Health-Related Quality of Life and Tamoxifen in Breast Cancer Prevention: A Report From the National Surgical Adjuvant Breast and Bowel Project P-1 Study

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Purpose: **This is the initial report from the health-related quality of life (HRQL) component of the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial. This report provides an overview of HRQL findings, comparing tamoxifen and placebo groups, and advice to clinicians counseling women about the use of tamoxifen in a prevention setting.**

Patients and Methods: **This report covers the baseline and the first 36 months of follow-up data on 11,064 women recruited over the first 24 months of the study. Findings are presented from the Center for Epidemiological Studies–Depression Scale (CES-D), the Medical Outcomes Study 36-Item Short Form Health Status Survey (MOS SF-36) and sexual functioning scale, and a symptom checklist.**

Results: **No differences were found between placebo and tamoxifen groups for the proportion of participants scoring above a clinically significant level on the CES-D. No differences were found between groups for the MOS SF-36 summary physical and mental scores. The mean number of symptoms reported was consistently higher in the tamoxifen group and was associated with vasomotor and gynecologic symptoms. Significant increases were found in the proportion of women on tamoxifen reporting problems of sexual functioning at a definite or serious level, although overall rates of sexual activity remained similar.**

Conclusion: **Women need to be informed of the increased frequency of vasomotor and gynecologic symptoms and problems of sexual functioning associated with tamoxifen use. Weight gain and depression, two clinical problems anecdotally associated with tamoxifen treatment, were not increased in frequency in this trial in healthy women, which is good news that also needs to be communicated.**

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THIS IS THE INITIAL report of the findings from the health-related quality of life (HRQL) component of the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (P-1), a multicenter, double-blinded, placebo-controlled clinical trial. The purpose of this report is to provide a concise overview of the P-1 HRQL findings and an assessment of the effects of tamoxifen, when used as a preventative agent, on self-reported symptoms and everyday physical, emotional, and social functioning. Recommendations have been provided that may be helpful to physicians involved in counseling women considering the use of tamoxifen in the setting of prevention.

The primary objective of the P-1 study was to evaluate whether 5 years of tamoxifen therapy would reduce the incidence of invasive breast cancer in women at an increased risk for the disease. Secondary objectives were to assess the incidence of ischemic heart disease, bone fractures, and other events, such as depression, that might be associated with the use of tamoxifen. Eligible participants were randomized either to 20 mg daily of tamoxifen or to a placebo for a planned 5 years.

Detailed descriptions of the rationale, planning, and design of the of the Breast Cancer Prevention Trial and the HRQL component of the P-1 study, as well as specific instruments, have been provided in separate reports.[1-3]

PATIENTS AND METHODS

Participant Cohort and HRQL Data

This report covers the baseline HRQL examination and the first 36 months of follow-up data on 11,064 women recruited over the first 24 months (June 1, 1992, to May 31, 1994) of the study. This cohort of women represents 82.6% of the total P-1 accrual (n = 13,388). Restrictions were imposed on the initial HRQL report for two reasons. First, by limiting our attention to this cohort of women, we avoided the potential bias created by events beginning in March 1994,[4,5] which resulted in a suspension of accrual to the P-1 study. Second, a focus on the first 36 months of data collection permitted improved control over types of missing HRQL data because all 11,064 participants should have completed the eight scheduled examinations before the disclosure of the results of the trial in the spring of 1998.

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Instruments

The 104-item P-1 HRQL Questionnaire[3] was composed of the Center for Epidemiological Studies–Depression Scale (CES-D, 20 items), the Medical Outcomes Study (MOS) 36-Item Short Form Health Status Survey (SF-36, 36 items), the MOS sexual functioning scale (five items), and a symptom checklist (SCL, 43 items). The questionnaire was scheduled to be administered to all participants before randomization (baseline), at 3 months, at each succeeding 6-month examination for the planned 5 years of treatment, and for 1 year after treatment was completed.

Data Completeness

The P-1 study has multiple, complex levels of missing and incomplete data. In the case of self-administered instruments, such as the HRQL questionnaire, participants could leave items blank by error or because they did not wish to answer the question.[6] Beyond this, the staffs of collaborating centers were generally unable to collect self-administered instruments on participants who quit taking pills because they no longer appeared for follow-up examinations, although many of these participants can still be observed for primary end points (eg, breast cancer and fractures). In addition, there are participants who did not complete all of the scheduled follow-up HRQL questionnaires because of the disclosure of the trial results in the spring of 1998,[1] although they are still observed for primary end points. Finally, a small proportion of participants (1.7%) were lost to follow-up, even for primary end points.

Statistical Analysis

The P-1 HRQL data set is composed of multiple HRQL instruments, each with its own psychometric properties and research history.[3] This complexity is magnified by the fact that data distributions and patterns of missing data differ across the various instruments included in the HRQL questionnaire. In addition, sample sizes are large, resulting in the possibility of statistically significant findings for clinically negligible effects. All of these considerations argue for future detailed analyses of the data from each specific instrument. In this initial report, however, our aims were essentially descriptive in nature and emphasized basic comparisons of the two trial groups. In making these comparisons, we seek to identify consistent differences, between the trial groups, using simple nonparametric procedures. The sign test[7] is used to examine the consistency of binary differences ($\pm$) between the two trial groups across time, independent of the magnitude of these differences. A one-sided alternative is routinely used because tamoxifen is expected to have a negative effect on most short-term measures of HRQL. Friedman's test,[7] implemented as a generalization of the paired sign test,[8] was used as a nonparametric analog to the two-way analysis of variance when we wanted to block on a specific factor, such as age group. Positive findings, with regard to consistent differences between trial groups, were independently reviewed for magnitude to assess their clinical and functional significance for the participants' quality of life.

Clinical experience, as well as initial statistical investigations of the P-1 HRQL data set, suggested that the age of the study participants was a key factor contributing to the observed distribution of HRQL measures. Hence, the results presented here from various HRQL instruments were routinely stratified by three age groups (35 to 49 years, 50 to 59 years, and 60 years or older) that generally paralleled menopausal status. Relative risks (RRs) or absolute differences in mean counts are presented in the tables to estimate differences in effect size between the two groups.

Imputation procedures for missing items in otherwise complete scales were only used for eight SF-36 subscales, as recommended in the SF-36 scoring manual.[9] No data imputation was carried out for other scales, and incomplete scales were considered missing.[6]

RESULTS

Table 1 lists the demographic, medical, and behavioral characteristics of our participant cohort of 11,064 women by trial group. These data show that the women in the P-1 study were predominately white (96%), well educated (65% $\geq$ some college), married (70%), professional and technically trained (68.2%), currently employed (64.9%), and reported a middle- to upper-middle class family income (median, $35,000 to $49,999). None of the variables in Table 1 show a striking imbalance between the two trial groups.

Figure 1 charts the overall proportion and total numbers of women completing the HRQL questionnaire at each examination. It provides a general measure of comparative participant adherence with regard to the HRQL questionnaire in the two trial groups. Both trial groups showed a consistent decline in HRQL adherence across the first 36 months of the study, averaging 4.2% per examination in the placebo group and 4.6% per examination in the tamoxifen group. The proportion of HRQL-adherent participants was smaller in the tamoxifen than in the placebo group at every one of the seven follow-up examinations (sign test, $P = .0078$), with a maximum difference of 3.1% occurring at 36 months.

A number of demographic, clinical, and HRQL variables were examined to investigate whether differences could be detected between the women who failed to complete the HRQL questionnaire at 36 months in the tamoxifen and the placebo groups. These variables included mean age (tamoxifen = 53.1 years *v* placebo = 53.5 years) and mean RR (5.42 *v* 5.43), treatment status (10.1% *v* 10.5% on treatment), breast cancer in a first-degree relative (76.89% *v* 78.40%), prior estrogen use (32.5% *v* 33.3%), mean maximum CES-D score (12.52 *v* 12.46), and mean maximum number of reported symptoms on the SCL (14.2 *v* 13.9). These comparisons suggested that participants who failed to complete the HRQL questionnaire in each group were similar cohorts of women.

When, within a treatment group, the same variables were used to compare HRQL adherent and nonadherent women, only the treatment status variable was different between the two groups. A significantly greater proportion of HRQL-adherent women in both groups remained on treatment (87.0% *v* 89.6%) compared with HRQL-nonadherent women (10.1% *v* 10.5%). In other words, adherence in the HRQL component of P-1 was largely a reflection of treatment adherence. This was because most collaborating centers did not have the staff resources to administer the HRQL

Table 1. Demographic, Clinical, and Health Behavior Characteristics of P-1 HRQL Study Participants (N = 11,064)

Characteristic	Placebo		Tamoxifen		Total	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Age, years						
Mean ± SD	53.83 ± 9.167		53.82 ± 9.184		53.83 ± 9.175	
Median	52		52		52	
Range	35-79		35-78		35-79	
Ethnicity						
White	5,290	95.54	5,282	95.57	10,572	95.55
Hispanic	63	1.14	49	0.89	112	1.01
Black	88	1.59	95	1.72	183	1.65
Asian	35	0.63	37	0.67	72	0.65
Other	47	0.84	39	0.71	86	0.78
Missing	14	0.25	25	0.45	39	0.35
Education						
Grade school	61	1.10	66	1.19	127	1.15
Some high school	248	4.48	218	3.94	466	4.21
High school graduate	1,003	18.11	1,009	18.26	2,012	18.19
Vocational school	593	10.71	614	11.11	1,207	10.91
Some college	1,180	21.31	1,194	21.60	2,374	21.46
Associate degree	349	6.30	349	6.31	698	6.31
College graduate	664	11.99	732	13.24	1,396	12.62
Professional school	546	9.86	519	9.39	1,065	9.63
Master's degree	726	13.11	684	12.38	1,410	12.74
Doctoral degree	133	2.40	106	1.92	239	2.16
Missing	34	0.61	36	0.65	70	0.63
Employment						
Unemployed	239	4.32	229	4.14	468	4.23
Retired	925	16.71	938	16.97	1,863	16.84
Full-time homemaker	660	11.92	670	12.12	1,330	12.02
Student	30	0.54	33	0.60	63	0.57
Employed full-time	2,713	49.00	2,682	48.53	5,395	48.76
Employed part-time	880	15.89	878	15.89	1,758	15.89
On medical leave	25	0.45	24	0.43	49	0.44
Permanently disabled	51	0.92	47	0.85	98	0.89
Missing	14	0.25	26	0.47	40	0.36
Occupation						
Homemaker	849	15.33	843	15.25	1,692	15.29
Professional	2,207	39.86	2,188	39.59	4,395	39.72
Technical	1,573	28.41	1,548	28.01	3,121	28.21
Services	487	8.80	487	8.81	974	8.80
Operators	92	1.66	94	1.70	186	1.68
Other	315	5.69	341	6.17	656	5.93
Missing	14	0.25	26	0.47	40	0.36
Income						
Under $10,000	211	3.81	161	2.91	372	3.36
$10,000-$19,999	549	9.91	571	10.33	1,120	10.12
$20,999-$34,999	1,127	21.35	1,170	21.17	2,297	20.76
$35,000-$49,999	936	16.90	984	17.80	1,920	17.35
$50,000-$74,999	1,153	20.82	1,151	20.83	2,304	20.82
$75,000-$99,000	511	9.23	478	8.65	989	8.94
$100,000 or more	564	10.19	521	9.43	1,085	9.81
Unanswered	296	5.35	301	5.45	597	5.40
Missing	190	3.43	190	3.44	380	3.43
RR of breast cancer						
1-2	416	7.51	416	7.53	832	7.52
2-3	929	16.78	865	15.65	1,794	16.21
3-5	2,074	37.46	2,154	38.97	4,228	38.21
5-10	1,618	29.22	1,605	29.04	3,223	29.13
10+	500	9.03	487	8.81	987	8.92
1st degree relatives w/breast cancer						
0	1,238	22.36	1,191	21.56	2,429	21.95
1	3,239	58.50	3,250	58.80	6,489	58.65
2	903	16.31	902	16.32	1,805	16.31
≥ 3	157	2.83	184	3.32	341	3.09
Marital status						
Never married	398	7.19	394	7.13	792	7.16
Presently married	3,843	69.41	3,876	70.43	7,719	69.77
Marriage-like	139	2.51	125	2.26	264	2.39
Divorced	748	13.51	707	12.79	1,455	13.15
Widowed	395	7.13	399	7.22	794	7.18
Unknown	0	0	1	0.02	1	0.01
Missing	14	0.25	25	0.45	39	0.35
Smoking						
Smoked at least 100 cigarettes in lifetime	2,697	48.83	2,729	49.60	5,470	50.39
Smoked at least 100 cigarettes in lifetime and currently smoke	705	12.76	712	12.94	1,417	12.85
Alcohol						
Never use	1,138	20.60	1,128	20.50	2,266	20.55
Some days	4,129	74.76	4,147	75.37	8,276	75.07
Every day	256	4.64	227	4.13	483	4.38
Previous estrogen use	1,171	31.98	1,838	33.25	3,609	32.62
Both ovaries removed	797	14.39	813	14.71	1,610	14.55
Menstrual period stopped	3,658	66.06	3,685	66.67	7,343	66.37

questionnaire via the telephone or mail to women who stopped treatment and failed to appear for their scheduled follow-up visits.

By the 36-month examination, 3,421 women had stopped their assigned treatment and failed to fill out the HRQL questionnaire for at least 6 months. Table 2 lists the primary reasons these women gave for stopping treatment. The placebo and tamoxifen groups did not differ with regard to protocol-specified events, such as invasive breast cancer, depression, or deep vein thrombosis, or other medical reasons, such as anxiety disorders or cardiovascular conditions. Hot flashes were clearly the most frequently reported sign or symptom that caused women to stop their assigned treatment (251 women); they occurred most often in the tamoxifen group (184 women). When stopping their as-

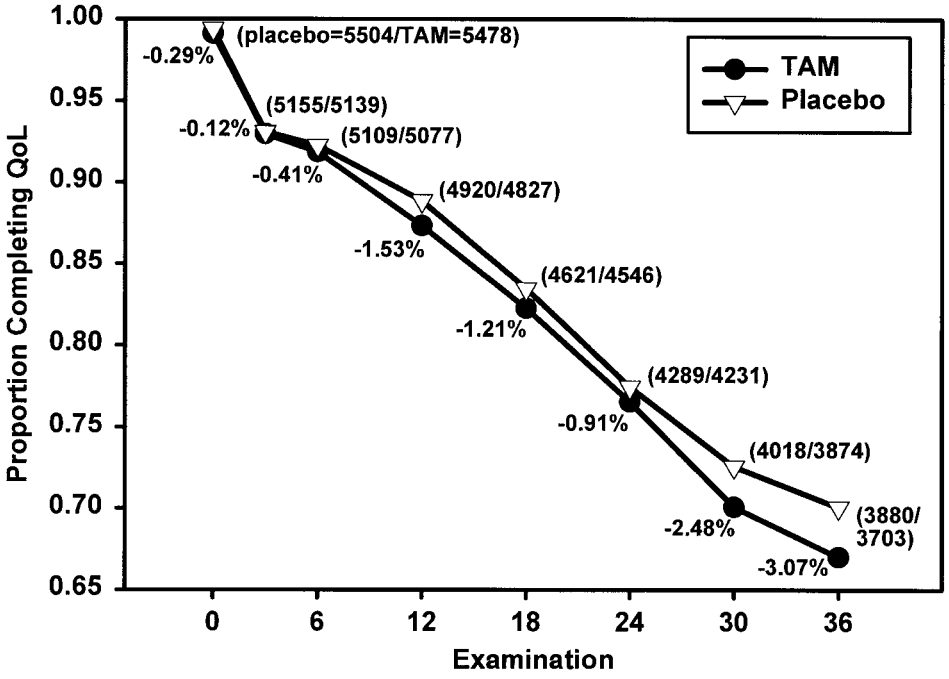

Fig 1. Proportion of participants in the tamoxifen group and placebo group completing HRQL questionnaire by examination (placebo, n = 5,537; tamoxifen, n = 5,527). Figures on chart are the number of women in the placebo/tamoxifen groups completing the HRQL questionnaire and the difference between TAM and placebo groups in terms of percent missing HRQL data.

signed treatment, participants in the placebo group were more likely to cite other nonmedical reasons, such as fear of side effects, change of mind, or desire to adopt an alternative therapy (eg, hormone replacement).

Table 3 shows the proportion of P-1 participants, by age group and examination, who scored above the most frequently used clinical cutoff (≥ 16) on the CES-D.[10,11] The youngest age group (35 to 49 years) in both trial groups consistently had the highest proportion of members scoring above the clinical cutoff, followed by the 50- to 59-year-old age group (Friedman test, $P = .001$ tamoxifen and placebo). The RRs listed in Table 3 show that, for all three age groups, the magnitude of the differences is small, and there was no consistent excess of participants in the tamoxifen group scoring above the clinical cutoff on the CES-D when compared with the placebo group. Similar findings with regard to the relationship between the two trial groups emerged from the analysis of the five-item mental health subscale on the MOS SF-36 (not shown).

The results of the SF-36 are summarized using the physical component summary (PCS) and mental component summary (MCS) scores[12] and the eight SF-36 subscales. The PCS and MCS scores represent aggregate measures that combine data from the eight subscales generally reported on the SF-36. The PCS aggregates data from the Physical Functioning, Role-Physical, Bodily Pain, and General Health subscales, while the MCS draws on data from the Vitality, Social Functioning, Role-Emotional, and Mental Health subscales. The PCS and MCS are scored using norm-based

Table 2. Reasons for Stopping Assigned Therapy by Participants Not Completing Quality of Life Questionnaire (Baseline to 36-Month Examination, n = 3421)

	Tamoxifen		Placebo		Total	
Reason for Stopping Assigned Therapy	No. of Patients	%	No. of Patients	%	No. of Patients	%
Protocol specified event	164	9.1	154	9.6	318	9.3
Reported signs or symptoms	545	30.2	336	20.8	881	25.8
Other medical	342	18.9	280	17.3	622	18.2
Other nonmedical	753	41.7	842	52.1	1595	46.6
Unknown	2	0.1	3	0.2	5	0.1
Total	1806	52.8	1615	47.2	3421	100.0

Table 3. Proportion of Participants in Tamoxifen Arm With a Clinically Significant Score (≧ 16) on the CES-D by Age Group and Examination

	Age Group							
	35-49 Years		50-59 Years		≥ 60 Years		Overall	
Examination	TAM	RR*	TAM	RR*	TAM	RR*	TAM	RR*
Baseline	0.074	1.03	0.082	1.28	0.058	0.918	0.071	1.07
3 months	0.122	1.10	0.104	1.05	0.085	1.08	0.105	1.08
6 months	0.138	1.06	0.114	1.00	0.093	0.910	0.117	1.00
12 months	0.128	0.937	0.122	0.999	0.096	0.989	0.116	0.968
18 months	0.139	0.892	0.126	0.918	0.101	0.929	0.123	0.908
24 months	0.143	1.02	0.124	0.980	0.095	0.924	0.122	0.980
30 months	0.142	0.978	0.107	0.961	0.104	0.934	0.120	0.959
36 months	0.135	0.898	0.111	1.04	0.097	0.887	0.116	0.930

Abbreviation: TAM, tamoxifen.

*RR = TAM/placebo.

methods; both component scores have a mean of 50 and a SD of 10 in the general United States (U.S.) population. This means that the PCS and MCS can be meaningfully compared with one another, and their scores have a direct interpretation in relation to the distribution of scores in the general U.S. population.

Figure 2 charts the PCS and MCS for the tamoxifen and placebo groups at each examination and by age group. As expected, mean PCS declines across the age groups. At follow-up examinations, the tamoxifen group was consistently lower on the PCS only in the 50- to 59-year-old age group (one-sided sign test, $P = .065$). However, the absolute differences were small, approximating one tenth of an SD. With regard to the MCS, all of the age groups scored above the mean MCS for the general U.S. population, and no consistent differences emerged between the two trial groups. Figure 3 summarizes the overall data from eight subscales on which the component subscores are based.

Table 4 lists the mean number of symptoms reported on the 43-item SCL by age group and examination. The mean number of symptoms reported was consistently highest in the 50- to 59-year-old age group, followed by the 35- to 49-year-old and 60 years or older age groups (Friedman test, $P = .001$ tamoxifen and placebo). The participants in the tamoxifen group also reported a small but consistent excess in the mean number of symptoms ($<$ one) reported at 19 of the 21 age-stratified follow-up examinations (3 to 36 months; one-sided sign test, 35 to 49 years, $P = .0078$; 50 to 59 years and $\geq$ 60 years, $P = .065$) (Table 4).

Table 5 provides information on the proportion of women in the tamoxifen and placebo groups who reported symptoms on the SCL at least once during the treatment period, ie, the period excluding baseline but including the seven follow-up examinations. The five symptoms with the greatest relative difference between the two trial groups are given for each age group, and the 10 symptoms with the greatest relative difference are presented for all participants combined.

Tables 6 and 7 give detailed information, by age group and examination, on the reported frequency of hot flashes and vaginal discharge in the trial groups. The proportion of participants who reported hot flashes was elevated in all age groups of the tamoxifen group at every follow-up examination. Among the participants in the tamoxifen group, the 50- to 59-year-old age group had the largest proportion of women reporting hot flashes at each examination (median, 69.8%; Friedman test, $P = .001$), but the youngest age group (35 to 49 years) showed the greatest relative increase in proportion of women reporting hot flashes (median RR, 1.50; Friedman test, $P = .011$). Vaginal discharge was the most consistently elevated symptom in the tamoxifen group. The youngest age group (35 to 49 years) had the greatest proportion of participants reporting vaginal discharge at each examination (median, 35.5%; Friedman test, $P < .001$), and the oldest age group ($\geq$ 60 years) reported the greatest increase of vaginal discharge relative to the placebo controls (median RR, 3.05; Friedman test, $P = .005$).

Figure 4 summarizes the information from the five items on the MOS sexual functioning scale. Figure 4A shows that a greater proportion of participants in the tamoxifen group, as compared with the placebo group, reported being sexually active during the 6 months before each follow-up examination. Although apparently consistent ($P = .031$), the absolute difference was small (mean, 0.78%) and may have been caused by chance. Figure 4B through 4E show that a small but consistently larger percentage of participants in the tamoxifen group reported a definite or serious problem in three of the four specific domains of sexual functioning during the follow-up period.

DISCUSSION

We observed in our earlier article[3] that measuring the impact of new treatments on HRQL is particularly important within the context of disease-prevention and health-promotion trials. Compared with patients suffering from clinically manifest disease, decrements in overall quality of life are likely to have a much greater impact on the subjective appraisal of treatment acceptability and the maintenance of long-term treatment adherence among high-risk but otherwise healthy individuals. This report covers the initial HRQL findings from a large, multicenter chemoprevention trial, which has shown that tamoxifen reduced the risk of invasive breast cancer in high-risk women by 49% during the first 5 years of administration. Given the apparent clinical efficacy of tamoxifen in the prevention setting, it is important to assess whether the various secondary effects of the drug might act to reduce this practical efficacy.[13-15]

The cohort of women taking part in the P-1 study clearly was not representative of the general population. They were predominately white, well educated, and middle class, with a strong professional and technical orientation. The initial HRQL findings presented in this report must be assessed within the context of the socioeconomic and cultural characteristics of the P-1 study cohort.

The subcohort of women discussed in this report represent 82.6% of the total study cohort. This subcohort was chosen to exclude potential biases, because of external factors eventuating in the suspension of accrual in P-1, and to control for the amount and types of missing data. Despite this, we still lost 31.5% of our participants by the 36-month follow-up examination. This proportion closely approximates the 10%-per-year loss to follow-up rate predicted at

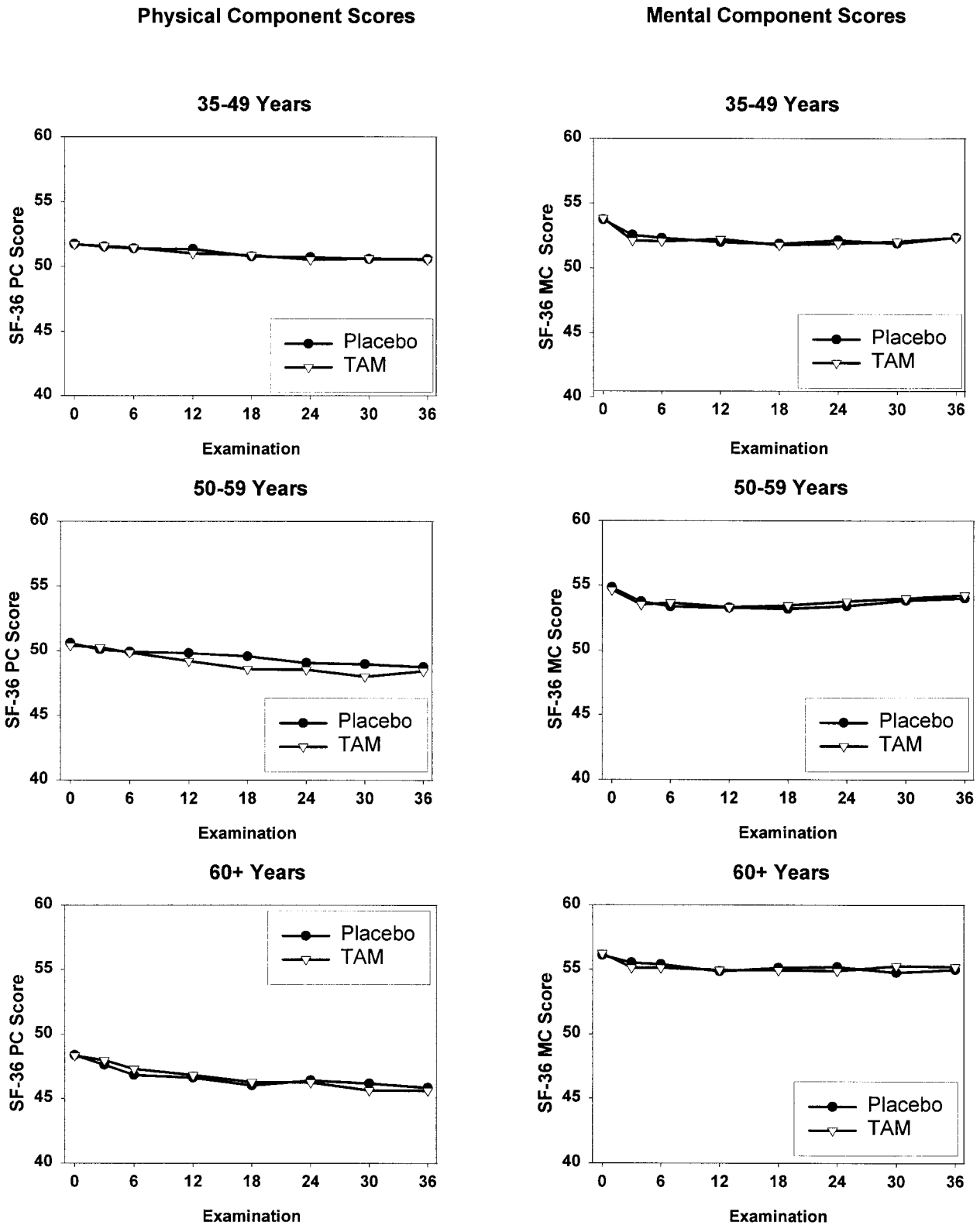

Fig 2. Mean scores by age group and examination on SF-36 physical and mental component scores (higher scores represent better quality of life).

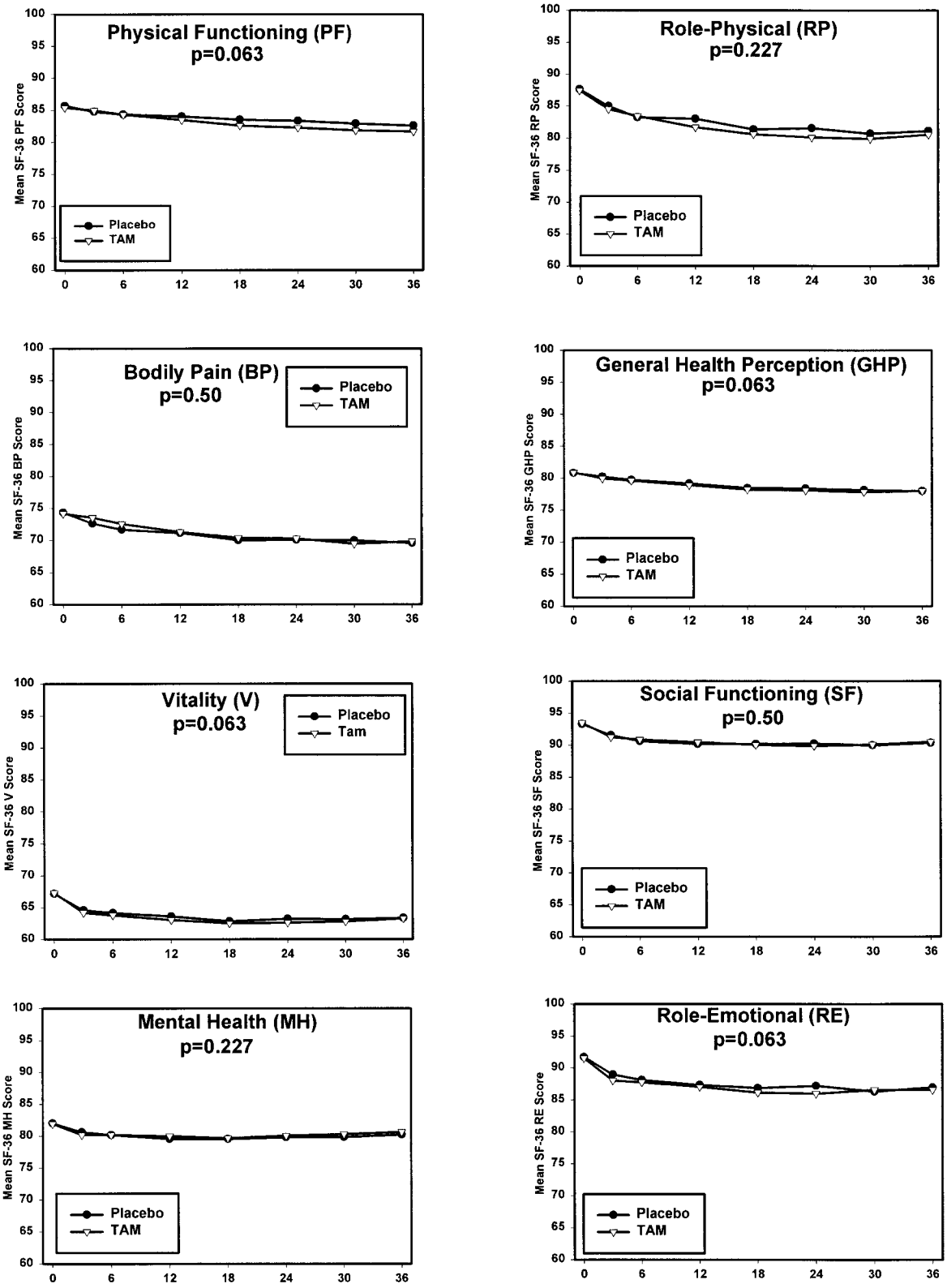

Fig 3. Mean SF-36 subscale scores by examination.

Table 4. Mean Number of Total Symptoms Reported on Symptom Checklist by Age Group and Examination

	Age Group							
	35-49 Years		50-59 Years		≥ 60 Years		Overall	
Examination	TAM	Difference*	TAM	Difference*	TAM	Difference*	TAM	Difference*
Baseline	8.84	+ 0.114	9.76	+ 0.236	8.89	− 0.030	9.14	+ 0.110
3 months	9.96	+ 0.319	10.54	− 0.006	9.63	− 0.166	10.04	+ 0.077
6 months	10.43	+ 0.564	11.06	+ 0.304	10.06	+ 0.011	10.51	+ 0.322
12 months	10.87	+ 0.521	11.54	+ 0.655	10.43	+ 0.076	10.95	+ 0.429
18 months	11.08	+ 0.614	11.51	+ 0.452	10.65	+ 0.292	11.08	+ 0.469
24 months	11.05	+ 0.733	11.58	+ 0.549	10.68	+ 0.476	11.10	+ 0.602
30 months	10.27	+ 0.227	10.67	+ 0.547	10.15	+ 0.134	10.36	+ 0.299
36 months	10.79	+ 0.386	11.22	+ 0.700	10.50	+ 0.190	10.84	+ 0.426

Abbreviation: TAM, tamoxifen.

*Difference = tamoxifen minus placebo.

the beginning of the P-1 trial and is similar in pattern and number to the adherence data recently reported in a second large, multicenter chemoprevention trial of hormone replacement therapy for heart disease.[16] We have shown that there is only a small difference in the proportion of nonadherent participants in the tamoxifen and placebo groups and that the nonadherent women in both trial groups have generally similar key demographic, clinical, and HRQL variables. Given these considerations, it seems unlikely that a maximum difference of 3% in the HRQL follow-up rates between the two groups was sufficient to create a significant bias in our between-group comparisons.

HRQL adherence is closely related to treatment adherence. Based on the reasons for quitting treatment, it would seem that nonadherent women in both trial groups were those who were sensitive to the actual or possible occurrence of side effects caused by tamoxifen.

Much concern has been expressed about a potential relationship between tamoxifen use and the onset of depression.[17-21] Women who reported a history of depressive episodes or a history of treatment for nervous or mental disorders were not excluded from the trial. A brief eight-item affective screening questionnaire based on the CES-D and the Diagnostic Interview Schedule[22] was part of the baseline examination.[23] Using data from this brief screening instrument, local investigators were alerted to eligible participants showing signs of potentially serious affective distress at the baseline examination and caution was advised regarding their enrollment onto the trial. However, women who showed current signs of affective distress or depression were not routinely excluded from the trial.

With regard to the primary screening instrument used in the follow-up examinations, it has been pointed out that ''the items in... (the CES-D) are generally related to affective distress but not to any particular psychiatric disorder.''[11] For this reason, the numbers listed in Table 3 refer not to the prevalence of clinically diagnosable depressive disorders but, instead, to the prevalence of clinically significant affective distress that might be associated with a number of specific psychiatric disorders. However, if tamoxifen use was associated with the onset of clinically diagnosable depression, we would have expected to see a consistent excess of individuals scoring ≥ 16 on the CES-D in the tamoxifen group. No such consistent excess was observed. These findings agreed with the data from the mental health scale on the SF-36.

The MOS SF-36 served in this study as a measure of overall HRQL. For this initial report, we have presented data from the SF-36 in terms of two high-level component scores[12] and the eight basic subscales generally used in scoring this instrument.[9] Neither of these two methods of summarizing the SF-36 data demonstrated any clinically significant differences between the tamoxifen and placebo groups.

The first clear signs of consistent differences between the tamoxifen and placebo groups were observed in the SCL. In 19 out of 21 follow-up comparisons, the mean number of symptoms reported on the SCL were consistently different by age group (50 to 59 years > 35 to 49 years > 60+ years) and by trial group (tamoxifen > placebo). The absolute differences between the trial groups were relatively small and tended to be associated with the types of vasomotor, gynecologic, and sexual functioning symptoms previously reported for tamoxifen.[18,24,25]

The data from the MOS sexual functioning scale indicate that relatively small (< 4.0%) but consistent differences exist between the two groups in regard to the proportion of women reporting definite or serious problems in at least three specific domains of sexual functioning, sexual interest, arousal, and orgasm. These problems do not seem to be age group specific. Despite these findings for specific domains of functioning, there is no evidence that these problems result in a reduction of the overall proportion of women in the tamoxifen group who are sexually active.

Table 5. Symptoms Reported at Least Once Between Months 3 and 36 With the Largest Relative Difference Between Trial Arms

Age Group and Symptom	Placebo Arm Proportion (%)	Tamoxifen Arm Proportion (%)	RR (TAM/Placebo)
35-49 years			
Cold sweats	15.90	22.90	1.44
Vaginal discharge	46.29	62.55	1.35
Pain in intercourse	23.88	31.57	1.32
Night sweats	59.58	74.16	1.24
Hot flashes	65.54	81.28	1.24
50-59 years			
Cold sweats	16.11	27.00	1.68
Vaginal discharge	32.51	53.47	1.64
Genital itching	36.93	45.24	1.23
Night sweats	62.77	75.88	1.21
Bladder control (laugh)	47.67	56.94	1.19
≥ 60 years			
Vaginal bleeding	4.64	10.92	2.35
Vaginal discharge	19.82	45.81	2.31
Genital itching	32.05	40.96	1.28
Hot flashes	51.51	63.59	1.23
Bladder control (laugh)	49.88	56.49	1.13
Overall			
Vaginal discharge	34.13	54.77	1.60
Cold sweats	14.77	21.40	1.45
Genital itching	38.29	47.13	1.23
Night sweats	54.92	66.80	1.22
Hot flashes	65.04	77.66	1.19
Pain in intercourse	24.13	28.19	1.17
Bladder control (laugh)	46.65	52.51	1.13
Bladder control (other)	47.79	52.83	1.11
Weight loss	41.97	44.94	1.07
Vaginal bleeding	21.26	21.96	1.03

Abbreviation: TAM, tamoxifen.

Based on these data, we conclude that tamoxifen use is associated with an increase in specific vasomotor, gynecologic, and sexual functioning symptoms. At the same time, we did not observe any evidence that overall physical and emotional well being were significantly affected by these differences in the frequency of symptoms. We also found no evidence on the CES-D or the SF-36 mental health scale for an association in any age group between tamoxifen use and an increase in the proportion of women reporting clinically significant levels of affective distress and/or depression. How should clinicians integrate the results from the HRQL study data into decision-making and recommendations to women considering the use of tamoxifen in the setting of prevention? As demonstrated by the SCL data from the placebo group of the trial, many symptoms experienced by women who participated in this study are age and menopause related and exist independent of the use of tamoxifen. However, several symptoms are substantially more frequent in women using tamoxifen; these include vasomotor symptoms (cold sweats, night sweats, and hot flashes), vaginal discharge, and genital itching. Women need to be informed

Table 6. Proportion of Women Reporting Hot Flashes in Tamoxifen Arm and RR Compared to Placebo Arm by Age Group and Examination

	Age Group							
	35-49 Years		50-59 Years		≥ 60 Years		Overall	
Examination	TAM	RR*	TAM	RR*	TAM	RR*	TAM	RR*
Baseline	0.258	0.959	0.533	0.989	0.268	1.030	0.346	0.991
3 months	0.581	1.588	0.761	1.241	0.511	1.413	0.616	1.399
6 months	0.610	1.666	0.765	1.268	0.503	1.481	0.626	1.455
12 months	0.614	1.525	0.740	1.273	0.460	1.412	0.606	1.396
18 months	0.613	1.510	0.715	1.239	0.419	1.461	0.586	1.387
24 months	0.622	1.457	0.681	1.199	0.388	1.311	0.570	1.322
30 months	0.627	1.362	0.642	1.206	0.330	1.177	0.541	1.265
36 months	0.627	1.414	0.667	1.276	0.364	1.362	0.560	1.348

Abbreviation: TAM, tamoxifen.
*RR = TAM/placebo.

of these possible symptoms. Weight gain and depression, two clinical problems anecdotally associated with tamoxifen treatment in women with breast cancer, did not increase in frequency in this large placebo-controlled trial of healthy women. This is good news that must also be communicated to women. An informed discussion with a woman considering tamoxifen therapy should include these points in the risk/benefit discussion.

Disclosure of likely and unlikely symptoms should prepare a woman for what she might experience and reduce her anxiety or concerns should she begin preventive therapy. Without the detailed evaluation of HRQL data obtained in the P-1 trial, we would not be able to provide this level of information and reassurance to women considering preventive therapy. In addition, the setting of preventive therapy differs considerably from the treatment of breast cancer. Therefore, if a woman experiences untoward symptoms after starting tamoxifen treatment, the medication can be discontinued if the symptoms cannot be controlled or her personal assessment of the risks and benefits changes.

Table 7. Proportion of Women Reporting Vaginal Discharge in Tamoxifen Arm and RR Compared to Placebo Arm by Age Group and Examination

	Age Group							
	35-49 Years		50-59 Years		≥ 60 Years		Overall	
Examination	TAM	RR*	TAM	RR*	TAM	RR*	TAM	RR*
Baseline	0.201	0.957	0.135	1.041	0.058	0.907	0.138	0.975
3 months	0.379	1.549	0.308	2.023	0.275	3.665	0.326	1.972
6 months	0.391	1.686	0.302	1.931	0.269	3.057	0.327	1.973
12 months	0.380	1.700	0.304	1.973	0.262	3.333	0.321	2.020
18 months	0.363	1.558	0.278	2.251	0.252	3.029	0.303	1.961
24 months	0.341	1.797	0.272	1.991	0.238	2.994	0.288	2.052
30 months	0.325	1.633	0.282	2.404	0.246	3.075	0.288	2.083
36 months	0.316	1.671	0.264	2.332	0.241	3.096	0.277	2.095

Abbreviation: TAM, tamoxifen.
*RR = TAM/placebo.

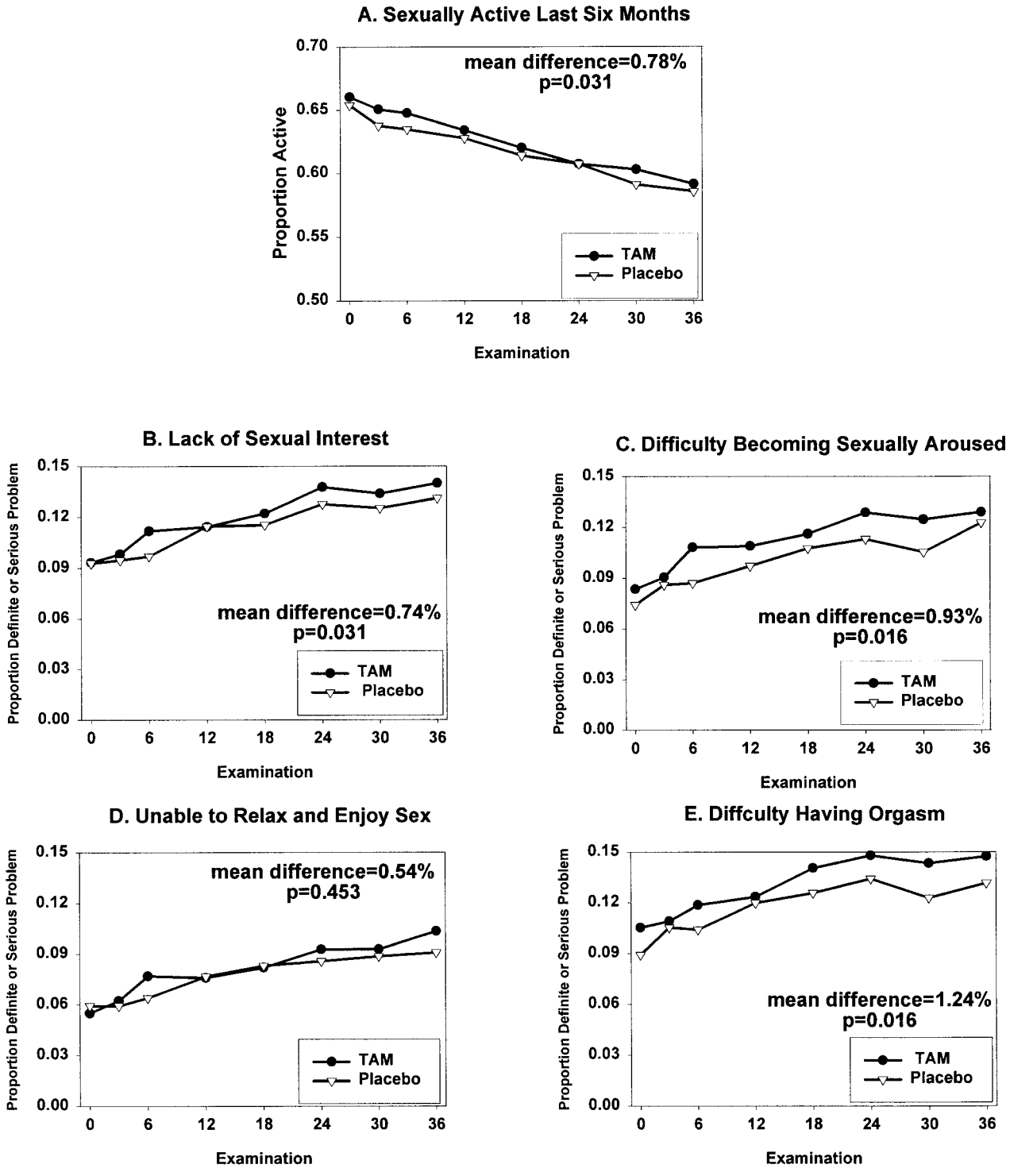

Fig 4. Proportion of women in the tamoxifen group and placebo group reporting a definite or serious problem in past 4 weeks on MOS sexual functioning scale (B through E, women who reported being sexually active in last 6 months).

The current report is a brief overview of the P-1 study HRQL data that focuses on important clinical and functional implications of tamoxifen use for women's overall HRQL. It will be supplemented in the future by a series of additional methodologic and clinical reports that will provide in-depth analyses of the data obtained from each one of the several P-1 study HRQL instruments.

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