Endocrine Responsiveness and Tailoring Adjuvant Therapy for Postmenopausal Lymph Node-Negative Breast Cancer: A Randomized Trial

International Breast Cancer Study Group (IBCSG)[1]

Background: **The role of adjuvant chemotherapy in postmenopausal patients with lymph node-negative breast cancer is controversial. After demonstrating the efficacy of chemotherapy combined with tamoxifen for postmenopausal patients with lymph node-positive disease, the International Breast Cancer Study Group launched a randomized trial (Trial IX) to evaluate the role of adjuvant chemotherapy preceding treatment with tamoxifen for patients with lymph node-negative disease.** ***Methods:*** **After stratification by estrogen receptor (ER) status, patients were randomly assigned to receive three 28-day courses of "classical" adjuvant CMF chemotherapy (cyclophosphamide at 100 mg/m^2 on days 1–14, orally; methotrexate at 40 mg/m^2 on days 1 and 8, intravenously; and 5-fluorouracil at 600 mg/m^2 on days 1 and 8, intravenously) followed by tamoxifen (20 mg/day, orally for 57 months) (CMF→tamoxifen) or to receive tamoxifen alone (20 mg/day, orally for 60 months). We enrolled 1669 eligible patients, 382 (23%) with ER-negative tumors, 1217 (73%) with ER-positive tumors, and 70 (4%) with unknown ER status. The median follow-up was 71 months. All statistical tests were two-sided.** ***Results:*** **The added benefit of CMF followed by tamoxifen over tamoxifen alone was statistically significantly dependent on ER status (tests for interaction: *P* = .01 for disease-free survival [DFS] and *P* = .07 for overall survival [OS]). For patients with ER-negative tumors, the addition of CMF statistically significantly improved DFS (5-year DFS = 84% for CMF→tamoxifen versus 69% for tamoxifen alone; difference = 15%; 95% confidence interval [CI] = 6% to 24%; risk ratio [RR] = 0.52; 95% CI = 0.34 to 0.79; *P* = .003) and OS (5-year OS = 89% for CMF→tamoxifen versus 81% for tamoxifen alone; difference = 8%; 95% CI = 0% to 16%; RR = 0.51; 95% CI = 0.30 to 0.87; *P* = .01). By contrast, for patients with ER-positive tumors, addition of CMF provided no benefit in terms of DFS (5-year DFS = 84% for CMF→tamoxifen versus 85% for tamoxifen alone; difference = –1; 95% CI = –6% to 4%; RR = 0.99; 95% CI = 0.75 to 1.30; *P* = .92) or OS (5-year OS = 95% for CMF→tamoxifen versus 93% for tamoxifen alone; difference = 2%; 95% CI = –1% to 5%; RR = 0.95; 95% CI = 0.64 to 1.40; *P* = .80).** ***Conclusions:*** **Postmenopausal patients with lymph node-negative breast cancer benefited substantially from adjuvant chemotherapy if their cancer was ER-negative (i.e., endocrine-nonresponsive). In contrast, if their cancer was ER-positive (i.e., endocrine-responsive), they obtained no benefit from the combination treatment compared with tamoxifen alone. [J Natl Cancer Inst 2002;94: 1054–65]**

More than 43% of all women who had surgery for nonmetastatic, invasive breast cancer in the United States between 1992 and 1996 were 50 years of age or older and had lymph node-negative disease *(1).* Tamoxifen given for at least 5 years to such women provides substantial reduction in relapses and death *(2–5).* For postmenopausal patients with axillary lymph node involvement, chemotherapy combined with tamoxifen has been shown to improve results compared with tamoxifen alone *(6–12).*

In 1988, data on the combination of chemotherapy and endocrine therapy in women with lymph node-negative breast cancer were scarce, and the role of adjuvant chemotherapy for postmenopausal women with lymph node-negative breast cancer was controversial. The International Breast Cancer Study Group (IBCSG) therefore initiated a trial (Trial IX) comparing chemotherapy followed by tamoxifen with tamoxifen alone in postmenopausal patients with lymph node-negative disease. Because data available suggested that tamoxifen might be more effective in patients with estrogen receptor (ER)-positive tumors *(6),* the randomization was prospectively stratified by the ER status of the primary tumor.

Patients and Methods

Study Design

From October 1988 to August 1999, 1715 postmenopausal patients were randomly assigned to receive either tamoxifen (20 mg/day) for 5 years or three 28-day courses of "classical" CMF

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See "Appendix" for the names and affiliations of the participants of the International Breast Cancer Study Group.

See "Notes" following "References."

(cyclophosphamide at 100 mg/m^2 orally on days 1–14, methotrexate at 40 mg/m^2 intravenously on days 1 and 8, and 5-fluorouracil at 600 mg/m^2 intravenously on days 1 and 8; this course of treatment was repeated every 28 days) followed by tamoxifen (20 mg/day) for 57 months. Systemic adjuvant therapy was to begin within 6 weeks of surgery, and tamoxifen following chemotherapy was to begin on day 15 of the final course of CMF. Informed consent was required according to the criteria established within the individual countries. The protocol was reviewed and approved by institutional review boards.

Randomization was conducted centrally (at coordinating centers in Bern, Switzerland, or Sydney, Australia) and stratified by ER status (negative, positive, or unknown), whether radiotherapy was planned after breast-conserving surgical procedure (yes or no), and by participating institution (*see* Appendix). The permuted blocks randomization schedule was produced by use of pseudorandom numbers generated by a congruence method.

Postmenopausal status was defined as having one of the following sets of characteristics: 1) older than 52 years with at least 1 year of amenorrhea; 2) 52 years old or younger with at least 3 years of amenorrhea; 3) 56 years old or older with hysterectomy but no bilateral oophorectomy; or 4) biochemical evidence of cessation of ovarian function (for doubtful cases).

All patients had a histologically proven unilateral breast cancer of stage T_{1a}, T_{1b}, T_{2a}, T_2, T_3, $_pN_0$, or M_0 [Union Internationale Contre le Cancer 1987 *(13)*], with either ER-positive or ER-negative primary tumors. The ER-unknown status was allowed only if ER determination was not possible because of the lack of tumor material. Steroid hormone receptor concentrations in the primary tumors were determined by standard methods *(14,15).* ER concentrations of greater than or equal to 10 fmol/mg of cytosol protein were considered positive; lower values were considered negative. Steroid hormone receptor determination by immunohistochemistry was allowed later in the study; ER status was determined by immunohistochemistry for 29% of the patients.

Surgery of the primary tumor was either a total mastectomy with axillary clearance or a lesser procedure (quadrantectomy or lumpectomy) with axillary lymph node dissection. Radiotherapy was recommended for completing breast conservation and was postponed until the end of chemotherapy, if applicable *(16).* Staging before randomization included chest x-ray, contralateral mammogram, bone scintogram (if clinically indicated), and hematologic, liver, and renal function tests.

Clinical, hematologic, and biochemical assessments were required every 3 months for the first year, every 6 months for the second year, and yearly thereafter. Modified WHO toxicity grading criteria were used *(17).* Mammography was performed yearly. The data management and medical staff reviewed all study records (initial data, treatment, toxicity, and recurrence) and conducted regular site visit audits. In particular, the study chair (M. Castiglione-Gertsch) reviewed the records for all grade 3 or worse toxicities and clarified attribution.

Patient self-assessments of quality of life using the IBCSG approach *(18–20)* were obtained at the beginning of treatment; at months 3 (before receiving the final CMF cycle), 6, 9, 12, 18, and 24; and yearly thereafter for 6 years. Single-item LASA (linear analog self-assessment) scales that were scored between 0 and 100 were used; higher values represented better quality of life or less severe symptoms. Four scales were used from the start of the trial to measure physical well-being, mood, appetite, and perceived adjustment/coping. After May 1, 1993, six additional LASA scales were added to measure tiredness, hot flashes, nausea/vomiting, perceived social support, arm restriction, and a patient-rated measure of utility. Scores were transformed to reduce skewing and the statistical significance of treatment differences at each time point was assessed with analysis of variance, adjusting for country/language group *(18,19).*

End Points and Statistical Considerations

Disease-free survival (DFS) was defined as the length of time from the date of randomization to any relapse (including ipsilateral breast recurrence), the appearance of a second primary cancer (including contralateral breast cancer), or death, whichever occurred first. Overall survival (OS) was defined as the length of time from the date of randomization to death from any cause.

DFS and OS percentages, standard errors, and treatment effect comparisons were obtained from the Kaplan–Meier method *(21),* Greenwood's formula *(22),* and log-rank tests *(23),* respectively. Cox proportional hazards regression models *(24)* were used to control for prognostic features, to estimate relative risks (RRs) and 95% confidence intervals (CIs) for the treatment comparisons, and to test for interactions between potential prognostic factors and treatment effects. All probability values were obtained from two-sided tests. Results are reported at a median follow-up of 71 months.

Treatment–covariate interactions were studied by use of the nonparametric STEPP (Subpopulation Treatment Effect Pattern Plot) methodology *(25,26).* STEPP involves defining several overlapping subgroups of patients on the basis of a covariate of interest and studying the resulting pattern of the treatment effects estimated within each subgroup. In this report, quantitative ER value was the covariate of interest, and the treatment effects estimated within each ER subgroup were measured in terms of both 5-year DFS percentages and RRs obtained from Cox models.

The randomization was stratified according to ER status, and the intention to perform separate analyses according to ER status was specified in the original protocol. The original sample size of 900 was changed to 1200 in 1993 and finally to 1600 in 1995 to increase the precision of the planned analyses according to ER status (80% power to detect a relative reduction in relapse risk of 33% for the ER-positive stratum and 50% for the ER-negative stratum). The sample size modifications were made before interim efficacy analyses. In 1998, a protocol amendment restricted enrollment to patients with ER-positive tumors on the basis of evidence from other trials that tamoxifen was not effective for patients with ER-negative tumors *(5).*

The Data and Safety Monitoring Committee reviewed accrual and safety data twice a year. Two predetermined interim efficacy analyses were performed (in April 1996 and July 1999), and study continuation was recommended on both occasions.

Patient Eligibility and Characteristics

Of the 1715 patients randomly assigned, 1669 (97%) were eligible and assessable. All seven patients from two noncompliant centers and 39 other patients who did not satisfy criteria for eligibility were excluded (Fig. 1).

The characteristics of the 1669 patients are shown in Table 1. The median age was 60 years (range = 34–81 years). Twenty-three percent (382) of the patients had primary tumors classified

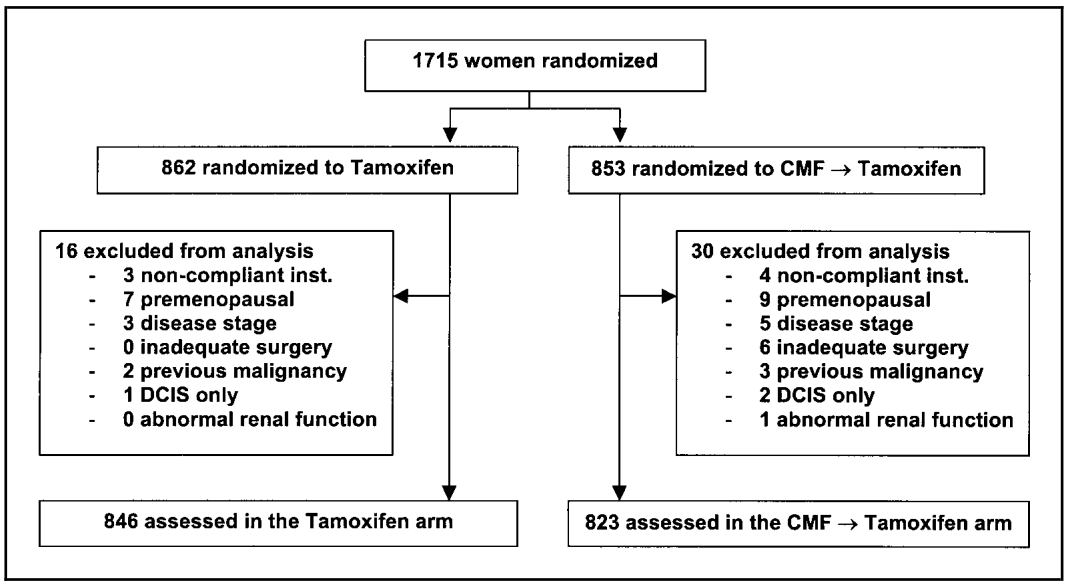

Fig. 1. Flow chart of enrollment and accessibility for the primary analysis. CMF = cyclophosphamide (100 mg/m^2 on days 1–14, orally), methotrexate (40 mg/m^2 on days 1 and 8, intravenously), and 5-fluorouracil (600 mg/m^2 on days 1 and 8, intravenously), repeated for three 28-day courses; DCIS = ductal carcinoma *in situ*.

as ER-negative; 73% (1217) were classified as ER-positive, and 4% (70) were classified as ER-unknown. The median number of axillary lymph nodes examined was 16 (range = 5–47 lymph nodes).

RESULTS

DFS and OS

DFS was better for patients who received three courses of CMF followed by tamoxifen than for patients who received tamoxifen alone ($P = .05$; Fig. 2, A and Table 2, A). There was also a trend in favor of better OS ($P = .07$; Fig. 2, B). Results of multiple regression analyses controlling for ER status, age, type of surgery, and tumor size and grade were essentially the same as the univariate analyses (DFS, $P = .05$; OS, $P = .08$).

The effect of chemotherapy was statistically significantly different for the two cohorts prospectively defined according to ER status (tests for interaction: $P = .01$ for DFS, $P = .07$ for OS). For the ER-negative cohort, there was a statistically significant benefit for the group receiving chemotherapy followed by tamoxifen in terms of DFS (5-year DFS = 84% with CMF versus 69% without CMF; difference = 15%; 95% CI = 6% to 24%; RR = 0.52; 95% CI = 0.34 to 0.79; $P = .003$) and OS (5-year OS = 89% with CMF versus 81% without CMF; difference = 8%; 95% CI = 0% to 16%; RR = 0.51; 95% CI = 0.30 to 0.87; $P = .01$) (Fig. 2, C and D). In contrast, no treatment difference was observed for the ER-positive cohort for DFS (5-year DFS = 84% with CMF versus 85% without CMF; difference = –1%; 95% CI = –6% to 4%; RR = 0.99; 95% CI = 0.75 to 1.30; $P = .92$) or OS (5-year OS = 95% with CMF versus 93% without CMF; difference = 2%; 95% CI = –1% to 5%; RR = 0.95; 95% CI = 0.64 to 1.40; $P = .80$) (Fig. 2, E and F).

Within the ER-negative cohort, addition of CMF was associated with statistically significantly improved DFS for all subpopulations defined by age, tumor size, and tumor grade, except for two small subsets—one subset of the 40 patients with tumors of 1 cm or less and the other of the 24 patients with grade 1 tumors (Methodologically, for tumors graded as grade 1, it is possible that the ER-negative classification might be false.) (Table 2, B). In contrast, for the ER-positive cohort, addition of CMF did not improve DFS compared with tamoxifen alone for any subgroup, including patients with larger or high-grade tumors (Table 2, C).

Multiple regression analyses to identify factors that influenced DFS were conducted separately for the ER-negative and ER-positive cohorts (Table 3). For the ER-negative cohort, treatment, tumor size, and tumor grade were prognostically significant and for the ER-positive cohort, age and tumor grade were prognostically significant. There were no statistically significant interactions between treatment effect and age, tumor size, or tumor grade within the cohorts defined by ER status.

STEPP methodology was used to explore the pattern of treatment effects by examining subpopulations defined by the quantitative ER values (from ligand-binding assays) available for 1178 patients (Fig. 3). For this sliding-window STEPP analysis, each subpopulation contained approximately 200 patients, and each subsequent subpopulation was formed by moving from left to right by dropping approximately 10 patients with the lowest values for ER and adding approximately 10 patients with the next higher values of ER. Fig. 3, A, shows the 5-year DFS for each treatment group and subpopulation. The 5-year DFS for the tamoxifen-alone arm increased with increasing values of ER. The improved 5-year DFS obtained by adding CMF was observed only for the subpopulations of patients with tumors expressing no or low levels of ER. Fig. 3, B, shows the STEPP analysis in terms of RRs and highlights the strong treatment effect (RR $\cong$ 0.5) associated with chemotherapy followed by tamoxifen for patients with tumors having no or low values of ER compared with virtually no improvement in DFS for patients with tumors having higher values of ER.

Sites of Treatment Failure

Of the 1669 patients, 304 (18.2%) relapsed or died (Table 4). For the ER-negative cohort, the addition of CMF resulted in a substantial reduction of visceral dominant metastases and local recurrences, whereas the patterns of relapse were similar between the treatment groups for patients in the ER-positive cohort.

Table 1. Patients' characteristics according to treatment*

	No. of patients (%)		
	Tamoxifen	CMF × 3† → Tamoxifen	Total
	A) Total eligible patients		
	(n = 846)	(n = 823)	(n = 1669)
ER status			
Negative	190 (22)	192 (23)	382 (23)
Positive	621 (73)	596 (72)	1217 (73)
Unknown	35 (4)	35 (4)	70 (4)
Age			
<55 y	152 (18)	154 (19)	306 (18)
55–59 y	207 (24)	224 (27)	431 (26)
60–64 y	248 (29)	210 (26)	458 (27)
⩾65 y	239 (28)	235 (29)	474 (28)
Surgical treatment			
Total mastectomy	415 (49)	412 (50)	827 (50)
Breast conservation	431 (51)	411 (50)	842 (50)
with RT planned	374 (87)	370 (90)	744 (88)
with no RT planned	57 (13)	41 (10)	98 (12)
Tumor size			
⩽1 cm	95 (11)	106 (13)	201 (12)
1.1–2.0 cm	397 (47)	386 (47)	783 (47)
>2 cm	328 (39)	304 (37)	632 (38)
Unknown	26 (3)	27 (3)	53 (3)
Tumor grade‡			
1	149 (18)	142 (17)	291 (17)
2	357 (42)	337 (41)	694 (42)
3	292 (35)	294 (36)	586 (35)
Unknown	48 (6)	50 (6)	98 (6)
	B) ER-negative cohort		
	(n = 190)	(n = 192)	(n = 382)
Age			
<60 y	82 (43)	91 (47)	173 (45)
⩾60 y	108 (57)	101 (53)	209 (55)
Surgical treatment			
Total mastectomy	108 (57)	99 (52)	207 (54)
Breast conservation	82 (43)	93 (48)	175 (46)
with RT planned	69 (84)	78 (84)	147 (84)
with no RT planned	13 (16)	15 (16)	28 (16)
Tumor size			
⩽1 cm	19 (10)	21 (11)	40 (10)
1.1–2.0 cm	79 (42)	76 (40)	155 (41)
>2 cm	88 (46)	89 (46)	177 (46)
Unknown	4 (2)	6 (3)	10 (3)
Tumor grade			
1§	13 (7)	11 (6)	24 (6)
2	50 (26)	51 (27)	101 (26)
3	117 (62)	118 (61)	235 (62)
Unknown	10 (5)	12 (6)	22 (6)
	C) ER-positive cohort		
	(n = 621)	(n = 596)	(n = 1217)
Age			
<60 y	262 (42)	276 (46)	538 (44)
⩾60 y	359 (58)	320 (54)	679 (56)
Surgical treatment			
Total mastectomy	292 (47)	300 (50)	592 (49)
Breast conservation	329 (53)	296 (50)	625 (51)
with RT planned	289 (88)	273 (92)	562 (90)
with no RT planned	40 (12)	23 (8)	63 (10)
Tumor size			
⩽1 cm	57 (9)	67 (11)	124 (10)
1.1–2.0 cm	310 (50)	300 (50)	610 (50)
>2 cm	232 (37)	209 (35)	441 (36)
Unknown	22 (4)	20 (3)	42 (3)

(Table continues)

Table 1 (continued). Patients' characteristics according to treatment*

	No. of patients (%)		
	Tamoxifen	CMF × 3† → Tamoxifen	Total
Tumor grade			
1	127 (20)	119 (20)	246 (20)
2	291 (47)	273 (46)	564 (46)
3	166 (27)	168 (28)	334 (27)
Unknown	37 (6)	36 (6)	73 (6)

*ER = estrogen receptor; RT = radiation therapy.

†CMF × 3 = (cyclophosphamide [100 mg/m^2 on days 1–14, orally], methotrexate [40 mg/m^2 on days 1 and 8, intravenously], and 5-fluorouracil [600 mg/m^2 on days 1 and 8, intravenously], repeated for three 28-day courses).

‡See *(27)*.

§Methodologically, for tumors graded as grade 1, it is possible that the ER-negative classification might be false.

CMF Treatment and Toxicity

Among the patients randomly assigned to receive three cycles of CMF followed by tamoxifen, 746 patients (91%) completed all three cycles and 31 patients (4%) did not receive any CMF. Grade 3 or worse toxicities were experienced by 10.7% of the patients during CMF, including two possible toxic deaths (one sudden cardiac death and one from probable infection in a diabetic patient), and two life-threatening toxicities (one febrile neutropenia with pneumonia and one pulmonary embolism). Only 12.0% of the patients receiving three courses of CMF reported alopecia requiring a wig.

Tamoxifen Treatment and Toxicity

At the time of this report, 663 patients (40%) had completed the full 5 years (or 57 months) of tamoxifen and 35 patients (2%) received no tamoxifen. Grade 3 or worse toxicities were experienced by 3.6% of patients during tamoxifen therapy (3.4% with tamoxifen alone and 3.7% with tamoxifen after CMF), including three possible toxic deaths (one from pulmonary embolism, one from myocardial infarction with ventricular rupture, and one sudden death, probably vascular) and 17 life-threatening toxicities (16 vascular and one infection). Five cases of endometrial cancer were diagnosed after patients received 8, 24, 36, 58, and 62 months of tamoxifen, respectively. One case of uterine sarcoma (after 37 months of tamoxifen) and one case of mixed Müllerian tumor (after 50 months of tamoxifen) were also reported.

Quality of Life

Quality of life was assessed for 1382 patients who had not relapsed and had completed at least one questionnaire up to month 18; 757 of these patients used the expanded 1993 version of the quality-of-life form. At 3 months, patients assigned to tamoxifen alone compared with patients assigned to CMF followed by tamoxifen reported lower (more severe) scores for hot flashes (medians = 60 for tamoxifen versus 81 for CMF followed by tamoxifen; $P<.001$) but statistically significantly better scores for coping (80 versus 70; $P<.001$), physical well-being (86 versus 83; $P = .006$), mood (84 versus 77; $P = .008$), appetite (93 versus 92; $P = .002$), nausea/vomiting (97 versus 86; $P<.001$), tiredness (70 versus 56; $P = .007$, Fig. 4), and subjective health rating (utility) scale (80 versus 74; $P = .007$). After completion of chemotherapy, there were no residual dif-

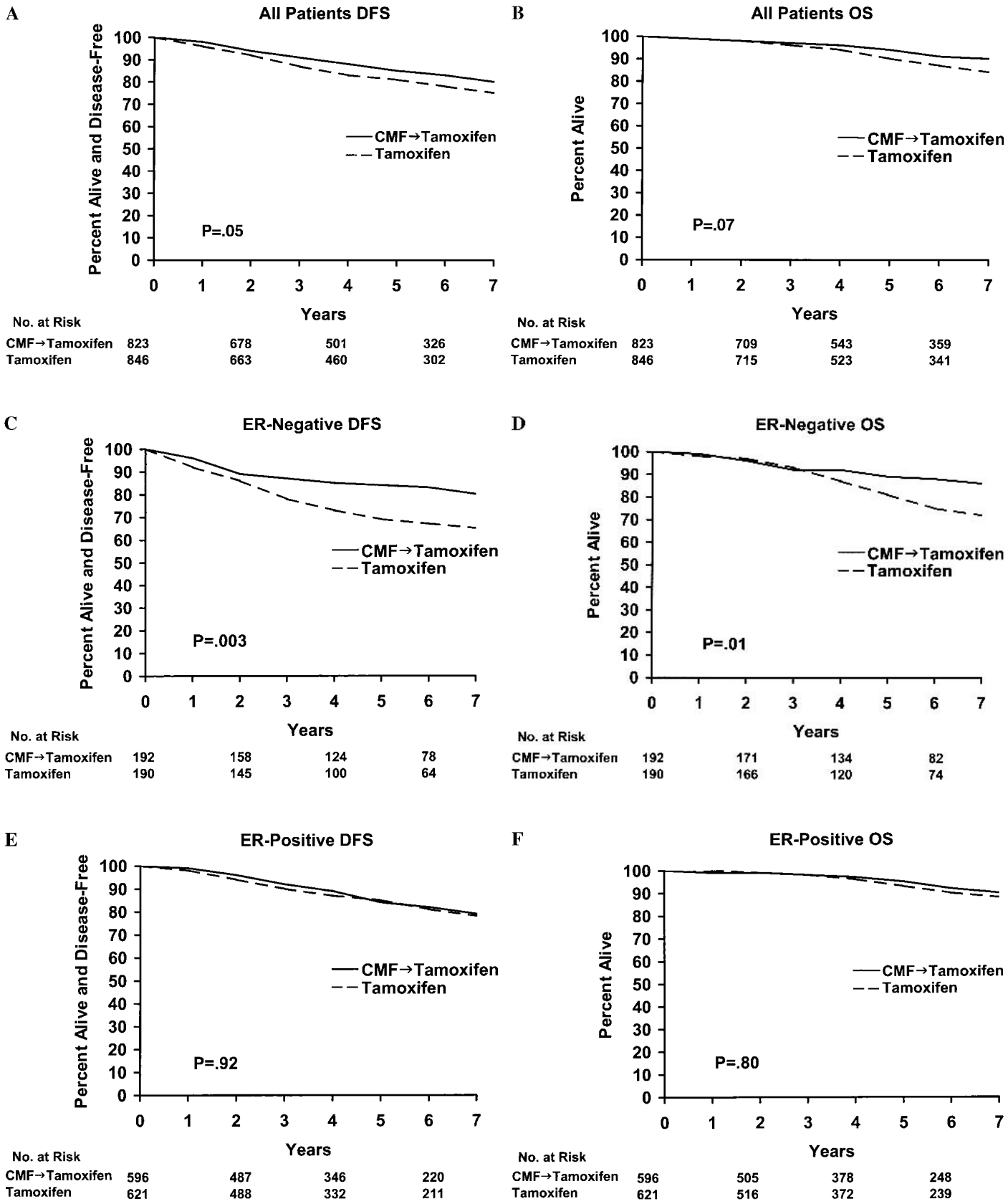

Fig. 2. Kaplan–Meier plots of disease-free survival (DFS) (**panel A**) and overall survival (OS) (**panel B**) for 1669 postmenopausal women with lymph node-negative breast cancer according to randomized treatment group at a median follow-up of 71 months. **A**) $P = .05$ for DFS for the two treatment groups. **B**) $P = .07$ for OS for the two treatment groups. Kaplan–Meier plots of DFS (**panel C**) and OS (**panel D**) for 382 postmenopausal women with lymph node-negative, ER-negative breast cancer according to randomized treatment group at a median follow-up of 71 months. **C**) $P = .003$ for DFS for the two treatment groups. **D**) $P = .01$ for OS for the two treatment groups. Kaplan–Meier plots of DFS (**panel E**) and OS (**panel F**) for 1217 postmenopausal women with lymph node-negative, ER-positive breast cancer according to randomized treatment group at a median follow-up of 71 months. **E**) $P = .92$ for DFS for the two treatment groups. **F**) $P = .80$ for OS for the two treatment groups. All statistical tests were two-sided.

Table 2. Disease-free survival according to treatment*

	No. of patients	5-y DFS (%)		Relative risk† (95% CI)	P‡
		Tamoxifen	CMF → Tamoxifen		
		A) All patients			
	1669	81 ± 2	85 ± 2	0.80 (0.64 to 1.00)	.05
ER status					
Negative	382	69 ± 4	84 ± 3	0.52 (0.34 to 0.79)	.003
Positive	1217	85 ± 2	84 ± 2	0.99 (0.75 to 1.30)	.92
Unknown	70	80 ± 7	97 ± 3	0.47 (0.14 to 1.57)	.22
Age					
<60 y	737	80 ± 2	85 ± 2	0.71 (0.50 to 1.02)	.06
⩾60 y	932	82 ± 2	85 ± 2	0.87 (0.65 to 1.16)	.34
Surgical treatment					
Total mastectomy	827	79 ± 2	85 ± 2	0.74 (0.55 to 0.99)	.04
Breast conservation	842	83 ± 2	84 ± 2	0.90 (0.63 to 1.27)	.54
with RT planned	744	84 ± 2	85 ± 2	0.94 (0.64 to 1.38)	.73
with no RT planned	98	79 ± 6	82 ± 6	0.84 (0.37 to 1.93)	.69
Tumor size					
⩽1 cm	201	87 ± 4	86 ± 4	0.95 (0.47 to 1.92)	.88
1.1–2.0 cm	783	85 ± 2	87 ± 2	0.90 (0.63 to 1.30)	.59
>2 cm	632	73 ± 3	81 ± 2	0.71 (0.52 to 0.98)	.04
Tumor grade§					
1	291	91 ± 3	91 ± 3	0.97 (0.50 to 1.89)	.94
2	694	81 ± 2	86 ± 3	0.75 (0.53 to 1.07)	.11
3	586	74 ± 3	79 ± 3	0.81 (0.58 to 1.15)	.24
		B) ER-negative cohort			
Age					
<60 y	173	69 ± 6	86 ± 4	0.48 (0.24 to 0.95)	.03
⩾60 y	209	68 ± 5	83 ± 4	0.56 (0.32 to 0.97)	.04
Surgical treatment					
Total mastectomy	207	70 ± 5	86 ± 4	0.51 (0.28 to 0.92)	.03
Breast conservation	175	67 ± 6	82 ± 4	0.51 (0.28 to 0.95)	.03
with RT planned	147	66 ± 6	85 ± 4	0.37 (0.18 to 0.77)	.008
with no RT planned	28	74 ± 13	66 ± 12	1.51 (0.42 to 5.38)	.52
Tumor size					
⩽1 cm	40	95 ± 5	89 ± 7	0.77 (0.11 to 5.47)	.79
1.1–2.0 cm	155	74 ± 5	87 ± 4	0.51 (0 to 1.06)	.07
>2 cm	177	57 ± 6	80 ± 4	0.52 (0.30 to 0.91)	.02
Tumor grade					
1‖	24	100	100	—	—
2	101	64 ± 7	89 ± 5	0.38 (0.17 to 0.88)	.02
3	235	67 ± 5	80 ± 4	0.62 (0.37 to 1.02)	.06
		C) ER-positive cohort			
Age					
<60 y	538	85 ± 3	84 ± 3	0.93 (0.60 to 1.44)	.76
⩾60 y	679	85 ± 2	84 ± 2	1.04 (0.73 to 1.48)	.83
Surgical treatment					
Total mastectomy	592	82 ± 2	84 ± 2	0.84 (0.59 to 1.20)	.35
Breast conservation	625	88 ± 2	83 ± 3	1.24 (0.79 to 1.94)	.34
with RT planned	562	89 ± 2	83 ± 3	1.55 (0.94 to 2.53)	.08
with no RT planned	63	81 ± 7	88 ± 8	0.31 (0.07 to 1.43)	.13
Tumor size					
⩽1 cm	124	90 ± 4	81 ± 6	1.48 (0.57 to 3.84)	.41
1.1–2.0	610	87 ± 2	87 ± 2	1.06 (0.69 to 1.64)	.79
>2 cm	441	80 ± 3	80 ± 3	0.86 (0.58 to 1.27)	.45
Tumor grade					
1	246	90 ± 3	89 ± 3	0.98 (0.49 to 1.99)	.97
2	564	85 ± 2	85 ± 2	0.86 (0.58 to 1.29)	.47
3	334	81 ± 4	77 ± 4	1.22 (0.75 to 1.99)	.43

*DFS = disease-free survival; CMF = cyclophosphamide (100 mg/m^2 on days 1–14, orally), methotrexate (40 mg/m^2 on days 1 and 8, intravenously), and 5-fluorouracil (600 mg/m^2 on days 1 and 8, intravenously), repeated for three 28-day courses; CI = confidence interval; ER = estrogen receptor; RT = radiation therapy; – = no estimate for standard error (because there were no failures among the 24 grade 1, ER-negative cases). Data for DFS are expressed as 5-year percents derived from the Kaplan–Meier method ± standard error.

†Relative risk = CMF → tamoxifen versus tamoxifen.

‡All statistical tests were two-sided.

§See *(27)*.

‖Methodologically, for tumors graded as grade 1, it is possible that the ER-negative classification might be false.

Table 3. Multiple regression analyses for estrogen receptor-negative and -positive cohorts*

Cohort	*P*†	Relative risk (95% CI)‡
ER-negative		
Treatment: CMF → tamoxifen vs. tamoxifen alone	.001	0.48 (0.31 to 0.75)
Age: ⩾60 y vs. <60 y	.42	1.19 (0.78 to 1.82)
Local treatment	.09	
BCS without RT vs. mastectomy		2.12 (1.04 to 4.30)
BCS with RT vs. mastectomy		1.43 (0.89 to 2.31)
Tumor size	.003	
1.1–2.0 cm vs. ⩽1 cm		2.05 (0.72 to 5.83)
>2 cm vs. ⩽1 cm		3.70 (1.32 to 10.37)
Grade§	.005	
2 vs. 1‖		5.80 (0.78 to 43.09)
3 vs. 1‖		6.19 (1.32 to 45.18)
ER-positive		
Treatment: CMF → tamoxifen vs. tamoxifen alone	.94	0.99 (0.75 to 1.31)
Age: ⩾60 vs. <60	.81	1.04 (0.78 to 1.38)
Local treatment	.45	
BCS without RT vs. mastectomy		0.97 (0.53 to 1.78)
BCS with RT vs. mastectomy		0.82 (0.59 to 1.13)
Tumor size	.02	
1.1–2.0 cm vs. ⩽1 cm		0.87 (0.51 to 1.46)
>2 cm vs. ⩽1 cm		1.23 (0.72 to 2.11)
Grade	.24	
2 vs. 1		1.34 (0.89 to 2.01)
3 vs. 1		1.56 (1.00 to 2.41)

*CI = confidence interval; ER = estrogen receptor; CMF = cyclophosphamide (100 mg/m^2 on days 1–14, orally), methotrexate (40 mg/m^2 on days 1 and 8, intravenously), and 5-fluorouracil (600 mg/m^2 on days 1 and 8, intravenously), repeated for three 28-day courses; BCS = breast conserving surgery; RT = radiation therapy.

†All statistical tests were two-sided.

‡Relative risk for each analysis is the risk of relapse for the first cohort listed compared with that for the second cohort listed. A value greater than 1.00 indicates an increased risk of relapse for the first cohort listed.

§See *(27)*.

‖Methodologically, for tumors graded as grade 1, it is possible that the ER-negative classification might be false.

ferences between the two treatment groups for any of the quality-of-life measures.

Discussion

IBCSG Trial IX is the largest randomized trial comparing chemotherapy followed by tamoxifen versus tamoxifen alone for postmenopausal women with lymph node-negative breast cancer. This trial demonstrated an overall benefit from the addition of three courses of adjuvant CMF. The most important finding of this trial, however, was the statistically significant difference in the magnitude of the chemotherapy effect according to ER status of the primary tumor. Patients with ER-negative tumors benefited substantially from adjuvant chemotherapy, but those with ER-positive disease obtained no benefit.

The results of IBCSG Trial IX for the ER-negative cohort are unique. To our knowledge, there are no other published trials of chemotherapy followed by tamoxifen versus tamoxifen alone for the population of postmenopausal women with lymph node-negative, ER-negative disease. Compared with administration of tamoxifen alone, administration of short-duration CMF chemotherapy followed by tamoxifen statistically significantly improved DFS. This observation was true for both the overall ER-negative cohort and for subgroups including patients older than 60 years of age. Analyses of sites of relapse indicated that the improved DFS was related primarily to a reduction in visceral dominant metastases.

The large magnitude of the chemotherapy effect for the ER-negative cohort in the IBCSG Trial IX (in which tamoxifen was given after chemotherapy) was similar to that observed in several chemotherapy trials conducted in the absence of tamoxifen. The National Surgical Adjuvant Breast and Bowel Project (NSABP) Study B-13 for lymph node-negative, ER-negative disease demonstrated a statistically significant advantage for twelve 28-day cycles of M→F (methotrexate [100 mg/m^2, intravenously], followed 1 hour later by 5-fluorouracil [600 mg/m^2, intravenously], followed 24 hours after methotrexate by intravenous leucovorin [10 mg/m^2, single dose], followed every 6 hours by oral leucovorin [10 mg/m^2, five doses], repeated on days 1 and 8 of each 28-day cycle) compared with no adjuvant treatment *(28)*. Surprisingly, the estimate of the benefit for women 50 years of age or older was larger than that for women less than 50 years old. Intergroup Study 0011 *(29),* in which 75% of patients had ER-negative tumors, also demonstrated the superiority of six 28-day courses of CMFP ("classical" CMF plus prednisone [40 mg/m^2 on days 1–14, orally]) chemotherapy compared with no adjuvant treatment, and again the estimated benefit was larger for postmenopausal patients than for premenopausal patients. In IBCSG/Ludwig Trial V, even a single course of perioperative chemotherapy statistically significantly improved outcome compared with no adjuvant therapy for postmenopausal women with lymph node-negative, ER-negative disease, whereas premenopausal women with ER-negative disease derived little benefit from the single cycle *(30–32)*. The issue of duration of chemotherapy has not been studied properly for patients with endocrine-nonresponsive disease *(33)*. The fact that one perioperative course provided substantial benefit for postmenopausal patients with lymph node-negative, endocrine-nonresponsive tumors suggests that the proper duration of cytotoxic treatment in this population might be shorter rather than longer.

Adjuvant chemotherapy is prescribed routinely in addition to tamoxifen for the majority of postmenopausal patients with lymph node-negative, ER-positive breast cancer, especially if they present with other high-risk characteristics *(34)*. Although many trials *(35)* have shown that adding chemotherapy to tamoxifen might be more beneficial than tamoxifen alone for postmenopausal patients with ER-positive tumors, almost all were conducted exclusively in patients with lymph node-positive disease. IBCSG Trial IX is, to our knowledge, the first study conducted specifically to define the worth of chemotherapy combined with tamoxifen for postmenopausal patients with lymph node-negative disease, and this trial demonstrated that three courses of CMF chemotherapy followed by tamoxifen provided no benefit compared with tamoxifen alone for patients with ER-positive tumors. This result was true for the overall analysis and the analyses within subgroups of patients including those with high-risk characteristics such as larger tumor size and higher tumor grade. In particular, older patients (60 years of age or older) with ER-positive tumors derived little benefit from adding CMF. Although IBCSG Trial IX does not prove that chemotherapy has no effect for this patient population, it does indicate that any benefit is likely to be small.

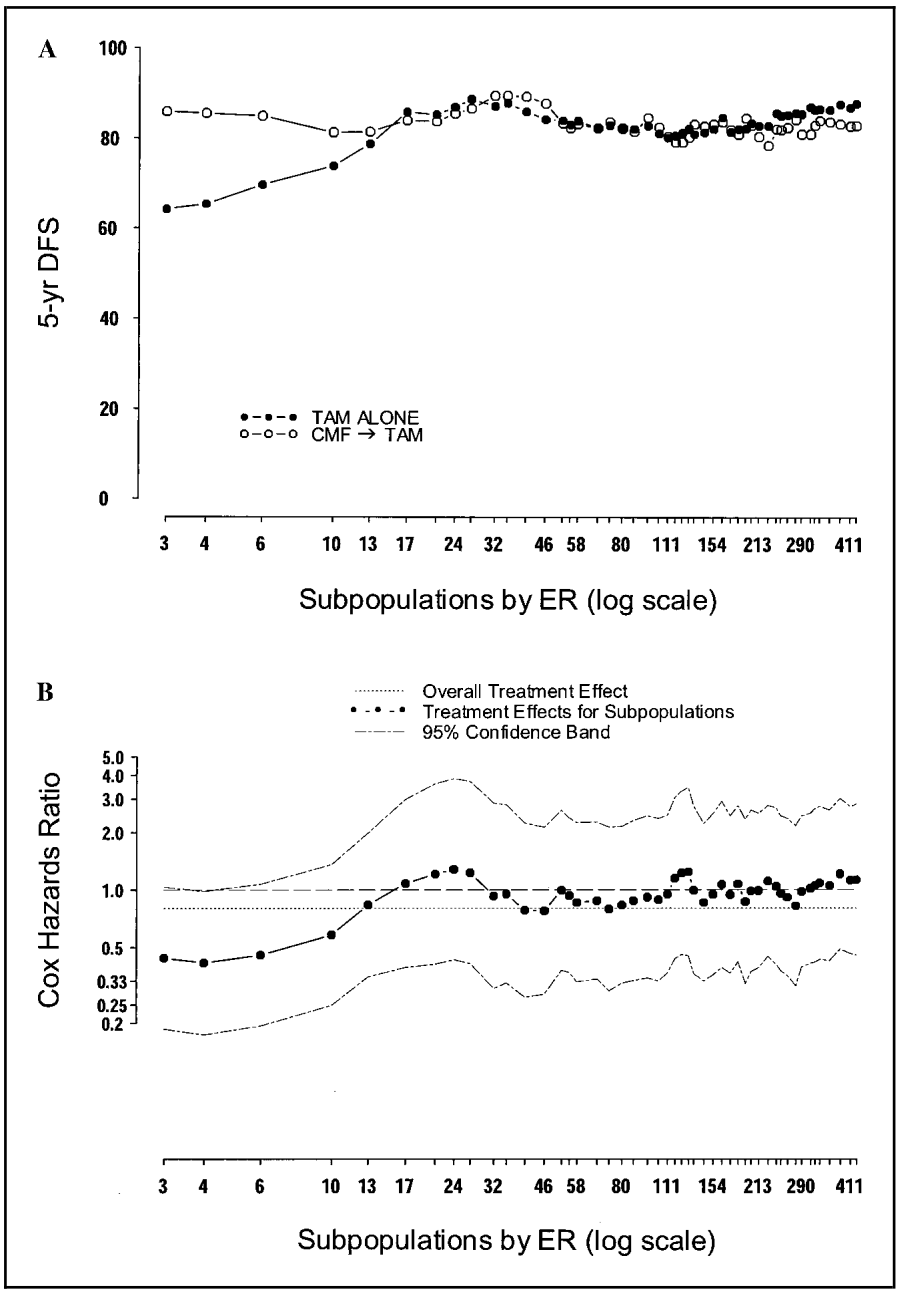

Fig. 3. A) Subpopulation Treatment Effect Pattern Plot (STEPP) showing 5-year disease-free survival (DFS) percent according to quantitative estrogen receptor (ER) values for women treated with CMF (cyclophosphamide [100 mg/m^2 on days 1–14, orally], methotrexate [40 mg/m^2 on days 1 and 8, intravenously], and 5-fluorouracil [600 mg/m^2 on days 1 and 8, intravenously], repeated for three 28-day courses) followed by tamoxifen and for women treated with tamoxifen alone. For this sliding-window STEPP analysis, each subpopulation contained approximately 200 patients, and each subsequent subpopulation was formed by moving from left to right by dropping approximately 10 patients with the lowest values for ER and adding approximately 10 patients with the next higher values of ER. The ***x*- axis** indicates the median ER value for the patients in each subpopulation. **B**) STEPP showing Cox model relative risk (RR) according to values for quantitative ER. **Horizontal dashed line** = no difference between treatments (RR = 1.0); **horizontal dotted line** = the observed treatment difference for the overall population (RR = 0.80). **Solid circles** = RRs for each of the sliding-window subpopulations; bands around these points = the simultaneous (across all subgroups) 95% confidence intervals for the RRs. This plot highlights the strong treatment effect (RR ≈ 0.5) associated with adding chemotherapy for patients with tumors expressing no or low levels of ER compared with virtually no improvement in DFS for patients with tumors having higher values of ER.

NSABP Study B-20 *(36)* is the only other trial comparing chemotherapy plus tamoxifen with tamoxifen alone that focused on patients with lymph node-negative, ER-positive disease. The study included both younger and older women, and results were evaluated according to age (≤49 years old versus ≥50 years old) rather than according to menopausal status. Six courses of methotrexate and 5-fluorouracil administered with tamoxifen (MFT) and six courses of classical CMF administered with tamoxifen (CMFT) were compared with tamoxifen alone. Tamoxifen was given for 5 years. For the 1264 patients 50 years of age or older in NSABP B-20 *(36),* the DFS benefit of adding chemotherapy was not statistically significant, and the estimated effect was much smaller than that observed for the 1042 patients under the age of 50 years. Some of the patients in the 50-years-or-older age group were undoubtedly pre- or perimenopausal at the time they enrolled in NSABP B-20; in fact, 358 of the 1264 patients (28%) were under 55 years old at study entry (Bryant J: personal communication). For these patients, some of the chemotherapy effect could have been obtained through suppression of ovarian function *(37).* Ovarian function suppression plus tamoxifen is more effective than tamoxifen alone in advanced breast cancer *(38).* Reexamination of NSABP B-20 to obtain estimates of the chemotherapy effect for patients who were clearly postmenopausal at the time of study entry (for example, 55 or 60 years of age or older) would be relevant to better define any benefit of adding chemotherapy to tamoxifen for postmenopausal patients with lymph node-negative, ER-positive tumors.

A potential limitation of the IBCSG Trial IX is the use of three courses of CMF. Although it is possible that longer duration chemotherapy would have provided a benefit for the patients with ER-positive tumors, all available evidence suggests otherwise. Three randomized trials have demonstrated that three and six courses of CMF provide similar results for older patients (especially for patients 40 years of age or older with ER-positive

Table 4. Sites of first treatment failure according to treatment*

	% of total at a median follow-up of 71 months								
	All patients			ER-negative cohort			ER-positive cohort		
	Tamoxifen (n = 846)	CMF → Tamoxifen (n = 823)	Total (n = 1669)	Tamoxifen (n = 190)	CMF → Tamoxifen (n = 192)	Total (n = 382)	Tamoxifen (n = 621)	CMF → Tamoxifen (n = 596)	Total (n = 1217)
Treatment failures	19.6	16.8	18.2	30.0	17.2	23.6	16.3	17.0	16.6
Deaths	11.1	8.9	10.0	20.0	10.9	15.4	8.2	8.4	8.3
Type of first event									
Local	3.9	2.4	3.2	4.2	2.1	3.1	3.7	2.5	3.1
Regional ± local	1.0	0.7	0.8	2.1	2.1	2.1	0.6	0.3	0.5
Soft tissue ± any above	0.7	0.5	0.8	1.6	1.6	1.6	0.5	0.2	0.3
Bone ± any above	2.0	1.9	2.0	1.1	1.0	1.0	2.1	2.4	2.2
Viscera ± any above	5.6	4.9	5.2	12.1	7.3	9.7	3.5	4.4	3.9
Contralateral breast	2.1	1.3	1.7	3.2	0.5	1.8	1.8	1.5	1.6
Second malignancy	2.1	2.7	2.4	2.6	1.0	1.8	1.9	3.4	2.6
Death without relapse	2.3	2.3	2.3	3.2	1.6	2.4	2.1	2.4	2.2

*ER = estrogen receptor; CMF = cyclophosphamide (100 mg/m^2 on days 1–14, orally), methotrexate (40 mg/m^2 on days 1 and 8, intravenously), and 5-fluorouracil (600 mg/m^2 on days 1 and 8, intravenously), repeated for three 28-day courses.

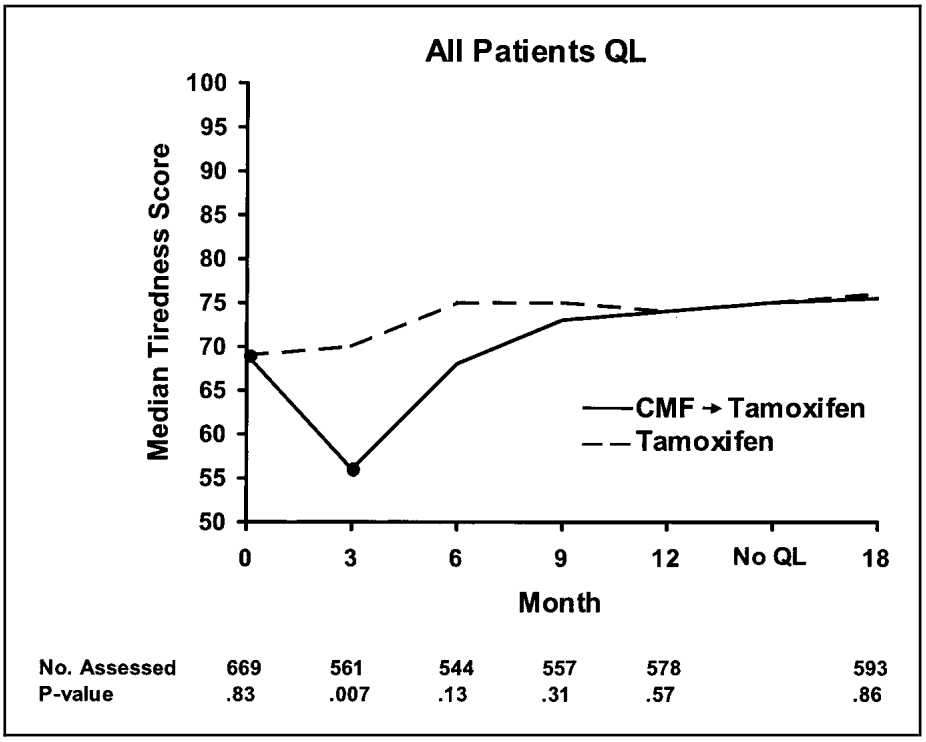

Fig. 4. Median tiredness scores assessed in the study since 1993 according to randomized treatment group and the number of months from randomization. Higher scores indicate less impact of tiredness (higher quality of life). The lower scores for the CMF-containing regimen (CMF = cyclophosphamide [100 mg/m^2 on days 1–14, orally], methotrexate [40 mg/m^2 on days 1 and 8, intravenously], and 5-fluorouracil [600 mg/m^2 on days 1 and 8, intravenously], repeated for three 28-day courses) seen at 3 months (P = .007) and at 6 months (P = .13) were transient, and by 12 months, there was no difference between the two groups. **Solid circles** = times at which patients were receiving CMF. All statistical tests were two-sided.

tumors) *(39–42).* All available studies that suggest a better outcome with longer duration chemotherapy include premenopausal patients and/or patients with ER-negative disease. Perhaps results for the ER-positive cohort in the IBCSG Trial IX would have been more positive if an anthracycline-containing regimen had been used. This conjecture is apparently supported by Intergroup Study 0102, which demonstrated that six courses of an anthracycline-containing regimen (CAF = cyclophosphamide, doxorubicin, 5-fluorouracil) is superior to six courses of CMF for patients with lymph node-negative breast cancer (one-sided statistical test, P = .03) *(43).* This study, however, was restricted to patients with high-risk, lymph node-negative disease, and most patients had characteristics that predict responsiveness to chemotherapy (e.g., ER-negative tumors and/or premenopausal status). In fact, the results of Intergroup Study 0102 have little relevance for postmenopausal patients with ER-positive tumors who receive 5 years of tamoxifen, because only 342 (12.7%) of the 2691 randomly assigned patients met these criteria (Green S: personal communication).

The EBCTCG (Early Breast Cancer Trialists' Collaborative Group) polychemotherapy overview analysis showed that the effect of chemotherapy in women aged 50–69 years was relatively small but statistically significant *(12,44).* The overview estimates of the average magnitude of treatment effect are, however, derived from a mixture of evidence *(45–47)* that combines ER-negative and ER-positive cohorts. Overview results for women 50–69 years old with lymph node-negative breast cancer are completely consistent with IBCSG Trial IX (which was not part of the overview analysis); the benefit of chemotherapy was substantial for ER-negative tumors (somewhat greater than the

effect observed for women younger than 50 years old), but there was no advantage at all for the very few women (approximately 400) studied with ER-positive tumors who also received tamoxifen *(48,49)*.

Currently, immunohistochemical methods are used for ER determination, enabling a more precise evaluation of the association between the presence of ER and response to endocrine treatment. ER-absent tumors (0% expression) are nonresponsive to tamoxifen, whereas ER-positive primary tumors (10% or more expression) are clearly responsive. Tumors classified as ER low (1%–9% of cells expressing ER) have some responsiveness to treatment with tamoxifen *(50)*. Endocrine-responsive, endocrine-nonresponsive, and intermediate groups can be defined by using immunohistochemistry. Tamoxifen provides most of the treatment benefit for the endocrine-responsive group, chemotherapy provides most of the treatment benefit for the endocrine-nonresponsive group, and a mixture of effects is acting in the intermediate group. This continuum of responsiveness is clearly illustrated in the STEPP analyses (Fig. 3).

Short-term detrimental effects of chemotherapy on quality of life were demonstrated. Consequently, reliable evidence of benefit is required to justify the burden and expense of chemotherapy; such evidence is not available for postmenopausal patients with lymph node-negative, ER-positive disease. The detrimental effects on quality of life were, however, transient in all domains. The short courses of chemotherapy were well tolerated, and relatively few patients experienced alopecia severe enough to require a wig. Therefore, there is little justification for withholding chemotherapy for postmenopausal patients with lymph node-negative, ER-negative tumors.

Postmenopausal women with lymph node-negative breast cancer should be treated with a much more individualized adjuvant program than is currently being prescribed. Current practice is based largely on estimates of average chemotherapy effects obtained from patients with heterogeneous disease and menopausal status characteristics. Results of the IBCSG Trial IX and other evidence *(12,48,51)* indicate that postmenopausal patients with lymph node-negative, endocrine-nonresponsive disease benefit substantially from adjuvant chemotherapy, and chemotherapy-related questions should represent a major focus of future research in this population. In contrast, the worth of adjuvant chemotherapy for postmenopausal patients with lymph node-negative, endocrine-responsive disease should be questioned, and such patients should receive tamoxifen for at least 5 years. The focus of future research in this patient population should be the development of new endocrine regimens that improve upon the results already achieved with 5 years of tamoxifen treatment.

APPENDIX

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NOTES

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