Tamoxifen for Prevention of Breast Cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study

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Background: **The finding of a decrease in contralateral breast cancer incidence following tamoxifen administration for adjuvant therapy led to the concept that the drug might play a role in breast cancer prevention. To test this hypothesis, the National Surgical Adjuvant Breast and Bowel Project initiated the Breast Cancer Prevention Trial (P-1) in 1992.** ***Methods:*** **Women (N = 13 388) at increased risk for breast cancer because they 1) were 60 years of age or older, 2) were 35–59 years of age with a 5-year predicted risk for breast cancer of at least 1.66%, or 3) had a history of lobular carcinoma *in situ* were randomly assigned to receive placebo (n = 6707) or 20 mg/day tamoxifen (n = 6681) for 5 years. Gail's algorithm, based on a multivariate logistic regression model using combinations of risk factors, was used to estimate the probability (risk) of occurrence of breast cancer over time.** ***Results:*** **Tamoxifen reduced the risk of invasive breast cancer by 49% (two-sided *P*<.00001), with cumulative incidence through 69 months of follow-up of 43.4 versus 22.0 per 1000 women in the placebo and tamoxifen groups, respectively. The decreased risk occurred in women aged 49 years or younger (44%), 50–59 years (51%), and 60 years or older (55%); risk was also reduced in women with a history of lobular carcinoma *in situ* (56%) or atypical hyperplasia (86%) and in those with any category of predicted 5-year risk. Tamoxifen reduced the risk of noninvasive breast cancer by 50% (two-sided *P*<.002). Tamoxifen reduced the occurrence of estrogen receptor-positive tumors by 69%, but no difference in the occurrence of estrogen receptor-negative tumors was seen. Tamoxifen administration did not alter the average annual rate of ischemic heart disease; however, a reduction in hip, radius (Colles'), and spine fractures was observed. The rate of endometrial cancer was increased in the tamoxifen group (risk ratio = 2.53; 95% confidence interval = 1.35–4.97); this increased risk occurred predominantly in women aged 50 years or older. All endometrial cancers in the tamoxifen group were stage I (localized disease); no endometrial cancer deaths have occurred in this group. No liver cancers or increase in colon, rectal, ovarian, or other tumors was observed in the tamoxifen group. The rates of stroke, pulmonary embolism, and deep-vein thrombosis were elevated in the tamoxifen group; these events occurred more frequently in women aged 50 years or older.** ***Conclusions:*** **Tamoxifen decreases the incidence of invasive and noninvasive breast cancer. Despite side effects resulting from administration of tamoxifen, its use as a breast cancer preventive agent is appropriate in many women at increased risk for the disease. [J Natl Cancer Inst 1998;90:1371–88]**

On June 1, 1992, the National Surgical Adjuvant Breast and Bowel Project (NSABP) implemented a randomized clinical trial to evaluate the worth of tamoxifen for the prevention of breast cancer in women considered to be at increased risk for the disease. (The term ''prevention,'' as used in this article, indicates a reduction in the incidence [risk] of invasive breast cancer over the period of the study. Although tamoxifen prevented the appearance of a substantial number of breast cancers over the duration of this study, the term ''prevention'' does not necessarily imply that the initiation of breast cancers has been prevented or that the tumors have been permanently eliminated.) The primary aim of the NSABP Breast Cancer Prevention Trial (BCPT; P-1) was to determine whether tamoxifen administered for at least 5 years prevented invasive breast cancer in women at increased risk. Secondary aims were to determine whether tamoxifen administration would lower the incidence of fatal and nonfatal myocardial infarctions and reduce the incidence of bone fractures. Additional objectives were to evaluate breast cancer mortality and tamoxifen's adverse effects in order to assess the benefits and risks from the drug and, in keeping with recent advances, to obtain information with regard to breast cancer genetics.

Tamoxifen was chosen as the agent to be evaluated because of its demonstrated benefit when used alone as well as in combination with chemotherapy to treat advanced breast cancer *(1–5)* and because of its proven efficacy in reducing tumor re-

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See ''Notes'' following ''References.''

currence and prolonging survival when administered as postoperative adjuvant therapy in stages I and II disease *(6–10).* Findings indicating that tamoxifen-treated patients had a statistically significantly lower incidence of contralateral breast cancer *(9–13)* and that most patients used tamoxifen safely with good compliance and minimal side effects also provided justification for its evaluation as a preventive agent *(14).* Equally compelling was the extensive information related to the drug's pharmacokinetics, metabolism, and antitumor effects that had been observed in experimental animals and humans *(15–18).* In addition, there was evidence to indicate that tamoxifen interfered with the initiation and promotion of tumors in experimental systems and inhibited the growth of malignant cells by a variety of mechanisms *(19–21).*

Because tamoxifen had been shown to alter lipid and lipoprotein metabolism *(22–26),* which could reduce the risk of coronary artery disease, it seemed appropriate that the incidence of and mortality from ischemic heart disease also be assessed. In addition, there was evidence to indicate that, perhaps because of its estrogen agonist activity *(27,28),* tamoxifen might have a beneficial effect on osteoporosis. Consequently, the decision was made to determine whether tamoxifen reduced the incidence of bone fractures at selected sites.

By September 30, 1997, 13 388 women aged 35 years and older had been randomly assigned in the P-1 trial. Because this number was considered adequate to meet the study objectives as they related to breast cancer, participant entry was terminated. On March 24, 1998, an independent data-monitoring committee, which had provided oversight for the study since its inception, determined that, in accordance with prespecified rules for stopping the study, the findings indicating a reduction in breast cancer risk were sufficiently strong to justify disclosure of the results. This article is the first published report of the findings obtained from the P-1 study.

METHODS

Planning and Initiation of the Trial

In June 1990, the National Cancer Institute (NCI) invited proposals from clinical cooperative groups for a feasibility (pilot) study that, if approved, would permit the design and conduct of a protocol for a breast cancer prevention trial. These proposals were to be reviewed by the Cancer Control Protocol Review Committee in the NCI Division of Cancer Prevention and Control, by the Cancer Therapy Evaluation Program Review Committee, by representatives of the National Heart, Lung, and Blood Institute, and by other NCI/National Institutes of Health staff. In addition, external peer review was to be conducted by an *ad hoc* Special Review Committee convened by the Division of Extramural Activities of the NCI. In February 1991, the NCI and the National Cancer Advisory Board approved the application submitted by the NSABP; on July 3, 1991, the NSABP received approval from the Food and Drug Administration. Investigators from 131 clinical centers throughout the United States and Canada (*see* ''Appendix A'') were selected by a peer-review process to be contributors to the trial. All investigations conducted were approved by review boards at each institution and were in accord with an assurance filed with and approved by the U.S. Department of Health and Human Services. Each of the 131 clinical centers had on-site auditing to monitor and assess data quality. Screening for breast cancer risk eligibility was initiated on April 22, 1992, and randomization was begun on June 1, 1992.

During the first year of accrual, i.e., from June 1, 1992, through May 31, 1993, nearly half (48%) of the 16 000 women—the number originally projected as being necessary to accomplish the study goal—were accrued to the study. During the last 7 months of 1993 and the first 3 months of 1994, nearly 3300 additional participants were enrolled. Thus, by the end of March 1994, approximately 11 100 women had either been randomly assigned or had agreed to participate in the study. At that time, accrual was interrupted and was not resumed until March 1995. Randomization was completed on September 30, 1997. More detailed information regarding participant accrual has been published *(29).*

Conditions for Participant Eligibility

Women were deemed acceptable for the P-1 study if they met certain eligibility criteria defined in the protocol and were enrolled at one of the NSABP institutions that had been selected as contributors to the study. To be eligible for the trial, the participants had to have 1) signed a consent document that had been witnessed and dated before randomization; 2) been either 60 years of age or older or between the ages of 35 and 59 years with a 5-year predicted risk for breast cancer of at least 1.66% or had a history of lobular carcinoma *in situ* (LCIS); 3) had a life expectancy of at least 10 years; 4) had a breast examination that demonstrated no clinical evidence of cancer; 5) had a mammogram within 180 days before randomization that showed no evidence of breast cancer; 6) had normal white blood cell and platelet counts and normal hepatic and renal function tests; 7) not been pregnant upon entry into the study or planned not to become pregnant while on protocol therapy; 8) been accessible for follow-up; 9) undergone an endometrial sampling before randomization if they had a uterus and were randomly assigned after July 8, 1994 (Endometrial sampling upon study entry was optional for participants randomly assigned before that date.); 10) taken no estrogen or progesterone replacement therapy, oral contraceptives, or androgens for at least 3 months before randomization; and 11) had no history of deep vein thrombosis or pulmonary embolism.

Breast Cancer Risk Assessment

The algorithm for estimating breast cancer risk was based on the work of Gail et al. *(30),* who developed a multivariate logistic regression model in which combinations of risk factors were used to estimate the probability of occurrence of breast cancer over time. The variables included in the model were age, number of first-degree relatives with breast cancer, nulliparity or age at first live birth, number of breast biopsies, pathologic diagnosis of atypical hyperplasia, and age at menarche. In its original form, the model predicted the combined risk of invasive and noninvasive breast cancers for white women. Making appropriate modifications to account for a different attributable risk, we applied the risk ratio (RR) for each of the parameters used in the Gail model to the expected rates of invasive breast cancer only. Modifications to allow for race-specific determinations of breast cancer risk were also incorporated into the model. The 1984–1988 Surveillance, Epidemiology, and End Results (SEER)[1] rates of invasive breast cancer were used as the expected rates. The total U.S. mortality rates for the year 1988 were used to adjust for the age-specific competing risk of death from causes other than breast cancer.

Risk Benefit

Each woman screened was provided with a risk profile that identified her breast cancer risk and displayed a plot of projected risk over her lifetime (Fig. 1). To enable the women to make a more informed decision about their participation in the trial, each of them received information about the potential number of breast cancer and coronary artery cases that might be prevented from the use of tamoxifen, as well as the number of cases of endometrial cancer and pulmonary embolism that might be caused by the drug.

Statistical Methods

Randomization of participants in a double-blind fashion was performed centrally by the NSABP Biostatistical Center, and participants were stratified by age (35–49 years, 50–59 years, ⩾60 years), race (black, white, other), history of LCIS (yes, no), and breast cancer RR (<2.5, 2.5–3.9, ⩾4.0). To avoid imbalances in treatment assignment within a clinical center, an adaptive randomization scheme using the biased-coin method of Efron *(31)* was used.

The trial was monitored by an independent data-monitoring committee known as the Endpoint Review, Safety Monitoring and Advisory Committee (ERSMAC), which was composed of representatives with expertise in clinical trial methodology from a variety of disciplines, including oncology, gynecology, cardiology, biostatistics, epidemiology, and research ethics. The design of the study included formal interim monitoring for early stopping based on the primary end point of the trial, i.e., the incidence of invasive breast cancer. The stopping rule of Fleming et al. *(32)* was employed by the use of bounds that used less than 1% of alpha. In addition, as an informal tool to facilitate the monitoring

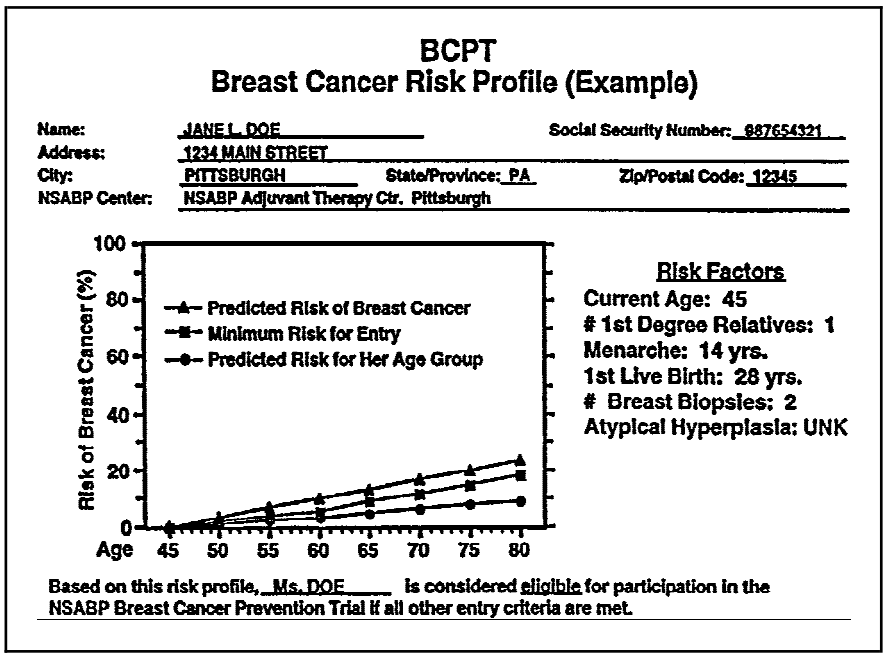

Fig. 1. Example of a breast cancer risk profile. NSABP = National Surgical Adjuvant Breast and Bowel Project; UNK = unknown. (Reproduced from Cancer Control 1997;4:78–86 with permission from the copyright holder.)

of multiple potential beneficial and detrimental outcomes, the ERSMAC adopted a form of global monitoring using a global index modeled after the one proposed by Freedman et al. *(33)* for the Women's Health Initiative trial. The use of this supplemental monitoring tool was not included in the protocol design but was adopted by the ERSMAC before the time of the first formal interim analysis.

All analyses were based on assigned treatment at the time of randomization, regardless of treatment status at the time of analysis. All randomly assigned participants with follow-up were included in the analyses. Average annual event rates for the study end points were calculated for each treatment group by means of a procedure in which the number of observed events was divided by the number of observed event-specific person-years of follow-up. *P* values (two-sided) for tests of differences between the treatment groups for the rates of invasive breast cancer, noninvasive breast cancer, and invasive endometrial cancer were determined by use of the exact method, assuming that the events came from a Poisson distribution and conditioning on the total number of events and the person-years at risk *(34)*. Under these conditions, the expected proportion of events in the tamoxifen group (p) has a binomial distribution and was defined as the number of person-years in the tamoxifen group (PY_{tam}) divided by the total number of person-years in both groups ($PY_{tam} + PY_{plac}$). The observed proportion of events (p_o) was defined as the number of events in the tamoxifen group (n_{tam}) divided by the total number of events in both groups ($n_{tam} + n_{plac}$). The *P* value for testing a difference in the event rates between the groups was then computed as an exact binomial test of the hypothesis that $p = p_o$. Event rates in the two treatment groups were also compared by use of the RR and 95% confidence intervals (CIs), in which the rate in the tamoxifen group was contrasted with that in the placebo group. CIs for RRs were also determined assuming that the events followed a Poisson distribution, conditioning on the total number of events and person-years at risk. Under this circumstance, the CI for an RR was determined by first finding the upper (p_U) and lower (p_L) limits of the CI for p_o, where $p_o = [(\text{RR})\ (PY_{tam})]/[\ (\text{RR})\ (PY_{tam} + PY_{plac})]$ and RR = 1. Then the CI for the RR was determined by solving the equation $\text{RR} = [(p)\ (PY_{plac})]/[(1 - p)\ (PY_{tam})]$, where p_U and p_L were substituted as the value of p, respectively. Cumulative incidence rates by follow-up time were determined, accounting for competing risk due to death *(35)*.

RESULTS

Study Screening, Accrual, and Follow-up Information

Breast cancer risk assessments were used to determine the eligibility of women for the study. From April 22, 1992, through May 20, 1997, risk assessments were performed for 98 018 women (Table 1); 57 641 (58.8%) of these women were deemed eligible, on the basis of their risk, for participation in the trial. Of this group, 14 453 women agreed to be medically evaluated for complete eligibility. A total of 13 954 women met all eligibility requirements. Of those, 13 388 (95.9%) were randomly assigned to receive, in a double-blind fashion, 20 mg per day of either tamoxifen or placebo for 5 years; 6707 were to receive placebo, and 6681 were to receive tamoxifen (Table 1). Both tamoxifen and placebo were supplied by Zeneca Pharmaceuticals, Wilmington, DE. After one of the participants had been randomly assigned, it was discovered that she had invasive breast cancer rather than a noninvasive lesion (LCIS), as had originally been reported following mammographic and pathologic examination. Therefore, she was not at risk for development of breast cancer and was not included in the analyses. At the time of analysis, there were 212 participants with no follow-up, 108 in the placebo group and 104 in the tamoxifen group. All of the 13 175 women at risk and with follow-up were included in the analyses. In each study group, 7.2% of the participants withdrew their consent but were followed until consent withdrawal. When the treatment groups were combined, 21.6% of the participants discontinued their assigned therapy for reasons not specified in the protocol. The proportion of women who stopped their therapy was greater in the tamoxifen group, i.e., 19.7% in the placebo group versus 23.7% in the tamoxifen group. Also, 1.6% of the participants in each study group were lost to follow-up. When the consent withdrawals were excluded,

Table 1. Summary of screening, accrual, and follow-up information for the study

Screening, accrual, and follow-up information	Placebo	Tamoxifen	Total
Breast cancer risk assessments	—	—	98 018
Women meeting risk eligibility requirement	—	—	57 641
Medical eligibility assessments	—	—	14 453
Women meeting both risk and medical eligibility requirements	—	—	13 954
Women randomly assigned	6707	6681	13 388
Not at risk for breast cancer*	0	1	1
Without follow-up	108	104	212
Included in analysis	6599	6576	13 175
Average follow-up time, mo	47.7	47.7	47.7
Median follow-up time, mo	54.6	54.5	54.6
% followed for >36 mo	74.0	73.7	73.9
% followed for >48 mo	66.7	67.0	67.0
% followed for >60 mo	37.1	36.4	36.8
Person-years of follow-up†	26 247	26 154	52 401

**See* text for details.

†Based on time at risk for death.

the percent of participants with complete follow-up was 92.4% in the placebo group and 92.3% in the tamoxifen group. The study was designed to maintain statistical power even if the rate of noncompliance, defined as permanently discontinuing tamoxifen therapy, was as high as 10% per year of follow-up. While the cumulative rate of noncompliance was below the planned level, the interruption of accrual in 1994 resulted in a substantial increase in the rates of noncompliance and of consent withdrawal. In the 6-month interval following the interruption, the proportion of women who became noncompliant or who withdrew their consent was two to three times higher than before or after that interval.

The mean time on the study for the 13 175 participants who were included in the analysis was 47.7 months; 73.9% had a follow-up exceeding 36 months, 67.0% were followed for more than 48 months, and 36.8% had follow-up exceeding 60 months. The median follow-up time was 54.6 months. All data included in this article are based on information received as of July 31, 1998, concerning follow-up through March 31, 1998. This was the cutoff point selected because it was the day before the trial was unblinded. On April 1, 1998, investigators were provided with lists identifying the treatment assignment for each participant.

Participant Characteristics

Of the 13 175 participants included in the analysis, 39.3% were 35–49 years old at randomization, 30.7% were 50–59 years old, and 30.0% were 60 years of age or older (Table 2). Only 2.6% of the participants were 35–39 years of age, and 6.0% were 70 years of age or older. Almost all participants were white (96.4%), more than one-third (37.1%) had had a hysterectomy, 6.3% had a history of LCIS, and 9.1% had a history of atypical hyperplasia. The distribution of participants among the placebo and tamoxifen groups relative to these characteristics was similar.

Almost one fourth (23.8%) of the participants had no first-degree relatives with breast cancer. More than one half (56.8%) had one first-degree relative with breast cancer, 16.4% had two, and 3.0% had three or more. About one quarter of the women had a 5-year predicted breast cancer risk that was 2.00% or less. Almost three fifths (57.6%) had a 5-year risk between 2.01% and 5.00%, and 17.4% had a risk of more than 5.00%.

Table 2. Participant characteristics at time of randomization for women included in the analyses

	Placebo		Tamoxifen	
Characteristic	No.	%	No.	%
Age, y				
35–39	185	2.8	159	2.4
40–49	2411	36.5	2422	36.8
50–59	2017	30.6	2031	30.9
60–69	1590	24.1	1571	23.9
⩾70	396	6.0	393	6.0
Race				
White	6359	96.4	6347	96.5
Black	111	1.7	109	1.7
Other	129	2.0	120	1.8
No. of first-degree relatives with breast cancer				
0	1595	24.2	1540	23.4
1	3731	56.5	3754	57.1
2	1092	16.5	1069	16.3
⩾3	181	2.7	213	3.2
Prior hysterectomy				
No	4194	63.6	4097	62.3
Yes	2405	36.4	2479	37.7
History of lobular carcinoma *in situ*				
No	6188	93.8	6161	93.7
Yes	411	6.2	415	6.3
History of atypical hyperplasia in the breast				
No	5985	90.7	5997	91.2
Yes	614	9.3	579	8.8
5-y predicted breast cancer risk, %				
⩽2.00	1660	25.2	1636	24.9
2.01–3.00	2031	30.8	2057	31.3
3.01–5.00	1791	27.1	1714	26.1
⩾5.01	1117	16.9	1169	17.8
Total	6599	100.0	6576	100.0

Breast Cancer Events

A total of 368 invasive and noninvasive breast cancers occurred among the 13 175 participants; 244 of these occurred in the placebo group and 124 in the tamoxifen group (Fig. 2). There was a highly significant reduction in the incidence of breast cancer as a result of tamoxifen administration; that decrease was observed for both invasive and noninvasive disease. For invasive breast cancer, there was a 49% reduction in the overall risk. There were 175 cases of invasive breast cancer in the placebo group, as compared with 89 in the tamoxifen group ($P<.00001$). The cumulative incidence through 69 months was 43.4 per 1000 women and 22.0 per 1000 women in the two groups, respectively. For noninvasive breast cancer, the reduction in risk was 50%; there were 69 cases in women receiving placebo and 35 in those receiving tamoxifen ($P<.002$). Through 69 months, the cumulative incidence of noninvasive breast cancer among the placebo group was 15.9 per 1000 women versus 7.7 per 1000 women in the tamoxifen group. The average annual rate of noninvasive breast cancer per 1000 women was 2.68 in the placebo group compared with 1.35 in the tamoxifen group, yielding an RR of 0.50 (95% CI = 0.33–0.77). The reduction in noninvasive cancers related to a decrease in the incidence of both ductal carcinoma *in situ* (DCIS) and LCIS. No survival differences were observed. Nine deaths were attributed to breast cancer, i.e., six in the group that received placebo and three in the tamoxifen group.

To assess the consistency of the effect of tamoxifen across the population, rates of invasive breast cancer were calculated for several subgroups of women. When age, history of LCIS, history of atypical hyperplasia, and levels of predicted risk of breast cancer were taken into consideration, tamoxifen was found to be effective in preventing breast cancer in all subgroups (Table 3). The reduction in the incidence of invasive breast cancer associated with tamoxifen ranged from 44% among women who were 49 years of age or younger at the time of randomization to 55% among those who were 60 years of age or older at randomization. Among women with a history of LCIS, the reduction in risk was 56%. The reduction was particularly noteworthy among those with a history of atypical hyperplasia—there were 23 cases

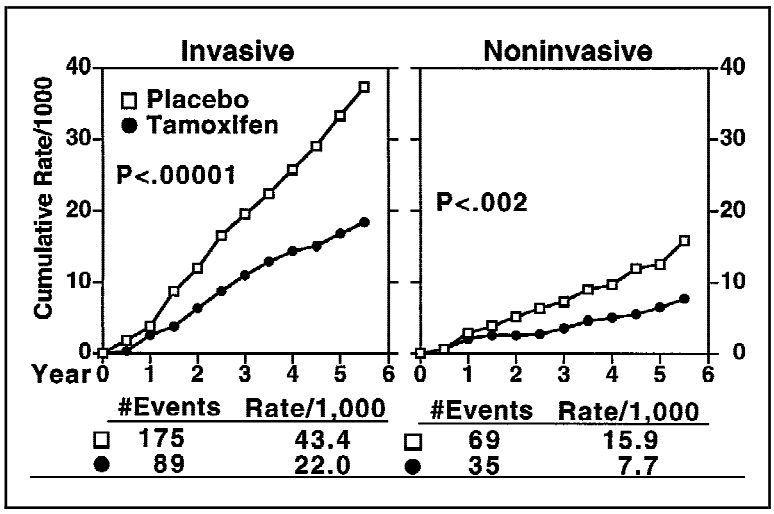

Fig. 2. Cumulative rates of invasive and noninvasive breast cancers occurring in participants receiving placebo or tamoxifen. The *P* values are two-sided.

of invasive breast cancer in the placebo group and three in the tamoxifen group. When related to the level of predicted risk among participants, the reduction of cancer risk ranged from 32% to 66%. Because the proportion of nonwhite women randomly assigned in the trial was small (3.6%), only nine invasive breast cancer events were observed in this population. Seven events occurred in black women and two in women of other races. Of the seven tumors that occurred among blacks, two were in the placebo group and five were in the tamoxifen group.

The effectiveness of tamoxifen in preventing invasive breast cancer was assessed by means of a comparison of the rates of the occurrence of that disease during each of the first 6 yearly intervals of follow-up (Fig. 3). When the average annual rate per 1000 women in the placebo group was compared with that in the tamoxifen group, there was a substantial reduction in risk for each year of follow-up in the latter group. The observed rates of reduction by year were 33%, 55%, 39%, 49%, 69%, and 55%.

Tumor Characteristics

Rates of invasive breast cancer by selected tumor characteristics are compared in Fig. 4. The annual rate of estrogen receptor (ER)-positive breast cancers was 69% less in women in the tamoxifen group. The rates were 5.02 per 1000 women in the placebo group compared with 1.58 per 1000 women in the tamoxifen group (RR = 0.31; 95% CI = 0.22–0.45). There was no evidence of a significant difference in the rates of tumors presenting as ER-negative (1.20 per 1000 women in the placebo group and 1.46 per 1000 women in the tamoxifen group; RR = 1.22; 95% CI = 0.74–2.03). Of the seven invasive breast cancers that occurred among black women, four were ER negative and three were ER positive. Of those that were ER positive, two were in the placebo group and one was in the tamoxifen group.

The rate of invasive breast cancer among women in the tamoxifen group was less than that among women in the placebo group in all tumor-size categories. The greatest difference between treatment groups was evident in the occurrence of tumors that were 2.0 cm or less in size at the time of diagnosis. The observed rates of occurrence of tumors of 1.0 cm or smaller were 2.43 per 1000 women in the placebo group and 1.43 per 1000 women in the tamoxifen group. The rates of occurrence of tumors 1.1–2.0 cm were 2.63 and 1.04 per 1000 women, respectively. The rates of occurrence of tumors of 2.1–3.0 cm were 0.85 per 1000 women in the placebo group and 0.54 per 1000 women in the tamoxifen group; for tumors 3.1 cm or larger, the rates were 0.73 and 0.42 per 1000 women, respectively.

Table 3. Average annual rates for invasive breast cancer by age, history of lobular carcinoma *in situ* (LCIS), history of atypical hyperplasia, 5-year predicted breast cancer risk, and number of first-degree relatives with breast cancer

Patient characteristic	No. of events		Rate per 1000 women		Risk ratio	95% confidence interval
	Placebo	Tamoxifen	Placebo	Tamoxifen		
All women	175	89	6.76	3.43	0.51	0.39–0.66
Age, y						
⩽49	68	38	6.70	3.77	0.56	0.37–0.85
50–59	50	25	6.28	3.10	0.49	0.29–0.81
⩾60	57	26	7.33	3.33	0.45	0.27–0.74
History of LCIS						
No	157	81	6.41	3.30	0.51	0.39–0.68
Yes	18	8	12.99	5.69	0.44	0.16–1.06
History of atypical hyperplasia						
No	152	86	6.44	3.61	0.56	0.42–0.73
Yes	23	3	10.11	1.43	0.14	0.03–0.47
5-y predicted breast cancer risk, %						
⩽2.00	35	13	5.54	2.06	0.37	0.18–0.72
2.01–3.00	42	29	5.18	3.51	0.68	0.41–1.11
3.01–5.00	43	27	5.88	3.88	0.66	0.39–1.09
⩾5.01	55	20	13.28	4.52	0.34	0.19–0.58
No. of first-degree relatives with breast cancer						
0	38	17	6.45	2.97	0.46	0.24–0.84
1	90	46	6.00	3.03	0.51	0.35–0.73
2	37	20	8.68	4.75	0.55	0.30–0.97
⩾3	10	6	13.72	7.02	0.51	0.15–1.55

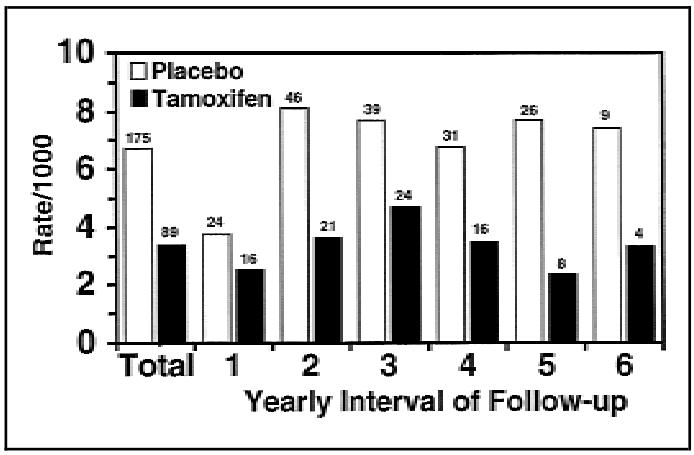

Fig. 3. Rates of invasive breast cancer occurring in participants receiving placebo or tamoxifen, by yearly interval of follow-up. Numbers above the bars indicate numbers of events.

The rate of invasive breast cancer by nodal status at the time of diagnosis differed in the two treatment groups. Because axillary dissection was not performed for all cases of invasive breast cancer, pathologic nodal status was not available for 12 women in the placebo group and for three women in the tamoxifen group. The rates of breast cancers presenting without nodal involvement were 4.48 and 2.31 per 1000 women in the placebo and tamoxifen groups, respectively. The rates of occurrence of tumors presenting with one to three involved nodes were 1.39 and 0.54 per 1000 women, respectively. The rates for cancers presenting with four or more positive axillary nodes were the same in both study groups.

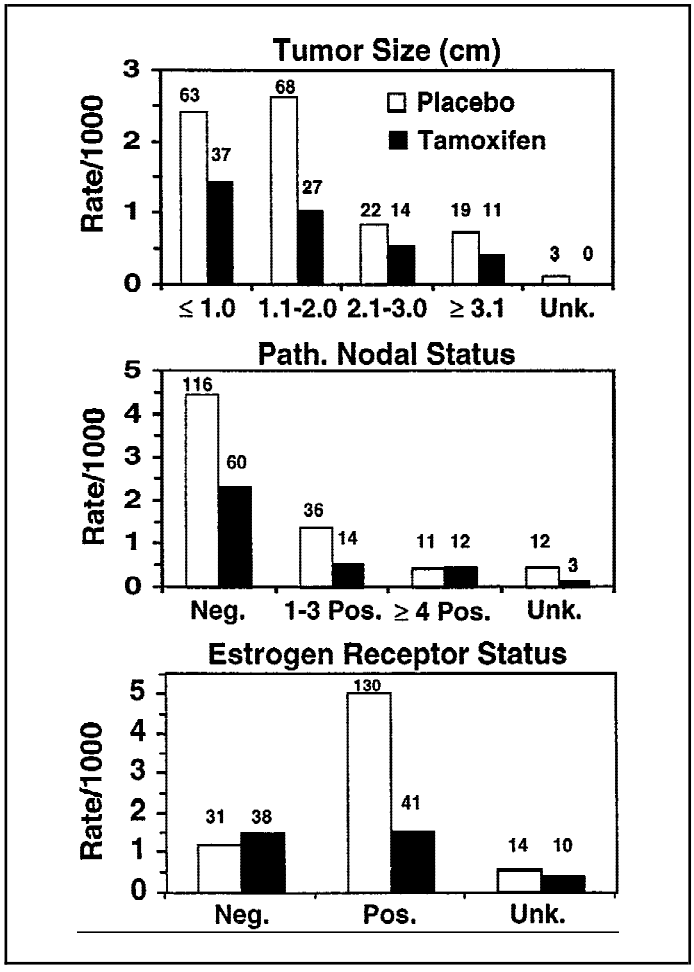

Fig. 4. Rates of invasive breast cancer occurring in participants receiving placebo or tamoxifen, by tumor size, lymph node status, and estrogen receptor status. Numbers above the bars indicate numbers of events. UNK. = unknown; Path. = pathologic; Neg. = negative; Pos. = positive.

Endometrial Cancer

Participants who received tamoxifen had a 2.53 times greater risk of developing an invasive endometrial cancer (95% CI = 1.35–4.97) than did women who received placebo, an average annual rate per 1000 participants of 2.30 in the former group and 0.91 in the latter group (Table 4). The increased risk was predominantly in women 50 years of age or older. The RR of women aged 49 years or younger was 1.21 (95% CI = 0.41–3.60), whereas it was 4.01 (95% CI = 1.70–10.90) in women aged 50 years or older. The increase in incidence after tamoxifen administration was observed early in the follow-up period (Fig. 5). Through 66 months of follow-up, the cumulative incidence was 5.4 per 1000 women and 13.0 per 1000 women in the placebo and tamoxifen groups, respectively. Fourteen (93%) of the 15 invasive endometrial cancers that occurred in the placebo group were International Federation of Gynecology and Obstetrics (FIGO) stage I, and one (7%) was FIGO stage IV. All 36 invasive endometrial cancers that occurred in the group receiving tamoxifen were FIGO stage I. Four *in situ* endometrial cancers were reported; three of these occurred in the placebo group and one in the tamoxifen group.

Invasive Cancers Other Than Cancer of the Breast and Uterus (Endometrium)

Invasive cancers at sites other than the breast and endometrium were equally distributed, with 97 cases in each group (RR = 1.00; 95% CI = 0.75–1.35) (Table 5). At no site was there evidence of a disproportionate number of events. Of particular importance were the observations that no liver cancers occurred in either group and that there was no increase in the incidence of colon, rectal, ovarian, or other genitourinary tumors. The greatest incidence of tumors occurred in the lung, trachea, and bronchus (17 in the placebo group and 20 in the tamoxifen group).

Ischemic Heart Disease

Women who experienced more than one ischemic heart disease event were categorized according to the most severe event in decreasing order from fatal myocardial infarction to acute ischemic syndrome. The number of participants who had a myocardial infarction in the placebo and tamoxifen groups was 28 and 31, respectively. Eight (29%) of the 28 events that occurred in the placebo group were fatal, as compared with seven (23%) of the 31 events in the group that received tamoxifen (Table 6). Likewise, the number of participants who had angina requiring a coronary artery bypass graft or angioplasty was 14 in the placebo group and 13 in the tamoxifen group. The number of women reported as having acute ischemic syndrome was 20 in the placebo group and 27 in the tamoxifen group (RR = 1.36; 95% CI = 0.73–2.55). Of the total number of events related to ischemic heart disease, 62 occurred in the placebo group (five in women aged ⩽49 years and 57 in women aged ⩾50 years); 71 events occurred in the tamoxifen group (10 and 61 in the two age

Table 4. Average annual rates of invasive and *in situ* endometrial cancer

Type of event	No. of events		Rate per 1000 women*		Risk ratio	95% confidence interval
	Placebo	Tamoxifen	Placebo	Tamoxifen		
Invasive cancer	15	36	0.91	2.30	2.53	1.35–4.97
Age, y						
⩽49	8	9	1.09	1.32	1.21	0.41–3.60
⩾50	7	27	0.76	3.05	4.01	1.70–10.90
In situ cancer	3	1	0.18	0.06	0.35	0.01–4.38

*Women at risk; nonhysterectomized.

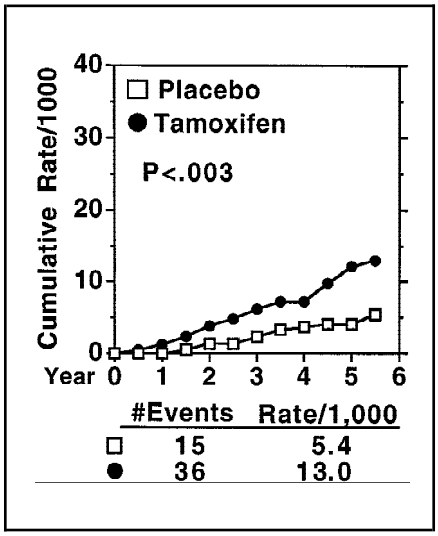

Fig. 5. Cumulative rates of invasive endometrial cancer occurring in participants receiving placebo or tamoxifen. The *P* value is two-sided.

Table 5. Distribution of invasive cancers other than breast and uterine (endometrial) cancer

Primary cancer site*	No. of cancers	
	Placebo	Tamoxifen
Mouth, pharynx, larynx	2	3
Stomach	2	1
Gallbladder	1	0
Pancreas	7	4
Retroperitoneum	1	0
Colon	9	11
Rectum	3	4
Liver	0	0
Lung, trachea, bronchus	17	20
Lymphatic, hematopoietic systems	11	14
Ovary/fallopian tube	11	10
Other genital	4	4
Urinary bladder	1	3
Kidney	3	2
Connective tissue	2	1
Skin	9	11
Nervous system	3	1
Thyroid gland	5	4
Unknown	6	4
Total	97	97
Average annual rate per 1000 women	3.72	3.73
Risk ratio (95% confidence interval)	1.00 (0.75–1.35)	

*International Classification of Diseases code 9 *(68)*.

groups, respectively). Overall, the average annual rate of ischemic heart disease was 2.37 per 1000 women in the placebo group and 2.73 per 1000 women in the tamoxifen group.

Fractures

Fractures of the hip and radius (Colles') were defined in the protocol as the primary fracture events to be evaluated in the trial. Soon after initiation of the study, fractures of the spine were also included. These three fracture sites were selected *a priori* as those that would most likely be associated with osteoporosis. Also, when the radiology reports were reviewed to identify fractures of the radius that were Colles' fractures, it became evident that, without the actual x-ray films, it was difficult to determine whether some of the lower radial fractures were Colles' or not. Thus, to ensure that reporting was complete, a fourth category of fractures, i.e., fractures of the lower radius other than Colles', was included. A total of 955 women experienced bone fractures, 483 and 472 in the placebo and tamoxifen groups, respectively. Fewer osteoporotic fracture events (combined hip, spine, and lower radius) occurred in women who received tamoxifen than in those who received placebo. Overall, 111 women in the tamoxifen group experienced fractures at one or more of these sites, as compared with 137 women in the placebo group; this represents a 19% reduction in the incidence of fractures, a reduction that almost reached statistical significance (RR = 0.81; 95% CI = 0.63–1.05) (Table 7). There was a 45% reduction in fractures of the hip (RR = 0.55; 95% CI = 0.25–1.15), a 39% reduction in Colles' fractures (RR = 0.61; 95% CI = 0.29–1.23), no reduction in other lower radial fractures (RR = 1.05; 95% CI = 0.73–1.51), and a 26% reduction in fractures of the spine (RR = 0.74; 95% CI = 0.41–1.32). The overall reduction was greater in the older age group (⩾50 years at entry) (RR = 0.79; 95% CI = 0.60–1.05).

Vascular Events

Women who experienced both a stroke and a transient ischemic attack or both a pulmonary embolism and a deep vein thrombosis were categorized according to the most severe event, i.e., stroke or pulmonary embolism, respectively. While not statistically significant at the traditional level (95% CI), the incidence of stroke increased from 24 events in the placebo group to 38 events in the tamoxifen group, i.e., from 0.92 per 1000 participants per year in the former group to 1.45 per 1000 participants per year in the latter group (Table 8). The RR was 1.59, and the 95% CI was 0.93–2.77. Fourteen of the 24 strokes that occurred in the placebo group were reported as being the result of vascular occlusion, and six were considered to be hemor-

Table 6. Average annual rates of ischemic heart disease

Type of event	No. of events		Rate per 1000 women		Risk ratio	95% confidence interval
	Placebo	Tamoxifen	Placebo	Tamoxifen		
Myocardial infarction*	28	31	1.07	1.19	1.11	0.65–1.92
Fatal	8	7	0.30	0.27	0.88	0.27–2.77
Nonfatal	20	24	0.76	0.92	1.20	0.64–2.30
Severe angina†	14	13	0.53	0.50	0.93	0.40–2.14
Acute ischemic syndrome‡	20	27	0.77	1.03	1.36	0.73–2.55
Total	62	71	2.37	2.73	1.15	0.81–1.64

*International Classification of Diseases codes 410–414 *(68).*

†Requiring angioplasty or coronary artery bypass graft.

‡New Q-wave on electrocardiogram without angina or elevation of serum enzymes or angina requiring hospitalization without surgery.

Table 7. Annual rates for fracture events among participants

Site of fracture	No. of events		Rate per 1000 women		Risk ratio	95% confidence interval
	Placebo	Tamoxifen	Placebo	Tamoxifen		
Hip	22	12	0.84	0.46	0.55	0.25–1.15
Spine	31	23	1.18	0.88	0.74	0.41–1.32
Radius, Colles'	23	14	0.88	0.54	0.61	0.29–1.23
Other lower radius*	63	66	2.41	2.54	1.05	0.73–1.51
Total	137†	111‡	5.28	4.29	0.81	0.63–1.05
≤49 y of age at entry	23	20	2.24	1.98	0.88	0.46–1.68
≥50 y of age at entry	114	91	7.27	5.76	0.79	0.60–1.05

*Excludes women who had a Colles' fracture.

†One woman had a hip fracture and a Colles' fracture, and one woman had a hip fracture and another lower radial fracture.

‡One woman had a hip fracture and a Colles' fracture, one woman had a hip fracture and a spine fracture, and two women had hip fractures and other lower radial fractures.

Table 8. Average annual rates of vascular-related events by age at study entry

Type of event by age at entry	No. of events		Rate per 1000 women		Risk ratio	95% confidence interval
	Placebo	Tamoxifen	Placebo	Tamoxifen		
Stroke*	24	38	0.92	1.45	1.59	0.93–2.77
≤49 y old	4	3	0.39	0.30	0.76	0.11–4.49
≥50 y old	20	35	1.26	2.20	1.75	0.98–3.20
Transient ischemic attack	25	19	0.96	0.73	0.76	0.40–1.44
≤49 y old	4	3	0.39	0.30	0.76	0.11–4.49
≥50 y old	21	16	1.32	1.01	0.76	0.37–1.53
Pulmonary embolism†	6	18	0.23	0.69	3.01	1.15–9.27
≤49 y old	1	2	0.10	0.20	2.03	0.11–119.62
≥50 y old	5	16	0.31	1.00	3.19	1.12–11.15
Deep vein thrombosis‡	22	35	0.84	1.34	1.60	0.91–2.86
≤49 y old	8	11	0.78	1.08	1.39	0.51–3.99
≥50 y old	14	24	0.88	1.51	1.71	0.85–3.58

*Seven cases were fatal (three in the placebo group and four in the tamoxifen group).

†Three cases in the tamoxifen group were fatal.

‡All but three cases in each group required hospitalization.

rhagic in origin. The etiology of four was unknown. Two deaths occurred in women who had the occlusive type, and one death occurred in a woman who had a stroke that was hemorrhagic in origin. Of the 38 strokes that occurred in the group receiving tamoxifen, 21 were occlusive, 10 were hemorrhagic in origin, and seven were of unknown etiology. Three of the hemorrhagic strokes were fatal. One death occurred among the seven women who experienced stroke of unknown etiology. Thus, three of the deaths that occurred in the placebo group and four that occurred in the tamoxifen group were related to stroke. When the distribution of strokes was examined according to age, the number of events in women aged 49 years or younger was similar, i.e., four in the placebo group and three in the tamoxifen group. Among women aged 50 years or older, 20 strokes occurred in those who received placebo and 35 in those who received tamoxifen. In that age group, the RR was 1.75, and the 95% CI was 0.98–3.20.

Twenty-five transient ischemic attacks occurred in the placebo group and 19 in the tamoxifen group (Table 8).

Pulmonary emboli were observed in almost three times as many women in the tamoxifen group as in the placebo group (18 versus six; RR = 3.01; 95% CI = 1.15–9.27) (Table 8). When the incidence of pulmonary embolism was related to the age of participants, there was an increase in those events in postmenopausal women who received tamoxifen. In women aged 49 years or younger, one event occurred in the placebo group and two events occurred in the tamoxifen group (RR = 2.03; 95% CI = 0.11–119.62); in contrast, in those aged 50 years or older, five events occurred in the former group and 16 in the latter group (RR = 3.19; 95% CI = 1.12–11.15).

More women who received tamoxifen developed deep vein thrombosis than did women who received placebo (35 versus 22 cases, respectively) (Table 8). The average annual rates per 1000 women were 1.34 versus 0.84 (RR = 1.60; 95% CI = 0.91–2.86). The excess risk appeared to be greater among women aged 50 years or older. For women aged 49 years or younger, the number of cases was eight in the placebo group versus 11 in the tamoxifen group (RR = 1.39; 95% CI = 0.51–3.99). In women 50 years of age or older, the number of cases was 14 versus 24, with an RR of 1.71 (95% CI = 0.85–3.58).

Cataracts

More than 1.5 years before the trial was stopped and the treatment assignments were unblinded (October 1996), the ERSMAC released information to the NSABP leadership with regard to an excess risk of cataracts and cataract surgery observed among women in the tamoxifen group. The NSABP leadership then informed officials of the NCI, the Office for Protection From Research Risks, and the principal investigators and participants in the trial. It was also provided (by the NCI) to chairpersons of the local Institutional Review Boards responsible for oversight of all breast cancer treatment trials in which tamoxifen was administered. The status regarding these outcomes at the time of this analysis is summarized in Table 9. Information on the development of cataracts was based on unconfirmed self-reporting. However, information regarding cataract surgery was verified and documented by examination of medical records. The rate of cataract development among women who were cataract-free at the time of randomization was 21.72 per 1000 women in the placebo group and 24.82 per 1000 women in the tamoxifen group. This represents an RR of 1.14, with CIs that indicate marginal statistical significance (95% CI = 1.01–1.29). There was also a difference by treatment group with respect to cataract surgery. In the placebo and tamoxifen groups, the rates of developing cataracts and undergoing cataract surgery were 3.00 and 4.72 per 1000 women, respectively (RR = 1.57; 95% CI = 1.16–2.14). A total of 943 women reported having cataracts at entry into the study. The RR of cataract surgery in these women was similar to that experienced by women who developed cataracts after randomization. This excess risk was observed primarily among women in the older age group.

Quality of Life

At each follow-up visit, participants were evaluated relative to tamoxifen-related, non-life-threatening side effects that could affect their quality of life. Information was collected with regard to the occurrence of hot flashes, vaginal discharge, irregular menses, fluid retention, nausea, skin changes, diarrhea, and weight gain or loss. A self-administered depression scale developed by the Center for Epidemiological Studies (CES-D) *(36)* was used to estimate the relation of tamoxifen to the occurrence of mental depression. Also self-reported at each visit were data from the Medical Outcomes Study Short Form 36 (MOSSF-36) and the Medical Outcomes Study (MOS) Sexual Functioning Scale *(37)*.

The only symptomatic differences noted between the placebo and tamoxifen groups were related to hot flashes and vaginal discharge, both of which occurred more often in the latter group (Table 10). The proportion of women who reported hot flashes as being quite a bit or extremely bothersome was 45.7% in the tamoxifen group, as compared with 28.7% in the placebo group. The proportion reporting vaginal discharge that was moderately bothersome or worse was 29.0% in the tamoxifen group, as compared with 13.0% in the placebo group. There were no notable differences between the two groups relative to any of the findings obtained from the various self-reporting instruments. Of particular note are the findings for depression scores determined from the CES-D scale. The distribution of participants in the two groups according to the various levels of clinical depression was almost identical. The highest depression score observed was less than or equal to 15 for 65.4% of the women in each group, and the proportion of women with a score that was greater than or equal to 30 was 9.0% in the placebo group and 8.8% in the tamoxifen group. The findings regarding quality of life will be presented in a subsequent publication.

Causes and Demographics of Deaths

Seventy-one deaths occurred among participants in the placebo group and 57 occurred among women in the tamoxifen group (RR = 0.81; 95% CI = 0.56–1.16) (Table 11). Forty-two deaths in the placebo group and 23 deaths in the tamoxifen group were due to cancer. Aside from the breast, uterus, ovary, and lung, a small number of deaths were related to cancer occurring at a variety of other sites, such as the brain, colon, pancreas,

Table 9. Average annual rates of cataracts and cataract surgery among participants

Status of participants	No. of women		Rate per 1000 women		Risk ratio	95% confidence interval
	Placebo	Tamoxifen	Placebo	Tamoxifen		
Without cataracts at randomization	6131	6101	—	—		
Developed cataracts	507	574	21.72	24.82	1.14	1.01–1.29
Developed cataracts and underwent cataract surgery	73	114	3.00	4.72	1.57	1.16–2.14

Table 10. Distribution of participants in the placebo and tamoxifen groups by highest level of hot flashes, vaginal discharge, and depression reported*

Symptom	% of participants	
	Placebo (n = 6498)	Tamoxifen (n = 6466)
Hot flashes, bothersome		
No	31.4	19.4
Slightly	18.2	14.1
Moderately	21.7	21.8
Quite a bit	18.6	28.1
Extremely	10.1	17.6
Vaginal discharge, bothersome		
No	65.2	44.8
Slightly	21.8	26.2
Moderately	8.5	16.6
Quite a bit	3.3	9.3
Extremely	1.2	3.1
Depression (CES-D)†		
0–15	65.4	65.4
16–22	16.1	15.6
23–29	9.5	10.1
30–36	5.4	5.1
⩾37	3.6	3.7

*The quality-of-life questionnaire that was used was a self-reporting instrument. Some participants opted not to complete the questionnaires. Thus, information is not available for 101 women in the placebo group and 110 in the tamoxifen group.

†CES-D refers to a self-administered depression scale developed by the Center for Epidemiological Studies *(36)*.

Table 11. Distribution of causes of death

Cause	No. of deaths	
	Placebo	Tamoxifen
Cancer	42	23
Brain	3	1
Breast	6	3
Colon	1	1
Uterus (endometrium)	1	0
Lung	11	8
Ovary	1	2
Lymphatic system	4	2
Pancreas	6	2
Extrahepatic bile duct	1	0
Kidney	2	0
Melanoma	0	1
Thyroid gland	1	0
Primary site unknown	5	3
Cardiac and vascular disease	15	22
Heart disease (ischemic and other)	12	13
Stroke	3	4
Pulmonary embolus	0	3
Arterial disease	0	2
Other	14	12
Amyotrophic lateral sclerosis	2	0
Automobile accident	2	1
Miscellaneous (11 different causes)	6	7
Unknown	4	4
Total deaths	71	57
Average annual rate per 1000 women	2.71	2.17
Risk ratio (95% confidence interval)	0.81 (0.56–1.16)	

thyroid gland, and kidney. Fifteen deaths in the placebo group and 22 deaths in the tamoxifen group were from causes related to the vascular system. Four women died of stroke in the tamoxifen group, whereas three women died of stroke in the placebo group. Two women in the tamoxifen group and none in the placebo group died of arterial disease other than stroke. Three women in the tamoxifen group and none in the placebo group died as a result of pulmonary embolism.

DISCUSSION

Although, in the past, consideration had been given to primary prevention, the aim of which was to prevent cancer by identifying and eliminating cancer-causing agents, and to secondary prevention, which involved screening individuals at increased risk for cancer in the hope that early detection and treatment would affect survival, it was not until the mid-1980s that serious attention was given to chemoprevention, an approach aimed at reducing cancer risk by the administration of natural or synthetic clinical compounds that prevent, reverse, or suppress carcinogenesis in individuals at increased risk for the disease *(38)*. Although biologic and clinical considerations related to chemoprevention have received much attention *(39–41)*, almost no studies have been directed toward evaluating the concept as it relates to breast cancer. Although information obtained in the l980s provided support for the theory that dietary fat might be associated with the occurrence of breast cancer and that restricting fat intake could perhaps reduce the incidence of the disease *(42)*, a trial to test that hypothesis has only recently been implemented. The use of retinoids for the prevention of breast cancer began to receive attention in 1987, when a study was initiated to evaluate the effectiveness of fenretinide (4-HPR) *(43)*. To date, as far as we are aware, no information with regard to breast cancer end points has been reported from that trial.

The findings in this article provide the first information from a randomized clinical trial to support the hypothesis that breast cancer can be prevented in a population of women at increased risk for the disease. They show that tamoxifen administration reduced the risk of invasive and noninvasive breast cancers by almost 50% in all age groups. Of particular importance is the finding that a benefit from tamoxifen was identified among women at various levels of risk within the spectrum of risks associated with participants in the P-1 study.

Because of the importance of knowing whether or not the finding that tamoxifen reduces the incidence of tumors can be generalized to all women, extensive effort was directed toward recruiting nonwhite participants. Despite great effort, the number of nonwhite participants was small, and there were few events among those women. For these reasons, the size of the treatment effect estimated from the total population (49% reduction of breast cancer risk) may not be a reliable estimate for nonwhite women.

Also of importance are the findings obtained in women who had a history of LCIS or atypical hyperplasia, pathologic entities thought to increase the risk of invasive breast cancer. Although the present study was not designed to address these issues, it provides the only quantitative information available from a clinical trial about the magnitude of the risk of invasive cancer in women with a reported history of LCIS or atypical hyperplasia

and presents the only information to demonstrate that tamoxifen can reduce the magnitude of that risk. When compared with women who had no history of LCIS or atypical hyperplasia, the finding of a 100% increase in the average annual rate of invasive cancer among women in the placebo group who had a history of LCIS and of a nearly 57% increase in this rate among women with a history of atypical hyperplasia clearly indicates that these pathologic entities are associated with a substantial increase in a woman's risk for invasive breast cancer. Even more important is the finding that tamoxifen administration dramatically reduced the risk of invasive cancer in women with a history of LCIS or atypical hyperplasia.

Although the findings indicating the extent to which the invasive cancer risk was reduced are compelling, the occurrence of a 50% reduction in the risk of noninvasive breast cancer is equally important for the following reasons. The expanded use of mammography has resulted in the more frequent detection of DCIS. In view of the cost involved and the effort required to diagnose these tumors and in light of the debate about both the initial and subsequent treatment of patients with DCIS and the putative relationship between DCIS and the subsequent occurrence of invasive breast cancer, a reduction in the risk of DCIS must be viewed as an important finding, since prevention of that disease would obviate the above considerations. Moreover, the reduction in the incidence of DCIS provokes consideration of the biologic significance of that finding. Cells comprising most DCIS lesions have been demonstrated to be ER positive *(44,45)*. Consequently, if DCIS is, indeed, a precursor of invasive cancer, at least some of the invasive tumors that were prevented by tamoxifen in the P-1 study could be the result of the elimination of occult DCIS by the drug. In that regard, the findings regarding the characteristics of the invasive breast cancers that occurred among the participants in the P-1 study are of importance. When the findings from tumors that occurred in the two groups were compared, it was observed that, in the tamoxifen group, there was a decreased rate of invasive cancers that were ER positive, that were 2.0 cm or less in size, or that were associated with negative lymph nodes. These observations provide insight relative to the biologic nature of the tumors that were prevented. These findings are consistent with the thesis that the benefit from tamoxifen results from its inhibition of the growth and progression of tumors that are ER positive, i.e., those that are more likely to exhibit slower growth and less likely to be associated with axillary nodal involvement. It is also of interest that LCIS and atypical hyperplasia are, most often, ER positive *(46,47)* and that there was a marked reduction in tumors that occurred in women with a history of those lesions. In view of these findings, a question to be answered relates to when cells in the biologic cascade of events leading from tumor initiation to the phenotypic expression of invasive tumors express their ER status and, thus, may be affected by tamoxifen.

Although the P-1 study was not designed to have the power to evaluate specifically the hypothesis that tamoxifen reduced the rate of heart disease, a secondary goal was to obtain information regarding the incidence of fatal and nonfatal myocardial infarctions. When the study was being designed, there was evidence that tamoxifen altered lipid and lipoprotein metabolism *(22–26)*. However, information about tamoxifen's effect on the cardiovascular system that had been obtained from clinical trials employing the drug for the treatment of breast cancer was inconclusive. The P-1 study findings that failed to demonstrate that tamoxifen reduced the risk of and mortality from ischemic heart disease differ from those obtained in the Stockholm *(48)* and the Scottish *(49)* studies, in which it was reported that tamoxifen reduced cardiac morbidity in breast cancer patients. These findings are similar, however, to those observed in the NSABP B-14 trial. In that study *(50)*, although there was a trend that suggested the possibility of such an effect, statistically significant differences in cardiovascular mortality were not observed in tamoxifen-treated patients. Thus, although tamoxifen can improve lipid profiles, its effect on the reduction of cardiovascular disease in women taking the drug remains uncertain. While the current findings suggest that tamoxifen does not play a role in preventing ischemic heart disease, they do show that, at least during the duration of the P-1 study, the drug did not have a detrimental effect on the heart.

One of the original aims of the P-1 study was to determine whether tamoxifen reduced the risk of fractures of the hip, radius (Colles'), and spine. The current findings indicating a 45%, 39%, and 26% reduction in fractures at those sites cannot be viewed as inconsequential. When considered in light of the estimate made in 1990 that 24 million American women suffer from osteoporosis, that 1.3 million fractures per year occur secondary to that disease, and that the estimate of the cost of treating such patients is $6.1 billion per year, the prevention of fractures is important for women at increased risk for breast cancer who are also at risk for osteoporosis as they age *(51)*. Because the findings with regard to fractures are based on a relatively small number of events, definitive conclusions relative to the effect of tamoxifen on the rate of fractures must await additional information.

Whether the benefit achieved from tamoxifen in the P-1 study was due to the drug's interference with the initiation and promotion of tumors or to hindrance of the growth of occult tumors is unknown. Because it is likely that a broad spectrum of molecular–biologic and pathologic changes in breast tissue existed among participants at the time of their entry into the trial, it might be assumed that both mechanisms were responsible for the finding. Nonetheless, the absence of specific information to resolve the issue does not detract from the evidence indicating that tamoxifen did, in fact, prevent the clinical expression of tumors, i.e., the goal of primary disease prevention.

The length of tamoxifen administration is another concern. It has been speculated that tamoxifen administration for only 5 years may merely delay tumor growth for a short time and that, if the drug fails to affect the process of tumor initiation and promotion, tumors will subsequently appear. In view of the time required for a tumor to become clinically evident, another concern that has been raised is that the administration of tamoxifen for only 5 years may be inadequate. Information from NSABP B-14, which indicated that the benefit from 5 years of tamoxifen administered to women with stage I ER-positive tumors remained through 10 years of follow-up, fails to support that concern *(52)*. Since the findings in that study also demonstrated that more than 5 years of tamoxifen did not enhance the drug's effect, in the P-1 study the drug was administered for only 5 years. However, additional studies with more prolonged tamoxifen administration and follow-up time are necessary before a hypothetical issue such as this one can be resolved.

Another question that has been raised by the study results relates to the timing of tamoxifen administration. In women at sufficient risk for receiving the drug, the issue of timing should not be considered critical. On the other hand, it is likely that the biologic changes that occurred in breast cells were present when participants who subsequently developed tumors were enrolled in the trial. Consequently, it is not unexpected that such tumors began to be diagnosed early in the follow-up period. Thus, it does not seem justified to delay administration of the drug to women such as those in the P-1 study who were at increased risk for breast cancer.

It is appropriate to consider whether the benefit from tamoxifen in reducing the incidence of breast cancer is sufficiently great to justify its use as a chemopreventive agent despite the risk of undesirable side effects. From the onset of the P-1 study, there has been considerable emphasis on the adverse effects of tamoxifen, particularly with regard to endometrial cancer and vascular-related toxic effects, which predominate in postmenopausal women. Recent reviews and individual studies of the relationship between tamoxifen and endometrial cancer indicate that the concern with regard to the level of excess risk of endometrial cancer may have been exaggerated and that, when endometrial cancers do occur in women who receive tamoxifen, they have as favorable a prognosis as those in women who do not receive the drug or who receive estrogen replacement therapy *(53–57)*.

In the P-1 trial, the average annual rate of invasive endometrial cancer in women 50 years of age or older who received tamoxifen was similar to what we had noted in the B-14 trial, i.e., about 2 per 1000 women per year. Of particular importance are the observations in this study that refute the claim that endometrial cancers occurring in tamoxifen-treated women are more aggressive, are less easily manageable, and cause more deaths than endometrial cancers that occur in non-tamoxifen-treated women or in those who have received hormone replacement therapy *(58)*. There is no evidence, either from this study or from any other NSABP trial *(59,60)*, to support those contentions. To date, all of the invasive endometrial cancers noted in the P-1 study in women who received tamoxifen were FIGO stage I, i.e., localized tumors. Thus, our findings fail to show that such tumors carry an unfavorable prognosis. Nonetheless, because of the increased risk of endometrial cancer, women receiving tamoxifen should have regular gynecologic examinations and should see their physicians if they experience abnormal vaginal bleeding.

Reports have appeared about the dangers of liver damage, hepatoma, colon cancer, and retinal toxicity resulting from tamoxifen administration. As the findings in this article and in reports from other NSABP studies attest, such concerns have not been substantiated. To date, no primary liver cancers have been reported in the P-1 trial and no increase in the incidence of either colon or any other second cancer, other than cancer of the uterus, has been observed. Also, no differences in the self-reporting of macular degeneration were observed (59 cases in the placebo group and 60 cases in the tamoxifen group). Reports suggesting that tamoxifen administration might be associated with ocular changes led to the conduct of a Tamoxifen Ophthalmic Evaluation Study in NSABP B-14. A recent report *(61)* from that study indicated that no cases of vision-threatening toxicity occurred among tamoxifen-treated women, although posterior subcapsular opacities were more frequently observed in that group. In this article, information is presented relative to the development of cataracts among women who were cataract free at the time of randomization. An increase in the rate of cataracts was found in the tamoxifen group. We do not consider the ophthalmic toxicities from tamoxifen administration sufficiently great to warrant withholding the drug from women such as those who participated in the P-1 trial.

Finally, as we *(10,62)* and others *(63,64)* have noted in previous investigations, certain vascular-related events reported in the P-1 study were more frequent in older women who received tamoxifen than in those who received placebo. While there was an overall increase in the average annual rate of stroke in women 50 years of age or older, uncertainty exists regarding the mechanism responsible for these results. There is also uncertainty regarding the cause of death in women who had a pulmonary embolism. Although three deaths were reported as being due to pulmonary embolism, all were associated with comorbid conditions that could have accounted for those deaths.

On the basis of the P-1 findings and this commentary, it is necessary to consider the question of who should receive tamoxifen to decrease their risk of breast cancer. The findings in this article indicate that women 50 years of age or younger who would have been eligible for the P-1 study are candidates for the drug. Similarly, women with a history of LCIS or atypical hyperplasia and postmenopausal women at high risk for breast cancer who have had a hysterectomy should be considered eligible for tamoxifen.

Women who have a history of DCIS may also be appropriate candidates for tamoxifen. Findings from other NSABP trials (B-17 and B-24) have demonstrated that the risk for an invasive breast cancer in women with localized DCIS is at least as high, if not higher, than that for women with a history of LCIS. In the current study, women in the placebo group who had a history of LCIS had an annual rate per thousand for breast cancer of 12.98. The annual rate of invasive cancer among women who underwent lumpectomy for DCIS was 23.7 (B-17) and, among those treated with lumpectomy and radiation therapy, it was 14.4 (B-24). In both of those studies, the risk of developing an invasive cancer was considerable. That risk could be substantially reduced by tamoxifen administration.

Another group of women who might also be candidates for tamoxifen are those at high risk for breast cancer because they carry BRCA1 or BRCA2 genetic mutations. In the P-1 study, blood that was obtained from participants for the conduct of future scientific investigations is now being used to determine how many of them had these mutations and whether tamoxifen decreased their breast cancer risk. While that information is, as yet, unavailable, offering women who carry these mutations the option of taking tamoxifen may be considered, since doing so provides an alternative to bilateral mastectomy.

Many women 50 years of age or older who have stopped menstruating, have not had a hysterectomy, and have no history of LCIS, DCIS, or atypical hyperplasia may also be eligible for tamoxifen. The decision relative to which of these women should or should not receive tamoxifen for breast cancer prevention is complex. The primary determinant for making such a decision relates to each woman's projected risk for breast cancer. The higher the risk, the more likely that tamoxifen would confer a benefit. Women whose breast cancer risk is sufficiently

high to offset the potential detrimental effects of tamoxifen would be candidates for the drug. However, women whose breast cancer risk is not as high should evaluate their individual benefits and risks with their physicians in order to make an informed decision with regard to the use of tamoxifen.

One way in which the benefit from tamoxifen can be estimated is to subtract the overall number of unfavorable events from the overall number of cancers prevented. Whether such a risk–benefit analysis is appropriate in deciding if tamoxifen should be used in the prevention setting is questionable. It seems inappropriate to view an endometrial cancer as being ''equivalent'' to a breast cancer, since, when endometrial cancers occur in women who receive tamoxifen, they are most often curable by hysterectomy and the mortality rate is minimal. Consequently, in the P-1 study, the breast cancers that would have occurred had tamoxifen not been used would have resulted in an estimated mortality rate that would likely have been higher than that observed from the undesirable effects of the drug. Moreover, the morbidity after hysterectomy would likely have been less than that resulting from the surgery, radiation, chemotherapy, and tamoxifen used to treat the unprevented breast cancer. Tools that can be used for determining a woman's breast cancer risk and the net effect from tamoxifen when used to prevent breast cancer are currently being developed.

As has been observed with the successive use of newer chemotherapeutic agents for the treatment of breast cancer, it is likely that new prevention agents will improve upon the benefits achieved with tamoxifen. The new NSABP chemoprevention trial P-2 represents such an effort. That trial will compare the toxicity, risks, and benefits of the selective ER modulator (SERM) raloxifene with those of tamoxifen. Raloxifene, which has been shown to prevent osteoporosis, will be evaluated in postmenopausal women to determine its value in preventing breast cancer without increasing the risk of endometrial cancer *(65)*.

The uncertainty of the clinical application of the current findings is analogous to uncertainties related to the use of systemic adjuvant therapy for breast cancer. With each demonstration of the worth of such therapy, questions continue to arise as to who should receive the treatment, i.e., who will benefit and who will not, who will not need the therapy because they will never demonstrate a treatment failure, how much of a benefit is worthwhile, and whether or not the toxicity and mortality encountered justify its administration. Despite these uncertainties, the use of adjuvant therapy was considered to be a major advance in the treatment of early stage breast cancer. The use of a chemopreventive agent denotes a similar advance in that it is being employed at an even earlier stage, i.e., during the origin and development of a phenotypically expressed cancer before its diagnosis.

Before submission of this article for publication, the results of two European studies were published *(66,67)* that failed to confirm the P-1 study findings. None of the information presented in them alters our conclusion that tamoxifen significantly reduces the probability of breast cancer in women at increased risk for the disease. The three studies are too dissimilar in design, population enrolled, and numerous other aspects to permit making valid comparisons among them. For a variety of reasons, it is unlikely that the European studies provided an adequate test of tamoxifen's effectiveness as a preventive agent. There were relatively few breast cancer events (70 in the British trial and 49 in the Italian study, as compared with 368 events in the P-1 study). It is likely that the paucity of events in the European studies was due to the relatively small number of participants and to the fact that the risk of breast cancer occurring among women in these trials was lower than that among participants in the P-1 trial. Because the criteria used for selecting participants in the Italian and the British studies were different from those used in the P-1 trial, women in those studies had a different risk for breast cancer than did P-1 trial participants, in that the expected proportion of ER-negative tumors could have been higher in them. This difference is important because tamoxifen is unlikely to prevent the occurrence of ER-negative tumors. The true statistical power of a study to detect an effect of tamoxifen would be a function of the number of tumors that are ER positive rather than a function of the total number of breast cancer events. Thus, if the expected proportion of ER-negative tumors is high, then the ability to show an effect of tamoxifen would be substantially reduced, since the statistical power that is based on the total number of events would be diminished. The fewer the number of events, the more likely it is that this reduction in statistical power is a critical factor affecting the ability to detect a difference between the study groups.

Noncompliance is another factor that affects the ability to detect differences, since it will result in a decrease of the anticipated effect of a drug. The rates of noncompliance were appreciable in the European trials. With small numbers of participants and relatively small numbers of events, as occurred in those trials, a high level of noncompliance will result in a substantial reduction in the likelihood of identifying a treatment effect. In the P-1 study, a high rate of noncompliance was used for sample-size estimates (10% per year of follow-up). Thus, the sample size was planned to be sufficiently large to preserve adequate power even in the presence of a high rate of noncompliance.

Perhaps the most important reason for the failure of the European studies to provide an adequate test of tamoxifen's effect could be due to the fact that 41% of the women in the British trial and 14% in the Italian study received hormone replacement therapy. This introduced a potential confounding factor that could have interfered with testing of the hypothesis that gave rise to the conduct of both trials. The use of hormone replacement therapy was considered to be a protocol violation in the P-1 trial. Until a clinical trial evaluating the efficacy of using tamoxifen with hormone replacement therapy is conducted, it is difficult to assess the relevance of findings from trials using that regimen.

The issue has been raised that the P-1 trial was stopped prematurely and that the findings were reported too early. The trial was stopped only when the independent monitoring committee for that study (ERSMAC), on the basis of stopping rules established before the onset of the trial, concluded that the primary study hypothesis had been confirmed beyond a reasonable doubt, i.e., that tamoxifen decreased the incidence rate of invasive breast cancer ($P<.00001$). It was concluded that additional follow-up would not have resulted in improved estimates of treatment effects that would have justified withholding from the participants on placebo the knowledge that tamoxifen was an effective prophylactic agent. This allows those women on placebo to consider taking tamoxifen. While additional studies are needed to address the issues that have arisen as a result of our findings, we consider it highly inappropriate to not offer tamoxifen to women who are similar to those in the P-1 study and who may benefit from its use as a breast cancer preventive agent.

Appendix A. Clinical centers participating*

Name of center	Principal investigator	Program coordinator
Albert Einstein Cancer Center, Philadelphia, PA	A. Desai	E. Barksdale
Allegheny Cancer Center Network, Pittsburgh, PA	N. Wolmark	D. Gosik
Alliant Health System, Louisville, KY	J. Hamm	B. MacCracken
Arizona Cancer Center, Tucson	D. Alberts	H. Fritz
Arrington Cancer Research and Treatment Center, Lubbock, TX	C. Geyer, Jr.	P. Hagan-Jones
Atlanta Breast Cancer Prevention Program	J. Lesesne	R. Hallett
Atlanta Community Women's Health Project, GA	F. Brescia	C. Shulman
Atlanta Regional CCOP	C. Austin	P. Remke
Baltimore Clinical Center, MD	G. Elias	S. Honts
Baptist Cancer Institute CCOP, Memphis, TN	L. Schwartzberg	T. Stewart
Baptist Health System, Birmingham, AL	T. Gaskin III	K. Hawkins
Baptist Regional Cancer Institute, Jacksonville	N. Abramson	P. Stokes
Bassett Hospital, Cooperstown, NY	A. Nafziger	L. Stragand
Bay Area Cancer Control Consortium, CA	J. Luce	M. Milian-Menendez
Baylor-Sammons Cancer Center, Dallas, TX	M. Grant	B. Quast
Boston University Medical Center, MA	M. Prout	L. Pottier
Breast Health Center, New England Medical Center, Boston, MA	R. Graham	C. Mullen
British Columbia Cancer Agency, Vancouver	U. Kuusk	L. Fearn
Carle Cancer Center CCOP, Urbana, IL	A. Hatfield	L. Foster
Cedar Rapids Oncology Project CCOP, IA	K. Wright	P. Brockschink
Central Illinois CCOP, Springfield	J. Wade	S. Shonkwiler
Central New York Group, Syracuse	J. Kirshner	K. Shedlock
Charleston/Morgantown Groups, WV	S. Jubelirer	E. Javins
City of Hope, Duarte, CA	L. Wagman	D. Hooks
Colorado Cancer Research Program CCOP, Denver	P. Raich	C. McElfatrick
Columbia River CCOP, Portland, OR	K. Lanier	L. Birenbaum
Columbus CCOP, OH	L. Laufman	S. Oxley
Connecticut Task Force, Hartford	P. DeFusco	J. Kulko
Credit Valley Hospital, Mississauga, ON	R. Myers	S. Neville
Creighton Cancer Center, Omaha, NE	J. Mailliard	C. Reed
Cross Cancer Institute, Edmonton, AB	A. Lees	C. Danbrook
Dana-Farber Consortium, Boston, MA	J. Garber	B. Cahoon
Dartmouth-Hitchcock Medical Center, Lebanon, NH	J. Ross	J. Strohbehn
Dayton Clinical Oncology CCOP, OH	H. Gross	E. Craddick
Duke University Medical Center, Durham, NC	L. Sutton	K. Warren
Duluth CCOP, MN	R Dalton	D. Swan
E. Carolina University, Greenville, NC	D. Lannin	M. Edwards
E. Maine Medical Center, Bangor	P. Brooks	A. Hayes-Crosby
Ellis Fischel Cancer Center, University of Missouri, Columbia	S. Standiford	T. Schulte
Fairfax Hospital, Falls Church, VA	N. Robert	M. Dittberner
Fox Chase Cancer Center, Philadelphia, PA	M. Daly	J. James
Geisinger Breast Clinic of Danville, PA	J. Evans	M. Lamey
Georgetown University Lombardi Cancer Center, Washington, DC	C. Isaacs	J. Dritschilo
Glens Falls Hospital Cancer Program, NY	D. Mastrianni	P. Maksymik
Greater Phoenix CCOP, AZ	D. King	P. Wade
Greenville CCOP, SC	J. Giguere	J. Martin
Hamilton Regional Cancer Center, ON	A. Arnold	S. Holohan
Harbor-UCLA, Torrance, CA	R. Chlebowski	V. Marsoobian
Hennepin County Medical Center, Minneapolis, MN	R. Zera	L. Tatro
Hoosier Oncology Group, Indianapolis, IN	P. Loehrer	F. Monaco
Huntsman Cancer Institute, Salt Lake City, UT	J. Ward	C. Walker
Illinois Cancer Center, Chicago, IL	A. Benson III	S. French
Illinois Masonic Cancer Center, Chicago	S. Taylor	P. Wellmann
Jewish General/St. Mary's Montreal, PQ	R. Margolese	N. Warrington
Kaiser Permanente CCOP, San Diego, CA	J. Polikoff	M. Wolgast
Lehigh Valley Hospital, Allentown, PA	M. Gittleman	E. Ladd
Long Beach Memorial Cancer Institute, CA	C. Forsthoff	F. Magy
Los Angeles Oncologic Institute, CA	C. Presant	M. Aldana
M. D. Anderson Cancer Center, Houston, TX	D. Booser	D. Weber
M. D. Anderson Cancer Network, Ft. Worth, TX	V. Stark-Vancs	E. Fisher
Main Line Health System CCOP, Wynnewood, PA	T. Frazier	L. O'Neill
Manitoba Cancer Foundation, Winnipeg, MB	D. Bowman	K. McDonald
Marshfield Clinic CCOP, WI	J. Hoehn	N. Goldberg
Mayo Clinic CCOP, Scottsdale, AZ	R. Wheeler	B. Roedig
Medical Center of Delaware CCOP, Wilmington	T. Wozniak	A. Steele
Medical College of Virginia MBCCOP, Richmond	C. Desch	G. Parker
Memorial Sloan-Kettering Cancer Center, New York, NY	A. Heerdt	R. Gross

Appendix A (continued). Clinical centers participating*

Name of center	Principal investigator	Program coordinator
Mercy Hospital CCOP, Scranton, PA	M. Hyzinski	V. Pauli
Metro-Minnesota Center, St. Louis Park	P. Flynn	A. Deshler
Midwest BCPT, Kansas City, MO	J. Paradelo	M. Goodpaster
Milwaukee Group, WI	W. Donegan	J. Jensen
Montana Group, Billings	D. Myers	S. Hall
Michigan State University, East Lansing, MI	N. Dimitrov	C. Robins
N.E. Ohio BCPT Group, Cleveland	R. Bornstein	L. Mamounas
New York Consortium: St. Vincent's Hospital/Guttman	M. Wallack	M. Montegari
N. New Jersey CCOP, Hackensack	R. Rosenbluth	J. Behr
N. Shore University Hospital CCOP, Manhasset, NY	L. Weiselberg	D. Mayberry
N.W./Virginia Mason CCOP, Tacoma, WA	I. Pierce	K. Hart
Ochsner CCOP, New Orleans, LA	C. Kardinal	M. Bateman
Ohio State/James Cancer Hospital, Columbus	W. Farrar	J. Bennett
Oklahoma City Consortium, OK	K. Boatman	M. Watson
Project for Prevention of Cancer, Sein, PQ	L. Deschenes	A. Christen
Puget Sound Oncology Consortium, Seattle, WA	R. Clarfeld	J. Machia
Roswell Park Cancer Institute, Buffalo, NY	S. Edge	P. Burke
Royal Victoria Hospital, Montreal, PQ	H. Shibata	R. Santos
Rush-Presbyterian-St. Luke Medical Center, Chicago, IL	J. Wolter	M. Escobar
S. Florida Group, Miami Beach	E. Davila	F. Cenciarelli
S. Nevada CCOP, Las Vegas	J. Ellerton	K. VanWagenen
San Joaquin Valley CGOP, Fresno, CA	R. Farah	J. Atchley
San Juan MBCCOP, Puerto Rico	W. Cáceres	D. Cuadrado
Scott & White Texas A&M, Temple, TX	K. Kimmey	E. Lagow
Sioux Community Cancer Consortium CCOP, Sioux Falls, SD	L. Tschetter	J. Norman
Southeast Cancer Control Consortium CCOP, Winston-Salem, NC	J. Atkins	R. Burgess
St. Francis Program CCOP, Tulsa, OK	G. Schnetzer III	S. Segler
St. Louis-Cape Girardeau CCOP, MO	A. Greco, Jr.	C. Antinora
St. Luke's Hospitals, CCOP, Fargo, ND	R. Levitt	D. Pilon
St. Mary/Long Beach Community, CA	S. Tchekmedyian	D. Jackson
Stanford University, Palo Alto, CA	R. Carlson	C. Schurman
Strang Cancer Prevention Center, New York, NY	M. Osborne	R. Weiss
Sutter/California Healthcare System Center, Sacramento, CA	V. Caggiano	L. Ayer-Rand
Texas Tech. University Health Sciences Center, Southwest Cancer Center, Lubbock	E. Cobos	S. Dixon
Thompson Cancer Center, Knoxville, TN	T. Panella	J. Rodgers
Toledo CCOP, OH	P. Schaefer	D. Frie
Tom Baker Cancer Centre, Calgary, AB	A. Paterson	A. Hades
Toronto Hospital Breast Group, ON	P. Goss	J. Smith
University of Alabama at Birmingham	J. Carpenter, Jr.	L. Crosby
University of Arkansas for Medical Science, Little Rock	S. Klimberg	M. Colvert
University of California–Davis Cancer Center, Sacramento	J. Goodnight, Jr.	L. Clawson
University of California–Los Angeles Center for Health Sciences	P. Ganz	B. Kahn
University of Chicago, IL	R. Arenas	B. Bulliner
University of Cincinnati Medical Center, OH	B. Aron	
University of Hawaii, Honolulu	R. Oishi	A. Kelminski
University of Iowa, Iowa City	P. Jochimsen	M. Spaight
University of Kansas, Kansas City	W. Jewell	E. Spizman
University of Kentucky Consortium, Lexington Clinic	E. Romond	M. Ashki
University of Michigan, Ann Arbor	L. Baker	B. Golden
University of Montreal, PQ	A. Robidoux	L. Robitaille
University of North Carolina, Chapel Hill	S. Bernard	B. Kaluzny
University of New Mexico Cancer Center, Albuquerque	A. Mangalik	A. Parsons
University of Pennsylvania Cancer Center, Philadelphia	M. Torosian	P. O'Neill
University of South Alabama MBCCOP, Mobile	M. Conrad	M. Grove
University of Texas Health Science Center, San Antonio	A. Cruz	I. Presas
University of Wisconsin Comprehensive Cancer Center, Madison	J. Stewart	T. Fass
Upstate Carolina CCOP, Spartanburg, SC	R. Sticca	K. Queen
USC/Norris Comprehensive Cancer Center, Los Angeles, CA	D. Spicer	E. Sales
Vermont Cancer Center/University of Vermont, Burlington	D. Krag	S. Dion
W. Pennsylvania Project, Pittsburgh, PA	V. Vogel III	L. Robertson
Wayne State University, Detroit, MI	M. Simon	C. Kresge
Wichita CCOP, KS	H. Hynes	M. Good
Wilford Hall Medical Center, TX	S. Wilks	B. Chaparro
Women's College Hospital, Toronto, ON	L. Lickley	M. Oldfield

*CCOP = Community Clinical Oncology Program; MBCCOP = Minority-Based Community Clinical Oncology Program; CGOP = Cooperative Group Outreach Program.

Appendix B. The following key personnel were involved in the planning, implementation, conduct, and analysis of the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (BCPT)

BCPT Steering Committee

Jeffrey Abrams	Nikolay V. Dimitrov	Charles Geyer, Jr.	Joan James	Richard Margolese	D. Lawrence Wickerham
Nancy Brinker	Bernard Fisher	Andrew Glass	C. Conrad Johnston, Jr.	Carol Redmond	H. Samuel Wieand
Susan Braun	John Flack	William Harlan	Carl Kardinal	Andre Robidoux	Norman Wolmark
Walter Cronin	Leslie Ford	Elizabeth Hart	Maureen Kavanah	Phillip Stott	
Mary Daly	Patricia Ganz	Brian Henderson	Joan McGowan	Victor Vogel	

Endpoint Review, Safety Monitoring, and Advisory Committee (ERSMAC)

Martin Abeloff	Theodore Colton	Laurence Freedman	Barbara Hulka	Elliot Rapaport	Barbara Tilley
Michele Carter	Polly Feigl	Lawrence Friedman	Howard Judd	Carol Redmond	

Participant Advisory Board

Elsie Anderson	Barbara Capuzelo	Elizabeth Lee	Beverly Munn	Marty Smith	Helene Wilson
Judith Bingham	Mary Ellen Gorman	Titas Marquez	Rici Rutkoff	Romenza Kaye Thomas	
Karen Brennan	Sandra Kanicki	Jeannie Morice	Mary Sankolewicz	Lonnie Williams	

BCPT Coordinator Committee

Robin Burgess	Joan James	Joelle Machia	Gwendolyn Parker	Barbara Simonick	Marilyn Zack
Anita Hades	Elisabeth Ladd	Mary Pat Matisko	Crystal Rabbas	Connie Szczepanek	
Donna Jackson	Deborah Lifsey	Nancy Morton	Sidney Shonkwiler	Diane Weber	

Osteoporosis Committee

Stewart Anderson	Sol Epstein	Carl Kardinal	Robert Lindsay	Joan McGowan	Janet Wolter
Alan Burshell	C. Conrad Johnston, Jr.				

Quality of Life Committee

David Cella	Patricia Ganz	Elizabeth Maunsell	A. H. G. Paterson	Harvey Schipper	Victor Vogel
Walter Cronin	Jean-Clause Lasry	Carol Moinpour	Wendy Schain	Sally Schumaker	John Ware, Jr.
Richard Day					

Gynecology Committee

Joseph Costantino	Charles Geyer, Jr.	Lawrence Levy	Carolyn Runowicz	D. Lawrence Wickerham	H. Samuel Wieand
Mary Daly	Maureen Kavanah	George Lewis, Jr.			

Recruitment, Promotion, and Compliance Committee

Erwin Bettinghaus	Paul Engstrom, Jr.	Mary Ketner	Rose Mary Padberg	Sherrie Reynolds	Rodger Winn
Cathy Coleman	Leslie Ford	Amy Langer	Lori Psillidis	Edmund Ricci	Antronette Yancey
Joseph Costantino	V. Craig Jordan				

Cardiovascular Committee

Joseph Costantino	William Harian	Santica Marcovina	Russell Tracy	D. Lawrence Wickerham	H. Samuel Wieand
John Flack	Lewis Kuller	Steven Reis			

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Les Butler					

National Cancer Institute (NCI)

Kathy Crosson	Jennifer Flach	Karen Johnson	Susan Nayfield	Jackie McNulty	Donna Shriner
Barbara Dunn	Leslie Ford	Sunita Kallarakal	Eleanor Nealon	Rose Mary Padberg	Kara Smigel
Alfred Fallavollita	Peter Greenwald	Richard Klausner	Barnett S. Kramer	Judy Patt	Crystal Wolfrey

NSABP Biostatistical Center

Lynne Anderson	Joseph Costantino	Arthur DeCillis	Lynn Holman	Darlene Kiniry	Michele Randolph
Stewart Anderson	Walter Cronin	Kenneth Duff	Regina Hopkins	Paul Magee	Carol Redmond
Gordon Bass	Deborah Darnbrough	Janet Famiglietti	Michael Hritz	Mary Passarello	H. Samuel Wieand
Wayne Baughman	Richard Day				

NSABP Operations Center

Jennifer Aikin	Bernard Fisher	Jacek Kopek	Colleen Meyers	Lori Psillidis	D. Lawrence Wickerham
Jill Bowlus	Gladys Hurst	Terry Mamounas	Joyce Mull	Donna Szczepankowski	Amy Wolenski
Lora Ann Bray	Mary Ketner	Mary Pat Matisko	Debra Pollak	Elizabeth Tan-Chiu	Norman Wolmark
Joan Dash					

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NOTES

[1]*Editor's note:* SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.

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