cancer and negative axillary lymph nodes experienced a prolonged benefit from 5 years of tamoxifen therapy. When these women were rerandomized to receive either placebo or more prolonged tamoxifen therapy, they obtained no additional advantage from tamoxifen through 4 years of follow-up. Because the optimal duration of tamoxifen administration continues to be controversial and because there have been 3 more years of follow-up and a substantial increase in the number of events since our last report, an update of the B-14 study is appropriate.** ***Methods:*** **Patients (n = 1172) who had completed 5 years of tamoxifen therapy and who were disease free were rerandomized to receive placebo (n = 579) or tamoxifen (n = 593). Survival, disease-free survival (DFS), and relapse-free survival (RFS) were estimated by the Kaplan–Meier method; the differences between the treatment groups were assessed by the log-rank test. Relative risks of failure (with 95% confidence intervals) were determined by the Cox proportional hazards model. *P* values were two-sided.** ***Results:*** **Through 7 years after reassignment of tamoxifen-treated patients to either placebo or continued tamoxifen therapy, a slight advantage was observed in patients who discontinued tamoxifen relative to those who continued to receive it: DFS = 82% versus 78% (*P* = .03), RFS = 94% versus 92% (*P* = .13), and survival = 94% versus 91% (*P* = .07), respectively. The lack of benefit from additional tamoxifen therapy was independent of age or other characteristics.** ***Conclusion:*** **Through 7 years of follow-up after rerandomization, there continues to be no additional benefit from tamoxifen administered beyond 5 years in women with ER-positive breast cancer and negative axillary lymph nodes. [J Natl Cancer Inst 2001;93: 684–90]**

In 1982, the National Surgical Adjuvant Breast and Bowel Project (NSABP) implemented the B-14 trial, a randomized, placebo-controlled clinical study in 4127 women. This study had been designed to evaluate the worth of tamoxifen in patients with estrogen receptor (ER)-positive breast tumors and negative axillary lymph nodes. First reports from B-14 demonstrated a benefit from tamoxifen in such patients *(1,2).* When the placebo and tamoxifen groups were compared, there was a highly statistically significant benefit in disease-free survival (DFS) through 5 years of follow-up among tamoxifen-treated women of all ages *(2).* That advantage was related to a reduction in the rate of tumor recurrence at local-regional and distant sites (this included ipsilateral breast tumor recurrence [IBTR] after lumpectomy and breast irradiation), as well as a decrease in the rate of occurrence of a second primary cancer in the contralateral breast. Subsequent findings, which were reported in 1996 *(3),* demonstrated that the 5-year benefit in DFS that had been observed after tamoxifen administration had persisted through at least 10 years of follow-up. A statistically significant survival benefit through 10 years was also observed.

A second aim of the B-14 study was to determine whether more than 5 years of tamoxifen administration would provide an advantage greater than that observed when administration of the drug was limited to 5 years. Consequently, women who had completed the initially assigned 5 years of tamoxifen therapy and who were free of disease were rerandomized to either an additional 5 years of tamoxifen therapy or to 5 years of placebo. Interim results at the third of four scheduled analyses demonstrated that continuation of the trial to its intended end point would not result in an advantage for additional tamoxifen therapy. Thus, the statisticians recommended to an independent data-monitoring committee (DMC) that the trial be unblinded and that the treatments be discontinued. After the DMC had concurred with that recommendation, use of those agents was terminated in November 1995, and the National Cancer Institute (Bethesda, MD) recommended that, outside a clinical trial, tamoxifen therapy should be limited to 5 years in women with lymph node-negative, ER-positive breast cancer *(4).* A more detailed account of the results obtained through 4 years of follow-up was subsequently reported in a peer-reviewed publication *(3).*

Although it has generally been accepted that the advantage from tamoxifen therapy is maintained for at least 10 years, the findings relative to the optimal duration of such therapy are controversial *(5–17),* and the question of how long to administer

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See "Notes" following "References."

the drug remains an issue of considerable clinical importance. Because there have been 3 years of additional follow-up since our previous report, an update of the B-14 findings as they relate to the efficacy of administering tamoxifen beyond 5 years is appropriate.

Subjects and Methods

A detailed account of 1) study design, 2) entry and eligibility requirements, 3) patient and tumor characteristics, 4) treatment, 5) compliance with therapy, and 6) statistical methods has been presented in prior reports of the B-14 trial *(1,3)*. The following is a summary of those aspects of the study that relate to a determination of the worth of 5 versus more than 5 years of tamoxifen therapy.

Study Design

Women with operable breast cancer and axillary lymph nodes that were determined to be negative on histologic examination were eligible for the B-14 study if their tumors were ER positive and if they fulfilled other eligibility criteria common to NSABP clinical trials. After patients had undergone surgery and had given written informed consent, they were stratified according to age, tumor size, type of surgery, and tumor ER content. From January 4, 1982, through January 25, 1988, a total of 2892 patients at participating NSABP institutions were randomly assigned within these strata to receive either placebo or tamoxifen. After completion of the first randomization, a second group of 1235 women who met the same eligibility requirements as the randomly assigned patients were entered in a registration arm of the study from January 26, 1988, through October 17, 1988, to receive tamoxifen for 5 years; this group of patients was recruited to provide additional tamoxifen-treated patients for the second randomization described below. For a comparison of the outcome of patients who received 5 years of tamoxifen with that of patients who received more than 5 years of the drug, women in both the randomized and registered groups who had completed the initially assigned 5 years of tamoxifen treatment, who did not discontinue therapy because of side effects or for other reasons, who did not have either a breast tumor recurrence or a second primary cancer, and who consented to participate were eligible for rerandomization to either 5 years of placebo or to a second 5 years of tamoxifen therapy. That double-blinded rerandomization began before the first report of findings from B-14 through 5 years of follow-up *(1)*. From April 7, 1987, through March l4, 1994, a total of 1172 patients were rerandomized—579 in the placebo group and 593 in the tamoxifen group (Table 1). Ninety-eight percent (1152) of the women in both groups were eligible with follow-up. The eligible cohort analyzed in this article excludes one patient who had been included in the 1996 report *(3)* and who was determined to have had an event before rerandomization.

Patient and Tumor Characteristics

Characteristics of eligible patients who participated in the randomization are shown in Table 2. Relevant characteristics were balanced across treatment groups. In both treatment groups, 26% of the patients were less than 50 years of age, 56% were treated with mastectomy, and about 67% had tumors less than or equal to 2.0 cm in size. The distribution of tumor ER and progesterone-receptor (PgR) levels, as well as of race, was similar.

Table 1. Treatment assignment and patient eligibility

	Placebo		Tamoxifen	
	No. of patients	%*	No. of patients	%*
Randomly assigned	579		593	
Ineligible	10	1.7	10	1.7
Events prior to 5 y	6		2	
Other	4		8	
Eligible with follow-up	569	98.3	583	98.3
Median follow-up time, mo		81		

*% of enrolled patients.

Table 2. Characteristics of eligible patients with follow-up data, according to treatment assigned at randomization

Characteristic*	Placebo, % (n = 569)	Tamoxifen, % (n = 583)
Age, y		
≤49	26	26
50–59	30	30
≥60	44	44
Mean ± standard deviation	56 ± 9	56 ± 10
Menopausal status		
Premenopausal/perimenopausal	25	27
Postmenopausal	74	73
Unknown	1	<1
Type of surgery		
Total mastectomy	56	56
Lumpectomy + XRT†	44	44
Clinical tumor size, cm		
≤2.0	65	68
2.1–4.0	33	28
≥4.1	2	4
Mean ± standard deviation	2.1 ± 1.1	2.0 ± 1.2
Estrogen receptor level, fmol/mg of cytosol protein		
10–49	40	44
50–99	25	21
≥100	35	35
Progesterone receptor level, fmol/mg of cytosol protein		
0–9	20	22
10–49	22	24
50–99	14	15
≥100	44	40
Unknown	0	0
Race		
White	92	92
Black	4	3
Other	3	4
Unknown	2	1

*At time of initial randomization or registration.
†XRT = radiation therapy.

Treatment and Compliance With Therapy

All patients received either tamoxifen (10 mg twice a day given orally) or placebo, similarly administered. Placebo and tamoxifen tablets were indistinguishable on the basis of both taste and physical appearance. The pharmacologic formulation of the placebo was identical to that of the tamoxifen, except for the absence of active drug. Double blinding was used so that, short of blood analyses, neither medical personnel nor study participants knew the type of treatment that was administered.

Information about compliance with protocol therapy was provided in our previous report; 1.9% of the women who were randomly assigned to receive placebo and 1.3% of those randomly assigned to receive tamoxifen did not begin therapy. An additional 11.7% and 15.0% of the women in the placebo and tamoxifen groups, respectively, discontinued therapy. Although women who received placebo stopped treatment more frequently for nonmedical reasons, medical reasons for discontinuing therapy were more frequent among tamoxifen-treated women.

The mean duration of tamoxifen therapy was 19 months in women who started the drug after rerandomization but who then discontinued it. The mean duration of therapy in women who were compliant, i.e., who took the drug for 5 years, until treatment failure or until it was discontinued when the study results were disclosed, was 38 months. These values were 16 and 40 months, respectively, for the placebo group.

Statistical Methods

DFS and overall survival were computed by use of the Kaplan–Meier estimator *(18)*. The events used in the determination of DFS included first local

recurrence of disease (including IBTR after lumpectomy), regional and distant metastases, occurrence of tumor in the contralateral breast, occurrence of second primary tumors, and deaths before these events. Events for determination of relapse-free survival (RFS) included a first recurrence of disease at local, regional, or distant sites. An IBTR was considered to be a local event. Although contralateral breast cancers were considered to be breast cancer events, they were not judged to be recurrences and were, therefore, not included in the determination of RFS. Contralateral breast cancers, other second primary cancers, and deaths that occurred before treatment failure were censored observations. Deaths from all causes were included in the analysis of overall survival.

The statistical significance of the differences between the treatments was determined by use of the log-rank test *(19).* Exact binomial tests were used to compare average annual hazard rates in the treatment groups according to the type of event. Treatment effects adjusted for covariates, prognostic significance for individual covariates, and potential covariate interactions were examined by use of the Cox proportional hazards model *(20).* The relative risk of failure with 95% confidence interval (CI) was determined by use of the Cox model. To assess proportionality of hazards, we categorized events according to whether they occurred within 5 years after the initiation of rerandomization or subsequent to 5 years. A time-dependent Cox model with terms representing treatment group, time period, and their interaction was fit to the data, and a test of the interaction term by means of a Wald test was used to assess proportionality of hazards. All *P* values were derived from a two-sided test for significance and relate to total follow-up time. Values below .05 were considered to be statistically significant.

All findings in this article, except for those that pertain to compliance, were derived from analyses that used all protocol-eligible patients (*see* Tables 1 and 2). An analysis that used all patients, regardless of their eligibility status, resulted in no substantive differences in conclusions. Analyses are based on information received at the NSABP Biostatistical Center as of March 31, 2000. The median duration of follow-up was 81 months.

RESULTS

DSF, RFS, and Survival (Fig. 1)

Evaluation of the 1152 eligible women with follow-up who, after 5 years of tamoxifen therapy, participated in a randomization that assigned them to receive an additional 5 years of either placebo or tamoxifen demonstrated that, through 7 years after randomization, the DFS of women who received placebo was 82% compared with 78% for women who continued tamoxifen therapy ($P = .03$). The RFS for women who received either placebo or tamoxifen was 94% and 92%, respectively ($P = .13$). The survival after 7 years of follow-up was 94% for women who received only 5 years of tamoxifen therapy and 91% for women who received tamoxifen for more than 5 years ($P = .07$).

Outcomes in Relation to Patient and Tumor Characteristics

When statistical modeling was used to determine if there was evidence of a differential effect of long-term tamoxifen according to patient or tumor characteristics (e.g., interaction between treatment and characteristics), outcomes did not differ statistically significantly by age at initial randomization (Fig. 2). In women 49 years of age or younger, the tamoxifen/placebo relative risk (RR) was 1.46 (95% CI = 0.68 to 3.15) for RFS, 1.50 (95% CI = 0.86 to 2.60) for DFS, and 0.95 (95% CI 0.25 to 3.81) for survival. For women 50 years of age or older, the RR was 1.37 (95% CI = 0.80 to 2.35) for RFS, 1.27 (95% CI = 0.95 to 1.69) for DFS, and 1.54 (95% CI = 1.01 to 2.36) for survival. The occurrence of only a few deaths among the younger patients accounts for the apparent disparity in survival when this end point was examined according to age. The effect of additional tamoxifen administration on outcomes was similar between patients with smaller and larger tumors and between those with lower and higher ER or PgR levels (data not shown).

Sites and Rates of First Events

The average annual rate (36.3) of all events (i.e., breast cancer or otherwise) per 1000 patients who received tamoxifen

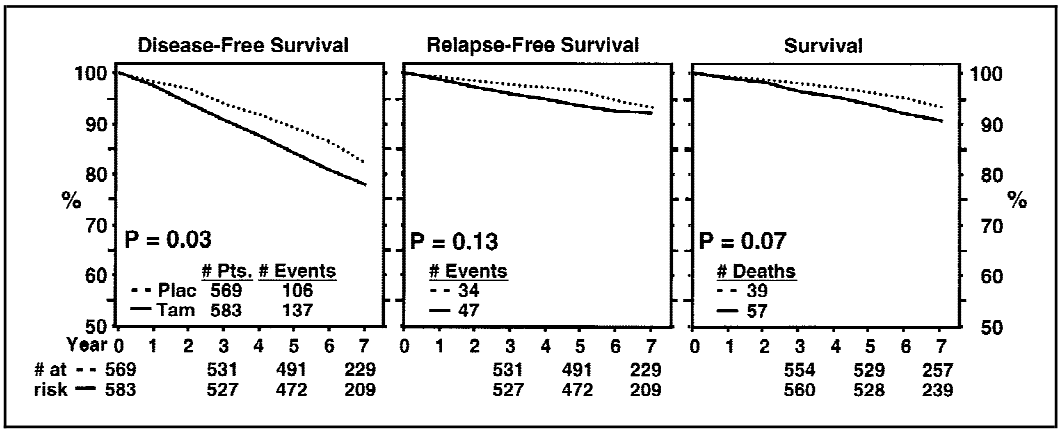

Fig. 1. Disease-free survival, relapse-free survival, and survival through 7 years of follow-up of all patients who were rerandomized after 5 years of tamoxifen to receive either placebo (Plac) or prolonged tamoxifen (Tam) therapy. All *P* values were two-sided.

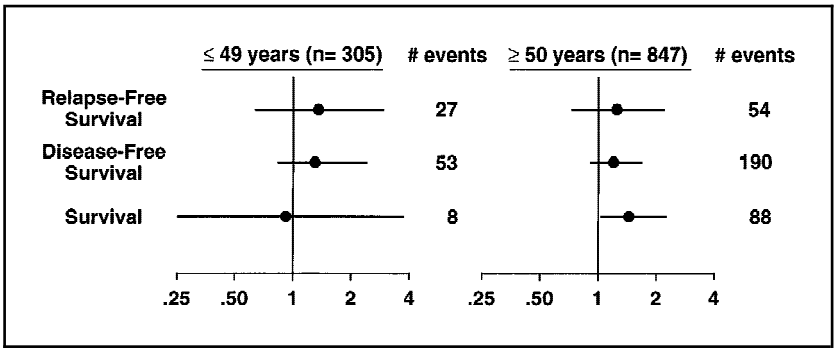

Fig. 2. Relation of relapse-free survival (RFS), disease-free survival (DFS), and survival to patient age at initial randomization: tamoxifen/placebo relative risks with 95% confidence intervals. Age by treatment interaction test: RFS, $P = .90$; DFS, $P = .56$; and survival, $P = .51$ (two-sided *P* values).

Table 3. Sites and rates of first events

Site	Placebo (n = 569)			Tamoxifen (n = 583)			Placebo versus tamoxifen		
	No. of events	%	Rate*	No. of events	%	Rate*	Rate ratio	95% confidence interval	P†
All breast cancer recurrences	34	6.0	8.9	47	8.1	12.5	1.4	0.9 to 2.2	.13
Local-regional‡	17	3.0	4.4	21	3.6	5.6	1.3	0.6 to 2.6	
Distant	17	3.0	4.4	26	4.5	6.9	1.6	0.8 to 3.1	
Second primary cancer	54	9.5	14.1	63	10.8	16.7	1.2	0.8 to 1.7	
Contralateral breast	20	3.5	5.2	17	2.9	4.5	0.9	0.4 to 1.7	
Endometrial	6	1.1	1.6	12	2.1	3.2	2.0	0.7 to 6.6	
Other	28	4.9	7.3	34	5.8	9.0	1.2	0.7 to 2.1	
Death, no evidence of disease	18	3.2	4.7	27	4.6	7.2	1.5	0.8 to 2.9	
All events	106	18.6	27.6	137	23.5	36.3	1.3	1.0 to 1.7	.03
Alive, event free	463	81.4	—	446	76.5	—			

*Average annual rate per 1000 patients.

†Two-sided *P* from log-rank test.

‡Includes ipsilateral breast tumor recurrence in patients treated with lumpectomy.

for longer than 5 years was greater than that (27.7) in women who received the drug for only 5 years (RR = 1.3; 95% CI = 1.0 to 1.7; $P = .03$) (Table 3). The findings suggest that the rate of a breast cancer recurrence was greater in the tamoxifen group, although the difference was not statistically significant (RR = 1.4; 95% CI = 0.9 to 2.2; $P = .13$). There was no difference between the placebo and tamoxifen groups in the rate of occurrence of a contralateral breast cancer (RR = 0.9; 95% CI = 0.4 to 1.7).

The incidence of endometrial cancer was six (1.1%) in women who received placebo and 12 (2.1%) in those who continued tamoxifen therapy (RR = 2.0; 95% CI = 0.7 to 6.6). There was no statistically significant difference in the rate of other second primary cancers (RR = 1.2; 95% CI = 0.7 to 2.1) or of deaths before evidence of a second tumor (RR = 1.5; 95% CI = 0.8 to 2.9). Sites of all second primary cancers (as first events) are listed in Table 4; causes of all deaths (as first events) are shown in Table 5.

Hazard Ratio as a Function of Time

An analysis of mortality from all causes, according to whether the deaths occurred either within the first 5 years after rerandomization or subsequently, is summarized in Table 6. The mortality RR was 1.7 in the first 5 years (i.e., the mortality rate was 70% higher among patients who continued to receive tamoxifen therapy) and was marginally statistically significant ($P = .05$). In contrast, the RR in years 6+ was 1.2 ($P = .61$). However, the difference in hazard ratios in the two time periods was not statistically significant ($P = .36$). A similar pattern was seen for DFS (Table 7, a and b). In the first 5 years, the event RR was 1.6 ($P = .007$); however, in years 6+, this ratio was attenuated to 1.00 ($P = .96$). Again, however, the difference between the two hazard ratios was not formally statistically significant ($P = .08$).

Table 7, a and b, provides a comparison of sites and rates of all first events (recurrences, second primary cancers, and deaths before recurrence or second primary cancers) according to whether these events occurred either within 5 years after rerandomization or subsequently. It is of interest that, for recurrences, the treatment failure RR was 2.0 in years 0–5 ($P = .02$), while, in years 6+, more recurrences occurred in the placebo group than among the tamoxifen-treated patients (16 versus 11; RR = 0.7; $P = .39$). For this end point, the time-by-treatment interaction was statistically significant ($P = .03$).

Table 4. Number of second primary cancers as first events

Site*	Placebo	Tamoxifen
Colon/rectum	7†	5
Liver	0	0
Other gastrointestinal organs	4	3
Lung and bronchus	4	6
Soft tissue	2	2
Skin (melanoma)	3	3
Endometrium	6	12
Urinary system	1	3
Lymphatic system (non-Hodgkin's lymphoma)	0	2
Other	8	9
Unknown	0	1
Total	35†	46

*Contralateral breast cancers were excluded.

†Includes one ineligible patient.

Discussion

The current findings continue to support our previously reported observations from the B-14 trial that there was no benefit from administering tamoxifen for longer than 5 years to women with ER-positive tumors and negative axillary lymph nodes *(3).* Some commentators considered the follow-up time of our first report (i.e., 4 years) too short and the number of events (i.e., recurrences and deaths) too few to permit formulating meaningful conclusions *(5,9,12,13,17).* In a detailed account, Dignam et al. *(21)* explain the statistical rationale that led to the

Table 5. Causes of death as first events

Cause of death	Placebo	Tamoxifen
Septicemia	2	2
Ischemic heart disease	2	6
Other heart disease	1	0
Cerebrovascular disease	1*	4
Diseases of the respiratory system	1	1
Diseases of the liver, gallbladder, and pancreas	1	2
Diseases of the genitourinary system	2	1
Miscellaneous	6	6
Unknown	3	5
Total	19*	27

*Includes one ineligible patient.

Table 6. Deaths that occurred within the first 5 years after rerandomization and thereafter

	Placebo (n = 569)				Tamoxifen (n = 583)				Placebo versus tamoxifen		
Years after rerandomization	No. at risk*	No. of deaths	%	Rate†	No. at risk*	No. of deaths	%	Rate†	Rate ratio	95% confidence interval	Two-sided *P*
1–5	569	20	3.5	7.2	583	35	6.0	12.4	1.7	1.0 to 3.2	.051
>5	529	19	3.6	14.9	528	22	4.2	17.4	1.2	0.6 to 2.3	.61
All	569	39	6.9	9.6	583	57	9.8	14.0	1.5	1.0 to 2.2	.07

*Beginning of the interval.

†Average annual rate per 1000 patients.

Table 7, a. Sites and rates of first events that occurred in the first 5 years after initiation of rerandomization

	Placebo (n = 569)			Tamoxifen (n = 583)			Placebo versus tamoxifen		
	No. of events	%	Rate*	No. of events	%	Rate*	Rate ratio	95% confidence interval (CI)	Two-sided *P*
All breast cancer recurrences	18	3.2	6.7	36	6.2	13.5	2.0	1.1 to 3.8	.02
Local-regional	9	1.6	3.3	14	2.4	5.2	1.6	0.6 to 4.1	
Distant	9	1.6	3.3	22	3.8	8.2	2.5	1.1 to 6.1	
Second primary cancer	31	5.4	11.5	41	7.0	15.4	1.3	0.8 to 2.2	
Contralateral breast	9	1.6	3.3	12	2.1	4.5	1.3	0.5 to 3.6	
Endometrium	4	0.7	1.5	8	1.4	3.0	2.0	0.5 to 9.1	
Other	18	3.2	6.7	21	3.6	7.9	1.2	0.6 to 2.3	
Death prior to recurrence or 2nd primary cancer	10	1.8	3.7	15	2.6	5.6	1.5	0.6 to 3.8	
All events	59	10.4	22.0	92	15.8	34.4	1.6	1.1 to 2.2	.007
Alive, event free	510	89.6		491	84.2				

Table 7, b. Sites and rates of first events that occurred more than 5 years after initiation of rerandomization

	Placebo (n = 491)			Tamoxifen (n = 472)			Placebo versus tamoxifen		
	No. of events	%	Rate*	No. of events	%	Rate*	Rate ratio	95% CI	*P*
All breast cancer recurrences	16	3.3	13.9	11	2.3	10.0	0.7	0.3 to 1.6	.39
Local-regional	8	1.6	7.0	7	1.5	6.3	0.9	0.3 to 2.9	
Distant	8	1.6	7.0	4	0.8	3.6	0.5	0.1 to 1.9	
Second primary cancer	23	4.7	20.0	22	4.7	19.9	1.0	0.5 to 1.9	
Contralateral breast	11	2.2	9.6	5	1.1	4.5	0.5	0.1 to 1.5	
Endometrium	2	0.4	1.7	4	0.8	3.6	2.1	0.3 to 23.0	
Other	10	2.0	8.7	13	2.8	11.8	1.4	0.6 to 3.4	
Death prior to recurrence or 2nd primary cancer	8	1.6	7.0	12	2.5	10.9	1.6	0.6 to 4.4	
All events	47	9.6	41.0	45	9.5	40.8	1.0	0.7 to 1.5	.96
Alive, event free	444	90.4		427	90.5				

*Average annual rate per 1000 patients.

decision to stop the trial. Briefly, the number of events necessary before a definitive analysis could have been undertaken and follow-up times at which to perform interim analyses were established *a priori.* After a third interim analysis, it was determined that, even had all of the remaining events necessary for the conduct of a definitive analysis occurred in the placebo group, the log-rank statistic would not have achieved statistical significance. The study was terminated because continuing it until the predefined number of events was reached could not have led to the conclusion that a benefit had been obtained. Moreover, there was concern that continuation of the drug could have been deleterious. At each scheduled interim analysis, a greater number of events were observed in the group of women who continued to take tamoxifen than in those who had received placebo. When the trial was terminated, a nominally statistically significant, or nearly statistically significant, advantage in DFS, distant DFS, and survival was observed in the group of women who received placebo. The current findings demonstrate that, after 7 years of follow-up, the overall number of events and deaths continues to remain greater in the tamoxifen group, and estimates of outcome still favor the placebo over the tamoxifen group. Moreover, there is still no evidence to indicate that continuing tamoxifen beyond 5 years results in a decrease in the rate of treatment failure at any site of the occurrence of a first event.

There are several reasons why our failure to observe a benefit from more than 5 years of tamoxifen administration is not surprising. Because the tamoxifen-treated women in this study had remained disease free through 5 years, their prognosis could be considered as having been good. Thus, their rate of subse-

quent breast cancer events, i.e., recurrences and contralateral breast tumors, was likely to be sufficiently low so that detection of a substantial reduction in absolute failure rates that would have occurred as a result of additional treatment with tamoxifen was unlikely. Even had continuation of the drug resulted in a small benefit, the worth of that advantage would need to be considered in conjunction with the few serious adverse events, such as endometrial cancer, pulmonary embolism, and stroke, that are associated with tamoxifen administration. Also, in view of the findings from a Swedish trial *(22)* that demonstrated only a 9% reduction in the relative risk of treatment failure when lymph node-negative patients who received tamoxifen for 5 years were compared with those who received it for 2 years, it might be conjectured that, when 5 versus more than 5 years of tamoxifen therapy are compared, the benefit might be further attenuated.

Several other studies that have evaluated the duration of tamoxifen therapy also require comment. The observations from a randomized trial conducted by the Scottish Cancer Trials Breast Group *(15),* which were described in our previous report *(3),* are concordant with our findings. Results from an exploratory trial that was conducted by the Eastern Cooperative Oncology Group to evaluate the worth of tamoxifen therapy given beyond 5 years to women with lymph node-positive and either ER-positive or ER-negative breast cancer have failed to note a statistically significant overall benefit from continuing tamoxifen beyond 5 years *(16).* When only ER-positive patients were considered, a statistically significant DFS but no survival advantage was observed. The authors of that study concluded, however, that further evaluation of adjuvant tamoxifen therapy beyond 5 years in women with lymph node-positive, ER-positive breast cancer was appropriate. Preliminary findings from a French study that compared 2 or 3 years of tamoxifen therapy with prolonged administration of the drug *(23)* suggest that the benefit from the latter is greater than that from the former. That study, however, was not designed to provide information about the worth of 5 versus more than 5 years of tamoxifen therapy.

In the data presented, there is evidence that, when the relative efficacy of continued tamoxifen therapy was compared with that of placebo, it was not constant over time. In the first 5 years after the initiation of rerandomization, women who received tamoxifen did worse than women who received placebo in terms of all-cause mortality, DFS, and RFS, with differences that were at least marginally statistically significant. Subsequent to 5 years, patients in both groups fared about equally well in terms of mortality and DFS, and patients randomly assigned to receive tamoxifen had fewer recurrences, although the numbers of events were small and the differences were not statistically significant. How these data might best be interpreted is not clear. The pattern is not well explained by the "carry-over effect," in which the continued benefit of tamoxifen beyond the period in which it is actually given might be expected to attenuate the relative benefit of continued treatment with the drug in comparison with placebo for some years beyond rerandomization. While the carry-over phenomenon would be expected to result in a time-dependent hazard ratio, it does not account for the presence of an early (relative) detrimental effect, as is suggested in the data presented here. In fact, the early relative detrimental effect observed for tamoxifen is largely a result of low event and mortality rates among placebo patients in the first 5 years after rerandomization. This observed pattern might be more consistent with phenomena associated with tamoxifen withdrawal or with tamoxifen-dependent tumor growth, but such explanations are clearly conjectural.

It has taken nearly 20 years from the time it was first shown that adjuvant tamoxifen therapy could reduce the risk of breast cancer to reach a consensus that the administration of tamoxifen for at least 5 years is preferable to administration of the drug for a shorter period of time *(24).* That conclusion was reached when it was noted that 2 years of therapy were better than 1 year *(11),* that 3 years were better than 2 *(25),* and that 5 years were better than either 2 or 3 *(11,22).* Consequently, it was reasonable to anticipate that more than 5 years of tamoxifen administration would result in a benefit greater than that observed after administration of the drug for 5 years. It was, thus, predictable that controversy would occur subsequent to our initial report that demonstrated that, when given for longer than 5 years, tamoxifen might fail to provide any additional benefit in ER-positive, lymph node-negative patients. The issue with regard to the duration of tamoxifen therapy is not likely to be completely resolved until the findings from two large British trials become available. One of those studies is the Adjuvant Tamoxifen Treatment, Offer More? (aTTom) trial *(26),* and the other is the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) Trial *(27).* Both of these trials are considered to be "pragmatic," in that patients who have undergone tamoxifen treatment are eligible, with randomization occurring when there is uncertainty about whether or not treatment should be continued *(9).* In the aTTom trial, patients who have received tamoxifen for at least 2 years are randomly assigned either to discontinue the drug or to receive it for at least 3 more years *(11).* In the ATLAS trial, women who receive tamoxifen for varying lengths of time (with 2 years being recommended, but not essential) are randomly assigned either to discontinue tamoxifen or to receive it for 5 more years *(11).*

Because it is anticipated that large populations of women (e.g., 20 000 in the ATLAS study alone) will be randomly assigned to both of these trials, it is not likely that the major findings will be available for about 10 years. Until information from these or other studies is available to indicate otherwise, the current findings provide substantial justification for our prior conclusion that there is no additional advantage for continuing tamoxifen therapy for more than 5 years in patients with ER-positive tumors and negative axillary lymph nodes.

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NOTES

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