Table 16. Average annual hazard rates for invasive breast cancer in the BCPT population as of 1/31/98 (BCPT technical report).

Age group	# Events		Rate/1000		Risk ratio	95%CI
	Placebo	Tamoxifen	Placebo	Tamoxifen		
≤ 49	59	38	6.33	4.11	0.65	0.43-0.98
50-59	46	24	6.31	3.26	0.52	0.32-0.85
≥ 60	49	23	6.88	3.22	0.47	0.29-0.77
TOTAL	154	85	6.49	3.58	0.55	0.42-0.72

The characteristics of the cancers, as reported by NSABP, are summarized in the following NSABP slides:

Figure 3.

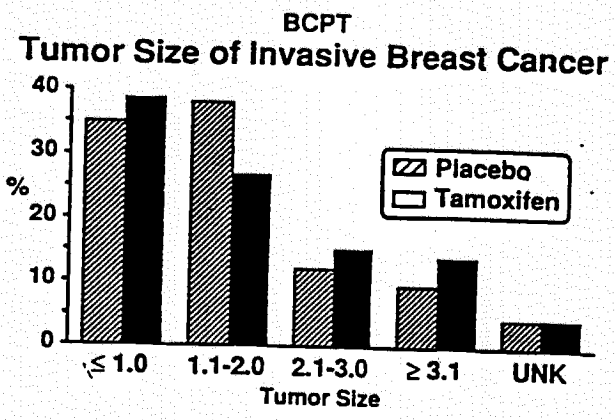
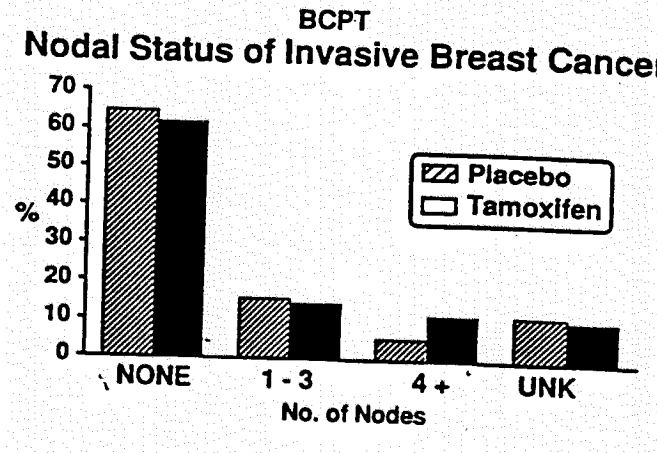


Figure 4.



From these slides, it appears that the tumor sizes at diagnosis were not statistically significantly different between treatment arms.

Approximately 60% of patients with invasive breast cancer, according to the slide, presented with node negative disease. Approximately 15% presented with 1-3 positive nodes. The rate of node negative disease is congruent with that reported from the 1998 SEER data (Landis S, Murray T, Bolden S, Wingo P. CA: J. Clin. 48: 6-30, 1998). From this slide, it appeared that no patient presented de novo with metastatic disease. However, 2 women were Stage IV at diagnosis (see Table 25).

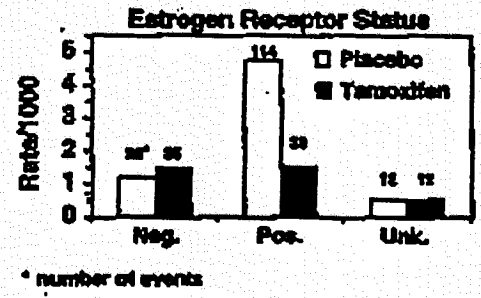
Another NSABP slide gave the ER status:

Table 17. ER status of invasive breast cancers, P-1

ER	Placebo (#)	Tamoxifen (#)
Negative	28	34
Positive	112	38
Unknown	14	13

These findings are shown graphically:

Figure 5. From Figure 4 in the P-1 manuscript



As confirmed by the NSABP, the receptor assays were performed at the local institution and forwarded. Local definitions of positive and negative were used.

From the data on this slide, it appears that tamoxifen can prevent ER(+) breast cancer, but does not affect the incidence of ER(-) breast cancer. In the placebo group, the incidence of ER(-) disease among women with breast cancer was 18%; this incidence is in keeping with what has been reported for postmenopausal women (15%) and premenopausal women (23%) (Wittliff JL. Cancer 1984; 53: 630-643).

The NSABP also presented data on the annual hazard rate for breast cancer relative to initial risks of LCIS and AH:

Table 18. Average annual hazard rates for invasive breast cancer

Pathology	Number of Events		Rate per 1000		RR
	Placebo	Tamoxifen	Placebo	Tamoxifen	
LCIS	16	7	12.7	5.50	0.43
AH	18	1	8.7	0.52	0.06

Reviewer Comment:

1. The absolute number of cases on the placebo arm was greater than on the tamoxifen arm, as was the average annual hazard rate.

2. Prospectively stratified groups included age (35-49, 50-59, and 60+), the presence or absence of LCIS, and relative risk groupings.

a. Age

Table 16 shows the absolute number of events by age, the rate per 1000, the relative risk reductions, and the 95% confidence intervals. These results are similar to those obtained in the overall trial. Of note, the number of events in younger women was slightly higher than the number of events in women over 50, validating the prospectively defined levels of risk required for study entry in this age group. These figures were validated by FDA Access queries of the electronic database and by manual review of the CRFs by Dr. Johnson.

b. LCIS

Table 18 shows the absolute number of events, the rate per 1000, and the relative risk of developing breast cancer in the subset of women with LCIS at study entry. Eight hundred thirty-four women in the trial had a diagnosis of LCIS at entry. Twenty-three of these women developed breast cancer, 16 on placebo and 7 on tamoxifen. A risk reduction similar to that seen in the overall trial was observed.

c. Relative risk levels

The FDA had information on the risk factors included in the Gail model as of 7/23/98 *(categorical but not continuous data), but did not have the software with which to calculate relative or absolute risk. Gail model software was provided in the second week of August 1998. However, it was still not possible to duplicate Gail model scores, because some of the risk factors were provided in groupings. For example, menarche was reported as* $\leq$ *age 11, age 12-13, and age* $\geq$ *14. The specific age is required to correctly calculate 5-year risk.*

In the P-1 manuscript, invasive breast cancer events by 5-year predicted breast cancer risk (%) was presented as follows:

Table 19. Average annual hazard rates for breast cancer by 5-year predicted risk

5-year Predicted Breast Cancer Risk (%)	Number of Events		Rate/1000 Women		Risk ratio (RR)	95% CI
	Placebo	Tamoxifen	Placebo	Tamoxifen		
≤2.00	30	13	5.19	2.26	0.44	0.21-0.86
2.01-3.00	39	28	5.25	3.70	0.71	0.42-1.18
3.01-5.00	36	26	5.37	4.06	0.76	0.44-1.29
≥ 5.01	49	18	12.89	4.46	0.35	0.19-0.61

Risk reductions were seen at all levels of risk, including women with the highest risk levels.

The reported risk strata do not match those prospectively outlined in the protocol, which included relative risks of < 2.5, 2.5-3.9, or > 4.0. The sponsor was asked to provide this information.

This information was provided August 12, 1998. Tamoxifen reduced the risk of breast cancer in each stratified relative risk category. The sponsor indicated that, although this stratification was used in the protocol, the baseline risk of an individual varies with age. For example, a woman of 65 with a given set of Gail model risk factors has a higher relative risk than a 35 year old woman with the same set of risk factors. The NSABP therefore chose to use 5-year predicted breast cancer risk as a better analysis of the data.

d. Summary

Overall, a risk reduction of approximately 45% was seen in the entire trial population and in the prospectively stratified groups. The internal consistency of the prospectively specified subset analyses in this large randomized double-blind trial confirms the robustness of the results.

3. Tamoxifen reduced the incidence of invasive breast cancer in the risk categories listed below, with the exception of women of color. Race and family history are discussed separately below.

Table 20. Reduction in breast cancer risk by baseline risk factors

Risk Factor	Placebo (# of Cases)	Tamoxifen (# of Cases)	% Reduction in Breast Cancer Cases
Age at Entry:			
≤ 49	59	38	36%
50-59	46	24	48%
≥ 60	49	23	53%
Race:			
White	151	79	48%
Black	2	5	-150%
Other	1	1	0
LCIS History:			
No	138	78	43%
Yes	16	7	56%
AH History:			
No	136	84	39%
Yes	18	1	94%
Age at Menarche ≤ 11:			
No	111	61	45%
Yes	43	24	44%
Age at first live birth			
None	36	15	58%
<20	13	7	46%
20-24	65	29	55%

25-29	30	26	13%
≥30	10	8	20%
Breast biopsy			
None	58	34	41%
One	52	22	58%
Two	44	29	34%

4. Because of the opposite results in non-white women, we examined the characteristics of this population.

Table 21. Breast cancer risk factors in women of color, P-1

Risk Factor	Placebo (n=252)	Tamoxifen (n=234)	Total (n=486)
Age:			
≤ 49	104 (41.3%)	88 (37.6%)	192 (39.5%)
50-59	56 (22%)	61 (26.1%)	117 (24.1%)
≥ 60	92 (36.5%)	85 (36.3%)	177 (36.4%)
Menarche:			
≤ 11	66 (26.2%)	73 (31.2%)	139 (28.6%)
12-13	129 (51.2%)	108 (46.2%)	237 (48.8%)
≥ 14	57 (22.6%)	53 (22.6%)	110 (22.6%)
Age at first live birth:			
None	36 (14.3%)	37 (15.8%)	73 (15.0%)
<20	58 (23.0%)	59 (25.2%)	117 (24.1%)
20-24	80 (31.2%)	75 (32.1%)	155 (31.9%)
25-29	55 (21.8%)	37 (15.8%)	92 (18.9%)
≥ 30	23 (9.1%)	26 (11.1%)	49 (10.1%)
Number of breast bxs:			
None	91 (36.1%)	98 (41.9%)	189 (38.9%)
1	73 (29.0%)	76 (32.5%)	149 (30.7%)
≥ 2	88 (34.9%)	60 (25.6%)	148 (30.5%)
Presence of AH:			
No	235 (93.3%)	210 (89.7%)	445 (91.6%)
Yes	17 (6.7%)	24 (10.3%)	41 (8.4%)
Presence of LCIS:			
No	229 (90.9%)	211 (90.2%)	440 (90.5%)
Yes	23 (9.1%)	23 (9.8%)	46 (9.5%)
No. 1° relatives with breast cancer:			
None	94 (37.3%)	89 (38.0%)	183 (37.7%)
1	108 (42.9%)	84 (35.9%)	192 (39.5%)
2	44 (17.5%)	49 (20.9%)	93 (19.1%)
3	5 (2.0%)	11 (4.7%)	16 (3.3%)
4	1 (0.4%)	0	1 (0.2%)
5	0	1 (0.4%)	1 (0.2%)

A somewhat higher percentage of non-white women were over the age of 60. Non-white women had a first live birth at a younger age, were somewhat more likely to have had a breast biopsy, had a higher incidence of LCIS (9.5% compared to 6.3% in the total population), and were more likely to have no family history of breast cancer (38% compared to 24% in the total population). Overall, however, the distribution of risk

factors was similar to that of the general population, and with the exception of a pre-existing diagnosis of AH (7% on placebo versus 10% on tamoxifen), factors were balanced between treatment arms.

Nine cancers were diagnosed in non-white women, 3 on the placebo arm and 6 on the tamoxifen arm. These cancers occurred from age 39 to 67 on placebo and from age 41 to 62 on tamoxifen. The number of affected first-degree relatives in these women ranged from 0-2 on the placebo arm and from 0-3 on the tamoxifen arm. The tumor sizes ranged from 1.4 to 5.5 cm on placebo and from 1.0 to 2.8 cm on tamoxifen. All of these cancers were node negative. The ER status was unknown in 1 participant on placebo and positive in 2 participants on placebo. On the tamoxifen arm, 2 tumors were ER(+), 2 were ER(-), and 2 had unknown ER status. Overall, there were no distinguishing characteristics of these tumors that set them apart from the general population.

The apparent increase in breast cancer in non-white women is probably due to the small number of events in this subgroup rather than to an adverse effect of tamoxifen.

5. We were interested in evaluating whether a family history of breast cancer alone identified most of the women who benefited from tamoxifen therapy. The following tables were generated through Access queries:

Table 22. Incidence of invasive breast cancer by family history: Entire P-1 study population

Family History	Placebo	Tamoxifen
None	31/1619 (1.9%)	16/1572 (1.0%)
1	80/3798 (2.1%)	45/3808 (1.2%)
2	34/1108 (3.1%)	18/1085 (1.7%)
3	9/144 (6.3%)	5/181 (2.8%)
4	0/30	1/28 (3.6%)
5	0/8	0/7
ALL	154/6707 (2.2%)	85/6681 (1.3%)

Table 23. Family history among women developing breast cancer

Number of affected relatives	Placebo (n=154) Number (%)	Tamoxifen (n=85) Number (%)	Total (n=239)
None	31 (20%)	16 (19%)	47
1	80 (52%)	45 (53%)	125
2	34 (22%)	18 (21%)	52
3	9 (6%)	5 (6%)	14
4	0	1 (1%)	1
≥ 5	0	0	0

The incidence of breast cancer increased with increasing numbers of affected first-degree relatives, as seen in the placebo column. However, tamoxifen reduced the risk of breast cancer by about 45% in all family history risk groups, including families with 3 affected first-degree relatives and in women without a family history of breast cancer. These data do not identify a subgroup of the women entered on the trial who did not benefit from therapy. In addition, they demonstrate that in this study, family history alone did not account for the elevated risk of breast cancer in the participants.

6. Because of the recent publication of the Royal Marsden study, we were also interested in whether younger women with more affected first-degree relatives benefited from tamoxifen.

Table 24. Family history and breast cancer risk reduction by age

Family history at Entry		Placebo (# of Cases)	Tamoxifen (# of Cases)	% Reduction in Breast Cancer Cases
Age ≤ 49	# 1° Relatives			
	0	9	7	22%
	1	30	19	37%
	2 or more	20	12	40%
Age 50-59	# 1° Relatives			
	0	8	1	88%
	1	30	16	47%
	2 or more	8	7	13%
Age ≥ 60	# 1° Relatives			
	0	14	8	43%
	1	20	10	50%
	2 or more	15	5	67%

Reductions in invasive breast cancer incidence were seen in all age groups regardless of family history with 2 exceptions:

Women aged 49 or less without first-degree relatives: This group comprised 6% of the study population and had few events. Given a small but non-significant effect in this retrospective subset analysis, this difference may be attributed to lack of power.

Women aged 50 to 59 with 2 or more affected first-degree relatives: This group had a non-significant 13% reduction in risk. Again, this group comprised a small segment of the study population and represents a retrospectively defined subgroup.

7. With regard to the reported invasive breast cancer cases, the FDA reviewers agreed that all cases represented invasive breast cancer. The characteristics of these tumors are discussed in the following comments.

8. The NSABP reported on the distribution of tumor size and nodal status. The CRFs were reviewed by Dr. Johnson to obtain this information, as the FDA did not

receive T and N status until 7/28/98. The FDA lists were then compared with information from the NSABP. The following discrepancies in reporting of tumor size (>0.5 cm difference) were found:

Placebo:

P16093BIL: This 44 year old woman was randomized to placebo and began study drug 10/17/96. She was diagnosed with invasive breast cancer 11/18/97. The NSABP reported the tumor size as 2.0 cm. The mammogram showed a 1.5 cm abnormality. The biopsy reported infiltrating ductal carcinoma of greater than 2.5 cm with extensive DCIS. A re-excision with axillary node dissection showed residual infiltrating ductal carcinoma and extensive intraductal carcinoma; margins were positive for both invasive and non-invasive cancer. The size was not given. The lymph nodes were negative. In a third procedure, a mastectomy, the pathology report indicated that there was 4 cm of tumor, comprised of infiltrating ductal carcinoma, infiltrating lobular carcinoma, lobular carcinoma in situ, and ductal carcinoma in situ. We estimate the tumor size as at least 4 cm and potentially greater. Her stage changes from Stage I to Stage II.

P49163CRO This 49 year old woman was randomized to placebo and began study drug 5/21/93. On July 21, 1993, she was diagnosed with infiltrating ductal carcinoma, 1.5 cm on biopsy. The NSABP reported the tumor size based on the biopsy. There is a note in the CRF signed by her medical oncologist that states that a re-excision showed residual cancer, the total tumor size was 2.6 cm, and 3 nodes were involved. Her stage does not change.

P04396EIN This 50 year old woman was randomized to placebo and began study drug on 2/26/94. On 8/14/96, she was diagnosed with infiltrating ductal carcinoma involving the entire biopsy specimen, which measured 5.5 cm. She was treated with a modified radical mastectomy. Residual cancer was seen in the mastectomy specimen near the biopsy cavity and within random sections of the upper outer and lower inner quadrants. Two nodes were involved with cancer. The NSABP assessed this case as an unknown tumor size; the FDA assessed this case as tumor size of at least 5.5 cm. Her stage changes from unknown to Stage III.

Tamoxifen:

P15102SCC This 41 year old participant was randomized to tamoxifen and began therapy 1/21/94. On 10/18/94, she was diagnosed with poorly differentiated infiltrating ductal carcinoma on a core biopsy. On 3/6/95, a mastectomy was performed and demonstrated a 6.2 cm tumor with 12 negative lymph nodes. The NSABP reported the tumor size as 1.3 cm. The FDA assesses tumor size at 6.2 cm based on the pathology report. Her stage changes from Stage I to Stage II.

Dr. Johnson's assessment of involved nodes generally matched that of the NSABP; in 2 cases on tamoxifen and one on placebo, the number of involved nodes differed by one and did not affect stage or sub-stage.

9. The sponsor was asked whether any participants were diagnosed with inflammatory breast cancer or metastatic breast cancer. Three participants had inflammatory breast cancer, 1 had metastatic breast cancer at presentation, and a fifth participant presented with a suspicious bone scan but was never documented to have metastatic disease at presentation. She subsequently died of breast cancer.

10. The following table represents the division's assessment of tumor size, nodal status, and stage by treatment arm:

Table 25. FDA assessment of tumor size, nodal status, and stage of breast cancer in P-1

Staging Parameter	Placebo	Tamoxifen	Total
Tumor size:			
T1	115	60	175
T2	28	20	48
T3	7	3	10
T4	1	2	3
Unknown	3	0	3
TOTAL	154	85	239
Nodal status:			
Negative	103	56	159
1-3 positive nodes	29	14	43
$\geq$ 4 positive nodes	10	12	22
$\geq$ 10 positive nodes*	[4*]	[3*]	[7*]
Unknown	12	3	15
TOTAL	154	85	239
Stage:			
I	88	47	135
II: node negative	15	9	24
II: node positive	33	22	55
III	6	4	10
IV	2**	0	2
Unknown	10	3	13
TOTAL	154	85	239

*Included in $\geq$ 4 positive nodes

**1 participant presented with a suspicious bone scan but did not have documented metastases. Subsequently died of metastatic breast cancer and is included here as Stage IV rather than stage unknown

The distribution of tumor size, nodal status, and stage was similar between the two arms. However, tamoxifen appeared to reduce the number of invasive breast cancers that were 2 cm or less. The absolute number of tumors that were 2 cm or greater was similar between the two arms. Tamoxifen reduced the absolute number of cases with negative nodes and with 1-3 positive nodes. There was no significant difference in the number of cases with 4 or more nodes although few invasive cancers met this criterion.

Tamoxifen appeared to be more effective in early stage tumors, or less aggressive tumors. Treatment with tamoxifen did not increase the rate of late stage or poor prognosis Stage II breast cancers.

9. The NSABP reported breast cancers by ER and PR status in the database sent 7/28/98. The reviewer performed the following Access queries:

Table 26. ER and PR status of invasive breast cancers, P-1

Receptor	Placebo (n=154)	Tamoxifen (n=85)	Total (n=239)
Estrogen receptor:			
Positive	114 (74%)	38 (45%)	152
Borderline	1 (0.6%)	0	0
Negative	27(18%)	35 (41%)	62
Unknown	12 (8%)	12 (14%)	24
Progesterone receptor:			
Positive	81 (53%)	34 (40%)	115
Borderline	1 (0.6%)	0	1
Negative	47 (31%)	32 (38%)	79
Unknown	25(16%)	19 (22%)	44
ER+, PR+	80 (52%)	28 (33%)	108
ER+, PR-	23 (15%)	6 (7%)	29
ER-, PR+	2 (1%)	6 (7%)	8
ER-, PR-	23 (15%)	26 (31%)	49
Unknown receptor combination	26 (17%)	19 (22%)	45

Many of the receptor assay results were not in the CRFs and could not be verified by Dr. Johnson. The NSABP confirmed that ER/PR status was determined locally and that the local definition of positive or negative was used. Tamoxifen decreased the number of estrogen receptor positive tumors but did not affect the incidence of ER negative tumors. Although the number of PgR positive cases overall appears less on the tamoxifen arm than on the placebo arm, the receptor combination information indicates that in this trial, the effect was limited to PgR positive tumors where the ER was also positive. There were, however, small numbers of ER(-)PR(+) tumors. Interestingly, tamoxifen decreased the incidence of ER(+)PR(-) tumors. This group of breast cancers has been thought to have a measurable but non-functional ER because of the absence of progesterone receptor protein.

Tamoxifen did not increase the number of receptor negative tumors, a concern raised at the inception of the study.

10. Concern was also raised at the start of the study that tamoxifen might cause an increased rate of cancer in young women, or breast tumors with adverse features. The reviewer performed the following Access queries:

Table 27. Tumor characteristics by age

Age group	Tumor characteristic	Placebo	Tamoxifen	Total
35-49		N=59	N=38	N=97
	T1	38 (64%)	25 (66%)	63
	T2	16 (27%)	10 (26%)	26
	T3	5 (8%)	3(8%)	8
	N0	39 (66%)	22 (58%)	61
	N1: 1-3	12 (20%)	9 (24%)	21
	N1: ≥4	3 (5%)	7 (18%)	10
	ER+	42 (71%)	18 (47%)	60
	ER-	12 (20%)	15 (39%)	27
	PR+	33 (56%)	16 (42%)	49
	PR-	18 (31%)	13 (34%)	31
50-59		N=46	N=24	N=70
	T1	38 (83%)	19 (79%)	57
	T2	6 (13%)	5 (21%)	11
	T3	2 (4%)	0	2
	N0	30 (65%)	16 (67%)	46
	N1: 1-3	10 (22%)	4 (17%)	14
	N1: ≥4	4 (9%)	3 (13%)	7
	ER+	34 (74%)	9 (38%)	43
	ER-	10 (22%)	12 (50%)	22
	PR+	25 (54%)	9 (38%)	34
	PR-	14 (30%)	9 (38%)	23
≥ 60		N=49	N=23	N=72
	T1	45 (92%)	17 (74%)	62
	T2	4 (8%)	6 (26%)	10
	T3	0	0	0
	N0	34 (69%)	18 (78%)	52
	N1: 1-3	7 (14%)	1 (4%)	8
	N1: ≥4	3 (6%)	2 (9%)	5
	ER+	39 (80%)	11 (48%)	50
	ER-	5 (10%)	8 (35%)	13
	PR+	24 (49%)	9 (39%)	33
	PR-	15 (31%)	10 (43%)	25

The distribution of tumor size and nodal status did not vary between treatment arms by age. There was no absolute increase in the number of estrogen receptor negative tumors. Instead, ER positive tumors were decreased by tamoxifen, leaving the ER(-) tumors as a greater percentage of the total breast cancers on the tamoxifen arm but with absolute numbers similar to the placebo arm.

11. In the course of her review of the CRFs, Dr. Johnson noted that some cancers were diagnosed early in the study, suggesting that the breast cancers were present prior to study entry. Other oncologists have raised the possibility that in this study, tamoxifen treated existing cancers rather than preventing new cancers.

If one looks at the time of diagnosis of breast cancers:

Table 28. Time of diagnosis of breast cancers, P-1

Time of diagnosis (months)	Placebo	Tamoxifen	% Reduction in breast cancer
0-6	12	2	83%
7-12	12	14	-17%*
13-24	45	20	56%
25-36	37	23	38%
37-48	30	16	47%
49-60	16	8	50%
> 60 months	2	2	None

*17% increase in breast cancer on tamoxifen

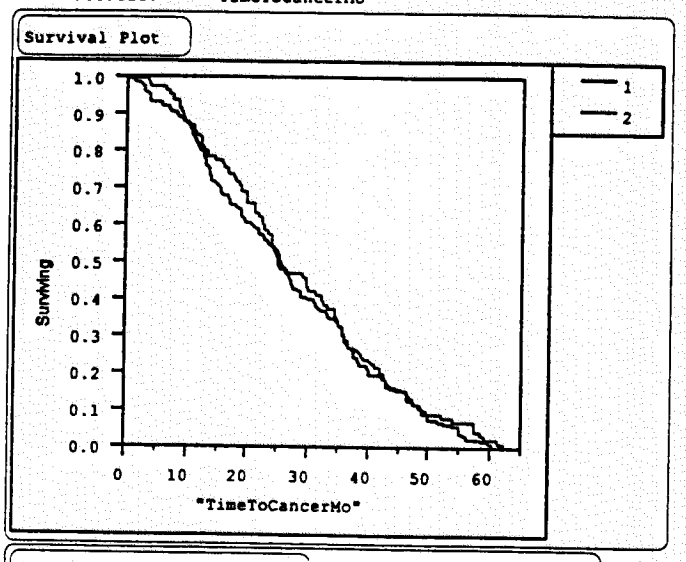
Tamoxifen reduced the number of invasive cancers in the first six months of treatment. While a slight increase was seen on the tamoxifen arm in the second six months, this change is probably attributed to small numbers of events, since a risk reduction was consistently seen throughout the course of the study. After 5 years, the number of cancers was the same in both treatment arms. However, there were few events during this time and, given the median follow-up of these patients, few women at risk. Further follow-up will be of interest.

If one looks at the time to diagnosis of invasive breast cancer:

Figure 6. Time to diagnosis of invasive breast cancer

Product-Limit Survival Estimates

Time Variable: "TimeToCancerMo"



Tests Between Groups

Test	Chi-Square	DF	Prob>ChiSq
Log-Rank	0.3673	1	0.5445
Wilcoxon	0.2104	1	0.6465

1

2

Combined

Arm 1: Placebo
Arm 2: Tamoxifen

The invasive cancers are diagnosed at the same rate over time. In other words, with the current follow-up, it does not appear that cancers are initially suppressed, followed by a rebound effect with increased growth and late diagnosis. This hypothesis is supported by the following graph from the NSABP's P-1 manuscript and also by Figure 1, where the curves separate early and remain distinct at 5 years of follow-up.