ARTICLES

Tamoxifen and Chemotherapy for Lymph Node-Negative, Estrogen Receptor-Positive Breast Cancer

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Background: **The B-20 study of the National Surgical Adjuvant Breast and Bowel Project (NSABP) was conducted to determine whether chemotherapy plus tamoxifen would be of greater benefit than tamoxifen alone in the treatment of patients with axillary lymph node-negative, estrogen receptor-positive breast cancer.** ***Methods:*** **Eligible patients (n = 2306) were randomly assigned to one of three treatment groups following surgery. A total of 771 patients with follow-up data received tamoxifen alone; 767 received methotrexate, fluorouracil, and tamoxifen (MFT); and 768 received cyclophosphamide, methotrexate, fluorouracil, and tamoxifen (CMFT). The Kaplan–Meier method was used to estimate disease-free survival, distant disease-free survival, and survival. Reported *P* values are two-sided.** ***Results:*** **Through 5 years of follow-up, chemotherapy plus tamoxifen resulted in significantly better disease-free survival than tamoxifen alone (90% for MFT versus 85% for tamoxifen [*P* = .01]; 89% for CMFT versus 85% for tamoxifen [*P* = .001]). A similar benefit was observed in both distant disease-free survival (92% for MFT versus 87% for tamoxifen [*P* = .008]; 91% for CMFT versus 87% for tamoxifen [*P* = .006]) and survival (97% for MFT versus 94% for tamoxifen [*P* = .05]; 96% for CMFT versus 94% for tamoxifen [*P* = .03]). Compared with tamoxifen alone, MFT and CMFT reduced the risk of ipsilateral breast tumor recurrence after lumpectomy and the risk of recurrence at other local, regional, and distant sites. Risk of treatment failure was reduced after both types of chemotherapy, regardless of tumor size, tumor estrogen or progesterone receptor level, or patient age; however, the reduction was greatest in patients aged 49 years or less. No subgroup of patients evaluated in this study failed to benefit from chemotherapy.** ***Conclusions:*** **Findings from this and other NSABP studies indicate that patients with breast cancer who meet NSABP protocol criteria, regardless of age, lymph node status, tumor size, or estrogen receptor status, are candidates for chemotherapy. [J Natl Cancer Inst 1997; 89:1673–82]**

In 1985, a National Institutes of Health (NIH) consensus conference was convened to evaluate data obtained from randomized clinical trials of adjuvant chemotherapy and endocrine therapy that had been conducted during the 1970s and early 1980s *(1)*. At that meeting, it was concluded that premenopausal patients with primary breast cancer and positive axillary lymph nodes should be treated with adjuvant chemotherapy and that postmenopausal women with positive nodes and estrogen receptor (ER)-positive tumors should receive tamoxifen. There was insufficient information to permit advocacy of a therapy other than surgery to treat women with negative nodes. Since 1985, however, data from three National Surgical Adjuvant Breast and Bowel Project (NSABP) trials involving 6000 patients with negative nodes *(2–4)* and findings from studies conducted by other investigators *(5–7)* have provided new information about the treatment of such patients. As a result of these findings, systemic therapy is now being used to manage patients with node-negative breast cancer, and a marked change in thinking regarding the biologic and clinical significance of tumors associated with negative nodes has occurred.

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

In 1981 and 1982, the NSABP conducted two studies aimed at assessing the value of systemic therapy in the management of patients with negative nodes. One of these, B-13, was carried out to determine the worth of an adjuvant chemotherapy regimen without an alkylating agent, i.e., methotrexate (M) and sequential fluorouracil (F) (MF) in women with ER-negative tumors, a population putatively at high risk for treatment failure *(2)*. The other trial, B-14, was conducted to evaluate tamoxifen therapy in women with ER-positive tumors, a group considered to have a better prognosis *(3)*. Data from both studies demonstrated the worth of the regimens being evaluated, yielded information about the natural history of patients with negative nodes, and provided justification for a new generation of NSABP trials to evaluate other therapeutic regimens for such patients.

Our initial finding of a significant improvement in disease-free survival following MF therapy and findings from other studies that demonstrated a benefit from cyclophosphamide (C), M, and F (CMF) in patients with negative nodes and ER-negative tumors prompted us to conduct another trial, B-19, to compare the worth of MF with conventional CMF in an effort to determine the need for an alkylating agent with the two antimetabolites (MF). Recent findings have indicated a benefit from both therapies in patients with negative nodes and ER-negative tumors *(4)*. In patients aged 49 years or less, the advantage from CMF was greater than that from MF.

Findings from the B-14 trial have indicated that tamoxifen therapy provides substantial benefit to patients with node-negative, ER-positive breast cancers through 10 years of follow-up but that no additional benefit is obtained when such therapy is continued for more than 5 years *(3,8)*. Tamoxifen therapy has also been shown to result in a significant reduction in the incidence of contralateral breast cancer. Before the B-14 findings were available, however, we concluded that the degree of benefit achieved with tamoxifen in this group of patients at putatively good risk was unlikely to be sufficient to eliminate the need for other trials to test potentially more effective therapeutic regimens. As a consequence of that judgment, in October 1988, a new NSABP trial, B-20, was implemented to test the hypothesis that the addition of chemotherapy, i.e., MF or CMF, to tamoxifen would result in a greater benefit than would tamoxifen alone in the treatment of patients with negative nodes and ER-positive tumors. The initial results from that study, which are presented in this article, support that concept and evoke consideration of the clinical and biologic significance of the findings.

Subjects and Methods

Women at participating NSABP institutions in the United States and Canada who had primary operable, histologically node-negative, ER-positive breast cancer and who had a life expectancy of at least 10 years were eligible for this study if they fulfilled other eligibility criteria (*see* Appendix Table 1). After surgery (total mastectomy and lymph node dissection or lumpectomy and lymph node dissection followed by breast irradiation) and after they had given written informed consent, the patients were stratified according to age ($\leq$49 or $\geq$50 years), tumor size determined by clinical examination ($\leq$2, 2.1–5.0, or $\geq$5.1 cm), type of surgery, and tumor ER level (10–49, 50–99, or $\geq$100 fmol/mg cytosol protein). Randomization was performed within these strata by use of a biased coin approach to ensure that treatment assignment was balanced with respect to these characteristics.

Between October 17, 1988, and March 5, 1993, patients were randomly assigned to one of three treatment groups following surgery: tamoxifen alone (TAM), tamoxifen (T) plus sequential methotrexate (M) and fluorouracil (F) (MFT), or T plus cyclophosphamide (C), M, and F (CMFT). Patient and treatment assignment information is shown in Table 1. A total of 2363 patients were randomly assigned in the study (788 to TAM, 786 to MFT, and 789 to CMFT); 2.2% of the patients were ineligible, and there was no follow-up information for an additional 0.3%. The average time on the study was 77 months (range, 49–102 months).

The distribution of patient and tumor characteristics employed as stratification variables was similar across the treatment groups (Table 2). Approximately 45% of the patients were less than 50 years of age; slightly more than two thirds of the tumors were 2.0 cm or less in size; about 20% of the tumors were progesterone receptor (PgR) negative, i.e., 0–9 fmol/mg cytosol protein; and about 45% of the patients had been treated by lumpectomy. Although measurement of both tumor ER and PgR concentrations was required for entry into the study, only the ER measurement was used to determine eligibility. Tumor specimens were assayed for both ER and PgR levels by means of sucrose density gradient, dextran-coated charcoal titration.

All patients received tamoxifen (10 mg orally twice a day) for 5 years. In all groups, treatment with tamoxifen began simultaneously with the administration of MF or CMF, i.e., between 14 and 35 days after surgery. MF followed by leucovorin was administered every 4 weeks for six cycles. M (100 mg) and F (600 mg), both per square meter of body surface area, were given as an intravenous bolus dose on days 1 and 8 every 4 weeks for six cycles. F was administered 1 hour after the administration of M, and leucovorin (15 mg/m^2) was

Table 1. Study information*

	TAM		MFT		CMFT		Total	
Patients	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%
Randomly assigned	788	—	786	—	789	—	2363	—
Ineligible	17	2.2	17	2.2	17	2.2	51	2.2
Delay in initiating treatment	2		4		4		10	
Advanced disease at study entry	9		5		3		17	
Estrogen receptor value unacceptable, out of range, or missing	3		6		5		14	
Other	3		2		5		10	
Without follow-up	0	0.0	2	0.3	4	0.5	6	0.3
Eligible with follow-up	771	97.8	767	97.6	768	97.3	2306	97.6
Mean time on study, mo†	77 (49–102)		77 (49–102)		77 (49–102)		77 (49–102)	

*TAM = tamoxifen only; MFT = methotrexate, fluorouracil, and tamoxifen; CMFT = cyclophosphamide, methotrexate, fluorouracil, and tamoxifen.
†Values in parentheses are ranges in months.

Table 2. Characteristics of the patients*

Characteristic	TAM (771 Pts.), %	MFT (767 Pts.), %	CMFT (768 Pts.), %
Age, y			
≤49	45	45	46
50–59	28	29	27
≥60	27	26	27
Race			
White	87	88	88
Black	6	6	6
Other	5	4	4
Unknown	2	2	2
Clinical tumor size, cm			
≤2.0	70	68	70
≤1.0	21	19	20
1.1–2.0	49	49	50
2.1–4.0	27	29	26
≥4.1	3	3	4
Type of surgery			
Lumpectomy	45	45	44
Mastectomy	55	55	56
Estrogen receptor level, fmol†			
10–49	44	45	45
50–99	22	22	22
≥100	34	33	33
Progesterone receptor level, fmol†			
0–9	18	17	18
10–49	16	22	19
50–99	14	16	15
≥100	52	45	48

*TAM = tamoxifen alone; MFT = methotrexate, fluorouracil, and tamoxifen; CMFT = cyclophosphamide, methotrexate, fluorouracil, and tamoxifen; Pts. = patients.

†Per mg cytosol protein.

administered orally every 6 hours for six consecutive doses beginning 24 hours after the administration of M. The criteria and schedule for dose modification of MF therapy in the event of drug toxicity have been reported *(2).*

CMF was administered in accordance with the standard Milan regimen and with NSABP B-19 *(4).* C (100 mg/m^2) was given orally as a single dose on days 1–14 inclusive every 28 days for six cycles. M (40 mg/m^2) and F (600 mg/m^2) were given intravenously on days 1 and 8 every 28 days for six cycles. Modification of the dose of CMF was similar to that described for MF, except that, when white blood cell counts were in the range of 2500–3499/μL or when platelet counts were 75 000–99 999/μL, 75% of each of the three drugs was administered, as compared with 50% of M and 50% of F in the MF combination.

Radiation therapy was administered to patients treated by lumpectomy who received MF after one course of chemotherapy and if there was no evidence of hematologic toxicity. When administered in conjunction with CMF, radiation therapy was begun within 1 week after day 8 of the first cycle of CMF. Subsequent doses of chemotherapy were administered in both the MF and CMF groups during radiation therapy. If hematologic toxicity occurred, dose reductions as described in the protocol were employed.

Statistical Methods

Disease-free survival was defined as time on the study without 1) recurrence of breast cancer at local, regional, or distant sites; 2) occurrence of a second primary cancer; or 3) occurrence of death prior to those events. Ipsilateral breast tumor recurrences after lumpectomy were also considered to be local events. Distant disease-free survival was defined as time on the study free of both tumor recurrence at distant sites and second primary cancers. Distant failures were included regardless of whether they occurred as first events or as events subsequent to local or regional failures. Deaths that occurred prior to distant treatment failures or to second primary cancers were censored. Events for the survival end point were deaths from any cause. Time-to-event distributions were computed by use of Kaplan–Meier estimates and were compared by use of two-sided logrank tests over all available observation time *(9,10).* Average annual rates of specific events comprising disease-free survival were computed and compared by use of exact binomial probabilities.

The Cox proportional hazards model was used to examine prognostic covariates and to test for interactions between treatment and the covariates *(11).* Age at diagnosis, clinical tumor size, ER status, and PgR status were evaluated for association with disease-free survival and survival. Outcomes with regard to age were evaluated in categories according to age, i.e., 49 years or less and 50 years or more, and as a continuous function of age. Outcomes with regard to clinical tumor size were evaluated in categories according to tumor size, i.e., 2 cm or less and greater than 2 cm, and as a continuous variable. Outcome was also evaluated relative to tumor PgR content, i.e., negative (<10 fmol/mg cytosol protein) or positive (≥10 fmol/mg cytosol protein), and to tumor ER content, which was examined as a continuous variable and categorized according to the stratification categories used at randomization. Model results have been summarized as relative risks (RRs) with associated 95% confidence intervals (CIs) and are expressed as percent reductions in risk relative to a comparison group.

Randomly assigned patients were analyzed as follows: 1) using all women regardless of whether or not they met eligibility criteria defined in the protocol and 2) including only those women who met eligibility criteria. The results of these analyses did not differ. Toxicity and compliance data were summarized for all patients for whom information was provided, regardless of their eligibility. The primary findings presented in this article pertain to all eligible patients with follow-up information received through March 31, 1997.

Results

Disease-Free Survival, Distant Disease-Free Survival, and Survival

There was a significant difference in disease-free survival distributions among the treatment groups through 5 years of follow-up ($P = .002$) (Fig. 1). Pairwise comparisons made between the TAM and the MFT or CMFT groups indicated that women in both groups who received chemotherapy in addition to tamoxifen had a significantly better disease-free survival than did women treated with tamoxifen alone (90% versus 85% [$P = .01$] for the comparison of MFT with TAM and 89% versus 85% [$P = .001$] for the comparison of CMFT with TAM). The event rate for women who received MFT was 28% less than that for women treated with TAM (RR = 0.72; 95% CI = 0.56–0.93) (Fig. 1). There was a 35% reduction in the event rate for women who received CMFT (RR = 0.65; 95% CI = 0.50–0.84) (Fig. 1). The distribution of the disease-free survival of the MFT and CMFT groups through 5 years was similar ($P = .44$).

Just as with disease-free survival, the distributions of distant disease-free survival among the treatment groups were significantly different ($P = .005$) (Fig. 1). Distant disease-free survival at 5 years was greater after treatment with MFT (92%; P = .008) and CMFT (91%; P = .006) than after TAM therapy (87%). There was a 32% reduction in risk relative to TAM as a result of treatment with MFT (RR = 0.68; 95% CI = 0.51–0.90) and a 33% reduction as a result of CMFT therapy (RR = 0.67; 95% CI = 0.50–0.89) (Fig. 1). The MFT and CMFT groups did not differ with respect to time to occurrence of distant disease ($P = .93$).

A comparison of survival distributions for the three groups indicated a significant difference in survival time (global $P = .04$) (Fig. 1). When the survival of women treated with TAM (94%) was compared with that of women who received MFT (97%) or with that of women treated with CMFT (96%), a significant improvement in survival was observed in those who received chemotherapy (pairwise comparisons: $P = .05$ and P

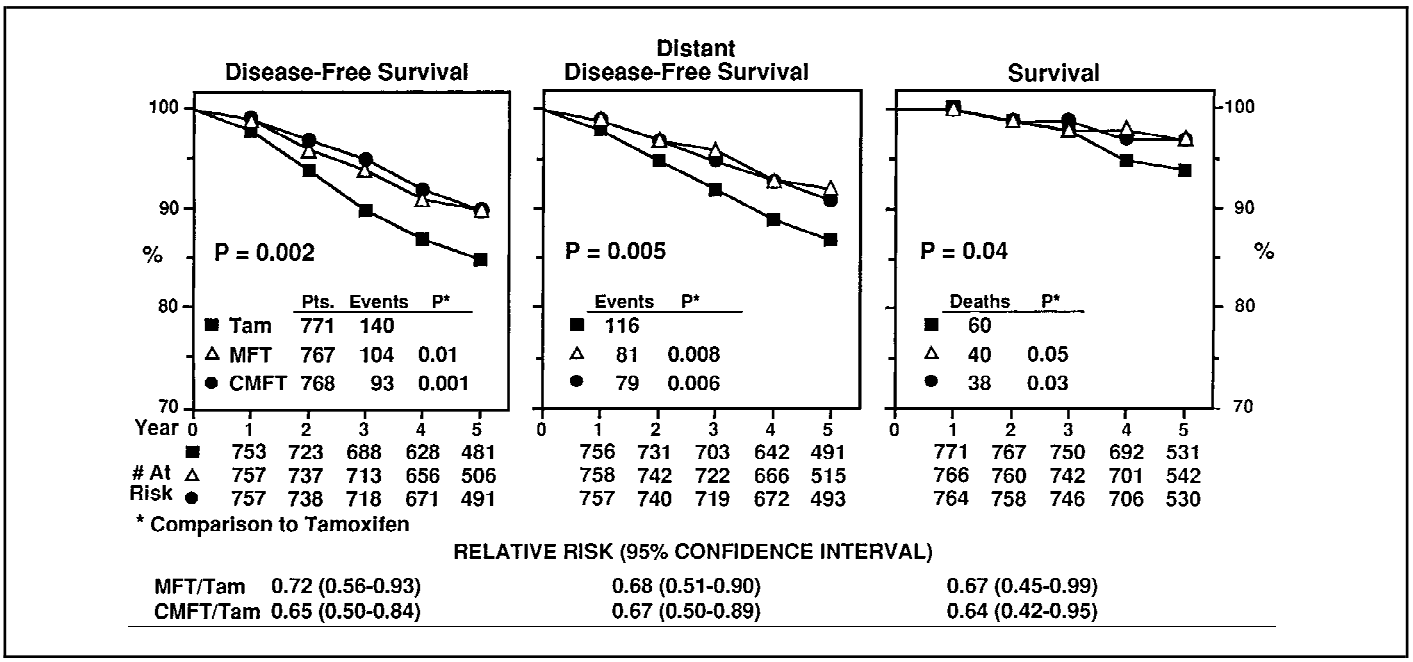

Fig. 1. Disease-free survival, distant disease-free survival, and survival according to treatment group. Benefit from MFT (methotrexate, fluorouracil, and tamoxifen) or CMFT (cyclophosphamide, methotrexate, fluorouracil, and tamoxifen) is further indicated by the relative risk (95% confidence interval) of the occurrence of events related to those outcomes. Pts. = patients; Tam = tamoxifen alone; # = number. The *P* values are two-sided.

= .03, respectively). There was a 33% reduction in the risk of death among women who received MFT and a 36% reduction in this risk among patients treated with CMFT when compared with the risk in patients treated with TAM. The RR (95% CI) was 0.67 (0.45–0.99) in the former and 0.64 (0.42–0.95) in the latter (Fig. 1). Survival distributions did not differ between patients who received MFT and CMFT ($P = .83$).

Rates and Relative Risks of Treatment Failure According to Site of Recurrence

A comparison of the three treatment regimens indicated a reduction in the rates of local, regional, and distant recurrences after MFT and CMFT therapy (Table 3 and Fig. 2). Although the decrease occurred following both therapies, it was greater at local–regional sites, including the ipsilateral breast, in the CMFT group. The risk of a distant recurrence was also significantly reduced by MFT and CMFT therapy ($P = .02$ for both treatment regimens). There was no significant reduction in the risk of contralateral breast cancer, second primary tumors, or deaths from causes other than breast cancer after treatment with either MFT or CMFT.

Rates and Relative Risks of Events Comprising Disease-Free Survival According to Tumor Size, ER Status, and PgR Status (Table 4 and Fig. 3)

When compared with TAM, both MFT and CMFT reduced the rates and the risks of the occurrence of events related to

Table 3. Sites and rates of first events according to treatment*

	TAM (771 Pts.)		MFT (767 Pts.)		CMFT (768 Pts.)	
Type of event	No. of events	Rate†	No. of events	Rate†	No. of events	Rate†
Local–regional recurrence	40	0.97	28	0.66	6	0.14§
Ipsilateral breast‡	16	0.88	9	0.48	4	0.22§
Other sites	24	0.58	19	0.45	2	0.05§
Distant recurrence	60	1.45	37	0.87§	38	0.89§
Contralateral breast cancer	12	0.29	10	0.24	8	0.19
Other second primary cancer	25	0.60	27	0.64	30	0.71
Deaths prior to recurrence or second primary cancer	3	0.07	2	0.05	10	0.24
Total events	140	3.39	104	2.45§	93	2.19§

*TAM = tamoxifen alone; MFT = methotrexate, fluorouracil, and tamoxifen; CMFT = cyclophosphamide, methotrexate, fluorouracil, and tamoxifen; Pts. = patients.

†Per 100 patients per year.

‡No. of patients treated with lumpectomy according to adjuvant therapy group as follows: TAM group, 346; MFT group, 345; CMFT group, 338.

§Difference between rate of MFT or CMFT compared with rate of TAM is significant (two-sided $P<.025$).

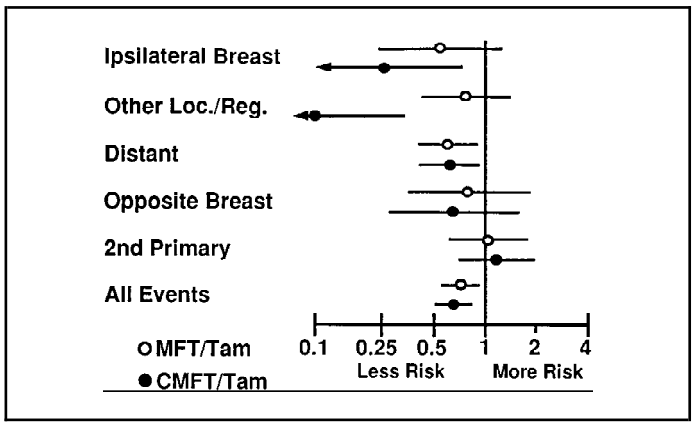

Fig. 2. Benefit from MFT (methotrexate, fluorouracil, and tamoxifen) or CMFT (cyclophosphamide, methotrexate, fluorouracil, and tamoxifen) relative to tamoxifen alone (Tam). Relative risks (open and closed circles) and 95% confidence intervals (horizontal lines) for sites of first events. Loc./Reg. = local–regional.

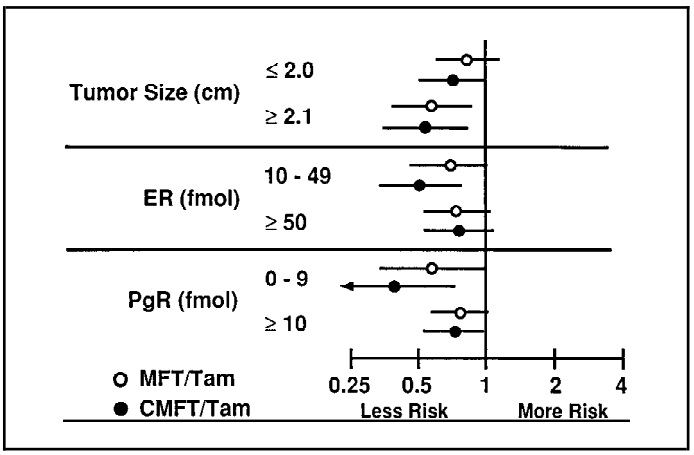

Fig. 3. Relative risks (open and closed circles) and 95% confidence intervals (horizontal lines) of occurrence of events related to disease-free survival according to tumor size, estrogen receptor (ER) status, and progesterone receptor (PgR) status. MFT = methotrexate, fluorouracil, and tamoxifen; CMFT = cyclophosphamide, methotrexate, fluorouracil, and tamoxifen; Tam = tamoxifen alone. Tumor ER and PgR contents are given as fmol/mg cytosol protein.

disease-free survival in patients with tumors less than or equal to 2.0 cm or greater than or equal to 2.1 cm in size. A similar benefit from MFT and CMFT was observed when patients were examined according to both the ER content (10–49 or ⩾50 fmol/mg cytosol protein) and the PgR content (0–9 or ⩾10 fmol/mg cytosol protein) of their tumors. A statistical test for interaction between these covariates and treatment did not indicate the presence of significant variation in the response to chemotherapy among the subgroups.

Rates and Relative Risks of Events Related to Disease-Free Survival, Distant Disease-Free Survival, and Death According to Age (Table 4 and Fig. 4)

When outcome was evaluated according to patient age at diagnosis, both chemotherapy regimens reduced the rates and the risks of the occurrence of events related to disease-free survival. In patients aged 49 years or less, the risk that occurred after treatment with TAM was reduced by 46% after MFT therapy and by 44% after CMFT therapy (RR = 0.54 [95% CI = 0.36–0.80] and RR = 0.56 [95% CI = 0.38–0.83], respectively). The findings relative to the risk of distant disease in patients 49 years of age or less were essentially the same as those observed relative to disease-free survival. There was a 50% reduction in the risk of distant disease following MFT therapy and a 42% reduction after CMFT therapy (RR = 0.50 [95% CI = 0.31–0.80] and RR = 0.59 [95% CI = 0.38–0.91], respectively). There was a 50% reduction in mortality following MFT therapy and a 28% reduction following CMFT therapy (RR = 0.50 [95% CI = 0.25–0.96] and RR = 0.72 [95% CI = 0.40–1.24], respectively).

In patients aged 50 years or more, the extent of the advantage from MFT or CMFT over TAM was not as great as that observed in the younger group. A 10% reduction in the risk of events related to disease-free survival occurred after MFT therapy (RR

Table 4. Disease-free survival event rates according to selected prognostic characteristics*

	TAM			MFT			CMFT		
Characteristic	No. of Pts.	No. of events	Rate†	No. of Pts.	No. of events	Rate†	No. of Pts.	No. of events	Rate†
Treatment	771	140	3.39	767	104	2.45	768	93	2.19
Clinical tumor size, cm									
⩽2.0	536	81	2.75	521	66	2.28	538	60	1.99
⩾2.1	235	59	4.96	246	38	2.83	230	33	2.69
ER level, fmol‡									
10–49	340	63	3.42	342	45	2.38	345	34	1.75
⩾50	431	77	3.36	425	59	2.51	423	59	2.57
PgR level, fmol‡									
0–9	137	35	4.96	131	21	2.88	142	16	2.01
⩾10	634	105	3.06	636	83	2.36	626	77	2.23
Age, y									
⩽49	345	67	3.73	343	38	2.01	354	40	2.07
⩾50	426	73	3.12	424	66	2.80	414	53	2.29

*TAM = tamoxifen alone; MFT = methotrexate, fluorouracil, and tamoxifen; CMFT = cyclophosphamide, methotrexate, fluorouracil, and tamoxifen; Pts. = patients; ER = estrogen receptor; PgR = progesterone receptor.

†Per 100 patients per year.

‡Per mg cytosol protein.

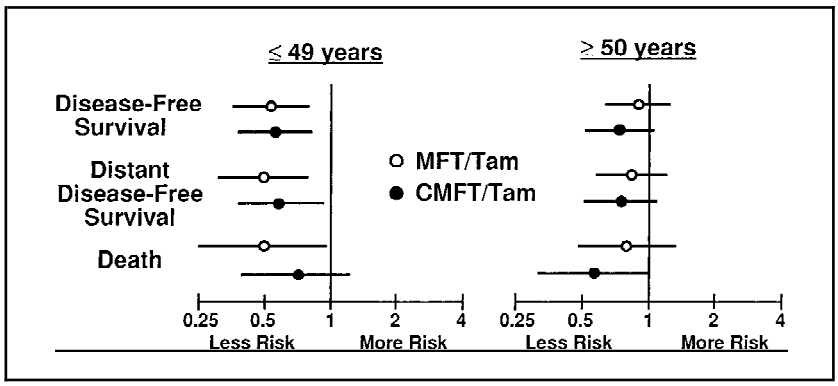

Fig. 4. Relative risks (open and closed circles) and 95% confidence intervals (horizontal lines) of occurrence of events related to disease-free survival, distant disease-free survival, and death according to patient age. MFT = methotrexate, fluorouracil, and tamoxifen; CMFT = cyclophosphamide, methotrexate, fluorouracil, and tamoxifen; Tam = tamoxifen alone.

= 0.90; 95% CI = 0.64–1.25) and a 26% reduction was observed following treatment with CMFT (RR = 0.74; 95% CI = 0.52–1.05) (Fig. 4). The risk of a distant treatment failure was reduced by 16% following MFT therapy (RR = 0.84; 95% CI = 0.58–1.20) and by 25% after CMFT therapy (RR = 0.75; 95% CI = 0.51–1.09). There was a 20% reduction in the risk of death following MFT (RR = 0.80; 95% CI = 0.48–1.32) and a 43% reduction after CMFT therapy (RR = 0.57; 95% CI = 0.32–1.00).

Dose Reductions and Toxicity

An assessment of the amount of protocol-stipulated dose received revealed that, among 1575 women randomly assigned to receive chemotherapy, nine patients (0.6%) (three in the MFT group and six in the CMFT group) did not begin treatment; 33 patients (2.1%) did not have adequate information for analysis on course-specific drug compliance. The proportion of the protocol-prescribed dose received was calculated for the remaining 1533 patients. Ninety percent of the patients randomly assigned to receive MFT and 85% of those randomly assigned to receive CMFT were given at least some portion of all six courses of the regimens. During the six-course regimen, 42% of the patients on MFT and 73% of the patients on CMFT received at least one reduction in their chemotherapy dose. More patients in the MFT group (80%) received more than 85% of the protocol-specified dose than did those in the CMFT group (59%). Dose reductions were similar among younger and older patients.

Toxicity information was reported for 2326 (98.4%) of the 2363 randomly assigned patients (Table 5). Of 471 patients who discontinued protocol therapy (including those who discontinued tamoxifen at some time within 5 years), 56% did so because of drug toxicity. Severe toxicity (i.e., toxicity of grade 3 or higher) was more frequent among patients treated with CMFT than among those treated with MFT. Severe leukopenia and more pronounced or complete alopecia occurred after CMFT therapy. Patients were considered to have developed a septic episode if they were granulocytopenic, developed a fever of 38.5 °C or higher and/or a systemic infection, and required hospitalization. Septic episodes were reported for 25 patients as follows: one in the TAM-treated group, six in the MFT-treated group, and 18 in the CMFT-treated group. Thromboembolic events were more often observed when chemotherapy was given in conjunction with tamoxifen than when tamoxifen was administered alone. Whereas in the TAM-treated group there were 16 events (1.8%), one of which was an embolism, and no deaths, in the MFT group there were 50 events (6.5%), eight of which were emboli, and two deaths. In the CMFT-treated group, there were 57 events (7.0%), nine of which were emboli, and no deaths. Among patients receiving MFT, three of the eight embolic events occurred in women during chemotherapy (one each during the fourth, fifth, and sixth courses). One event occurred shortly after a patient withdrew from the study subsequent to completion of one course of therapy, and events occurred in four patients after completion of therapy (at 12, 27, 48, and 57 months after entry into the study). Among the nine CMFT-treated patients who developed emboli, five events occurred during chemotherapy (two following two, one after three, and two after four courses), one followed shortly after the patient had completed the sixth course, and three were diagnosed in patients at 7, 12, and 48 months after study entry. An embolus occurred in one TAM-treated patient 36 months after she had entered the study.

Second Primary Cancers

The addition of chemotherapy to tamoxifen did not significantly alter the incidence of second primary cancers occurring as first events. These cancers were similarly distributed among the three groups (Table 6). The incidence of all second primary cancers except those in the opposite breast was 25 (3.2%) in the TAM-treated group, 27 (3.5%) in the MFT-treated group, and 30 (3.9%) in the CMFT-treated group.

Discussion

Although findings from NSABP B-14, first reported in 1989, indicated that, after 4 years of follow-up, there was a significant overall benefit from the use of tamoxifen in the treatment of patients with node-negative breast cancer who had ER-positive tumors, it was evident that the degree of benefit achieved was not sufficient to eliminate the need to evaluate potentially more effective therapies *(3).* One of every five women who received tamoxifen in the B-14 study demonstrated a treatment failure during the first 4 years of follow-up, and it was considered likely that the incidence of treatment failure would increase with more prolonged follow-up time. Such has, indeed, been the case. In a recent report *(4),* it was noted that nearly one third of the tamoxifen-treated patients experienced a treatment failure by 10 years and that one fourth had distant metastatic disease. Thus, the need for evaluating the use of additional therapy with tamoxifen in this group of patients, who were previously regarded as having a ''good'' prognosis, was confirmed.

When we concluded that there was justification for comparing tamoxifen with tamoxifen plus chemotherapy, the type of chemotherapy to be used became an issue. When B-20 was being designed, early information from the NSABP B-13 trial indicated that MF followed by leucovorin resulted in a benefit when patients with negative nodes and ER-negative tumors were

Table 5. Overall toxicity distribution and most common toxic effects*

Events	TAM (769 Pts.)†		MFT (779 Pts.)		CMFT (778 Pts.)	
	No. of Pts.	%	No. of Pts.	%	No. of Pts.	%
Overall toxicity‡						
None		53		9		3
Grade 1		26		30		15
Grade 2		17		44		57
Grade 3		3		12		20
Grade 4		1		5		5
Death		0		0.3		0.1
WBC count (per μL) (day 1 of each course)						
Grade 3 (1000–1999)	0	0.0	4	0.5	67	8.6
Grade 4 (<1000)	0	0.0	0	0.0	2	0.3
Infection						
Severe	3	0.4	5	0.6	16	2.1
Life-threatening	0	0.0	0	0.0	1	0.1
Septic episode	1	0.1	6	0.8	18	2.3
Nausea						
Decreased dietary intake (grade 2)	25	3.3	188	24.1	249	32.0
No dietary intake (grade 3)	3	0.4	22	2.8	25	3.2
Vomiting						
6–10 every 24 h	2	0.3	15	1.9	15	1.9
>10 every 24 h	0	0.0	7	0.9	3	0.4
Diarrhea						
7–9 episodes every 24 h	0	0.0	37	4.7	19	2.4
>10 episodes every 24 h; bloody, requiring parenteral support	1	0.1	12	1.5	2	0.3
Stomatitis						
Unable to eat	0	0.0	9	1.2	8	1.0
Requiring parenteral support	0	0.0	0	0.0	1	0.1
Alopecia						
Mild	28	3.6	121	15.5	190	24.4
Pronounced	2	0.3	17	2.2	193	24.8
Complete	1	0.1	3	0.4	84	10.8
Phlebitis–thromboembolism						
Superficial	7	0.9	18	2.3	23	3.0
Deep vein, not requiring hospitalization	3	0.4	4	0.5	2	0.3
Deep vein, requiring hospitalization	5	0.7	20	2.6	23	3.0
Embolism, nonfatal	1	0.1	8	0.8	9	1.2
Embolism, fatal	0	0.0	2	0.3	0	0.0

*TAM = tamoxifen alone; MFT = methotrexate, fluorouracil, and tamoxifen; CMFT = cyclophosphamide, methotrexate, fluorouracil, and tamoxifen; Pts. = patients; WBC = white blood cell.

†All patients with reported toxicity data are included here, regardless of their inclusion in the analyses.

‡Excludes alopecia and weight gain or loss. Septic episode (febrile neutropenia) is classified as grade 4.

evaluated overall as well as according to age, i.e., 49 years or less and 50 years or more. Other investigators *(5–7)* had also demonstrated a benefit from CMF in patients with negative nodes and ER-negative tumors. Consequently, it seemed important that the two regimens be compared so as to settle the issue of which regimen was better and to provide information relative to the need for including an alkylating agent in the combination of drugs to be administered. The NSABP B-19 study, also in patients with negative nodes and ER-negative tumors, was designed and implemented for that purpose. Because the B-20 trial had been conducted concurrently with B-19, no information was available regarding the relative merits of the two regimens. Consequently, we decided to implement a trial to compare the two chemotherapy regimens used in conjunction with tamoxifen. By evaluating the two regimens in patients with negative nodes and either ER-negative (B-19) or ER-positive (B-20) tumors, it was considered that, should a benefit from the use of one or the other regimen be demonstrated in both patient groups, it would then be possible to use the same treatment for all patients with negative nodes regardless of the ER status of their tumors.

The current findings indicate that, just as was previously demonstrated for patients with ER-negative tumors, both MF and CMF are effective in the treatment of patients with negative nodes and ER-positive tumors. When administered in conjunction with tamoxifen, each regimen has resulted in significantly better disease-free survival, distant disease-free survival, and survival outcomes than were achieved from the administration of tamoxifen alone. The 30%–40% reduction in the risk related to disease-free survival, distant disease-free survival, and mortality following the administration of MFT or CMFT and the sizable reductions in risks of all events related to breast cancer, i.e., ipsilateral breast tumor recurrence following lumpectomy and other local–regional disease, regardless of the chemotherapy regimen employed, attest to the benefit achieved from the use of chemotherapy. The remarkably low incidence of ipsilateral breast tumor recurrence that occurred in all groups of patients

Table 6. Second primary cancers occurring as first events*

Cancer site	TAM (771 Pts.)		MFT (767 Pts.)		CMFT (768 Pts.)		Total (2306 Pts.)	
	No. of cancers	%	No. of cancers	%	No. of cancers	%	No. of cancers	%
Gastrointestinal	5	0.6	4	0.5	5	0.7	14	0.6
Colon, rectum	3		2		4		9	
Other	2		2		1		5	
Genital tract	11	1.4	11	1.4	12	1.6	34	1.5
Endometrium	7	0.9	6	0.8	11	1.4	24	1.0
Ovary, cervix, vulva	4		5		1		9	
Opposite breast	12	1.6	10	1.3	8	1.0	30	1.3
Respiratory	3		2		1		6	
Lymphoid, myeloid, myeloproliferative	3		3		4		10	
Skin, connective tissue	0		5		5		10	
Miscellaneous sites	3		2		3		8	
All second primary cancers†	25	3.2	27	3.5	30	3.9	82	3.6

*TAM = tamoxifen alone; MFT = methotrexate, flurouracil, and tamoxifen; CMFT = cyclophosphamide, methotrexate, fluorouracil, and tamoxifen; Pts. = patients.

†Except opposite breast cancer.

following lumpectomy (4.6% in the TAM group, 2.6% in the MFT group, and 1.2% in the CMFT group) indicates that fear of such an event is no longer a reason for performing a mastectomy instead of a lumpectomy. These findings also support the contention by one of us (B. Fisher) that the surgical treatment of breast cancer should not be considered independent of the effect of systemic adjuvant therapy, since such therapy justifies the use of less extensive surgery.

Several issues have arisen from our previous reports of findings noting therapeutic benefits in patients with negative nodes. One of these issues relates to whether cohorts of patients could be identified who did not benefit from therapies that had demonstrated an overall advantage. After a benefit from tamoxifen had been demonstrated in patients with negative nodes and ER-positive tumors, the question arose as to whether that drug should be administered to all such patients. Statistical analyses carried out in search of inconsistencies in treatment effect among patients failed to identify any cohort that did not benefit from tamoxifen therapy *(12).* Similarly, when a benefit from MF therapy for patients with negative nodes and ER-negative tumors was identified, the test for interactions between the stratifying variables and the treatment failed to indicate that the effect of MF was absent in any subgroup of patients *(12).* Thus, it was not possible to define a particular cohort of patients who should not be treated with MF. Similar findings were obtained relative to the use of CMF for the treatment of patients with ER-negative tumors.

Even though the findings from B-20 indicate an overall benefit from chemotherapy, the question arises as to whether there are subgroups of patients who do not benefit from MFT or CMFT and for whom such therapy would be considered inappropriate. The data presented in this article indicate a benefit from both MFT and CMFT, regardless of the level of tumor ER positivity or of whether the tumors were PgR negative or positive. This benefit was also achieved regardless of tumor size. Although there was a reduction in the relative risk of events related to disease-free survival, distant disease-free survival, and death in patients 49 years of age or less as well as in those aged 50 years or more, there was a quantitative difference between the age groups relative to those outcomes; i.e., the extent of the benefit in the younger women was greater than that observed in the older age group. Longer follow-up time and an increased number of events will permit, with more certainty, estimation of the magnitude of the benefit from chemotherapy and tamoxifen among patients 50 years of age or more.

Because no evidence has been obtained from B-20 to indicate that a difference in drug compliance is responsible for the apparent quantitative age-related difference that has been observed, an explanation for this finding is only speculative. Recently, the International Breast Cancer Study Group *(13)* reported that postmenopausal patients with node-positive breast cancer treated with tamoxifen and chemotherapy had a better outcome than did patients who received tamoxifen alone. These findings are of particular relevance for several reasons. First, they support our previous findings *(14)* demonstrating the worth of chemotherapy and tamoxifen for patients with positive nodes and ER-positive tumors who were 50 years of age or more. Second, the International Breast Cancer Study Group noted that the magnitude of the effect was smaller for patients whose tumors contained high levels of ER. They speculated that the benefit from adding chemotherapy to tamoxifen in such patients might not be great enough to justify doing so. However, examination in the B-20 study of the risk of events related to disease-free survival for patients aged 50 years or more indicated that such a risk was similar regardless of whether tumor ER levels were 10–49 or 50 or more fmol/mg cytosol protein (data not shown). With the addition of chemotherapy, moderate reductions in events were seen for all patients with ER levels of 50 fmol or more, regardless of their age (Fig. 3).

The findings from B-20 fill a major gap in information regarding the use of systemic therapy for the treatment of primary breast cancer. It took nearly 20 years to determine that patients with breast cancer who were 49 years of age or less and 50 years of age or more who had positive axillary nodes and either ER-positive or ER-negative tumors benefited from the use of systemic chemotherapy, with or without tamoxifen. In less than a

decade, it has been demonstrated that chemotherapy benefits younger as well as older patients with negative nodes and ER-negative tumors, and now it has been shown that patients from either age group who have ER-positive tumors benefit from chemotherapy and tamoxifen. These findings give rise to several changes in thinking regarding the management of primary breast cancer. For the first time, a unified approach to the use of systemic adjuvant chemotherapy for the treatment of patients with stages 1 and 2 primary breast cancer could be justified, since some benefit was demonstrated in all patient cohorts in B-20, regardless of their age or the receptor content of their tumors. Although the value of MF and CMF has been demonstrated in previous NSABP studies, it is likely that other regimens that have shown a benefit when used to treat patients with positive nodes are likely to be appropriate for the treatment of patients with negative nodes as well. Because, for example, studies conducted by the NSABP and other investigators have demonstrated the worth of doxorubicin (Adriamycin; A) and cyclophosphamide (C) therapy (AC) for the treatment of patients with positive nodes, regardless of their age or tumor ER content, it is not unreasonable to consider the use of that regimen in patients with negative nodes as well. An NSABP protocol in progress (B-23), which compares AC with CMF and either regimen with or without tamoxifen in the treatment of patients with negative nodes and ER-negative tumors, should provide further information to either support or refute that thesis, as will an ongoing Cancer and Leukemia Group B intergroup study.

The current findings have several implications. One relates to the use of axillary lymph node dissection for the surgical management of primary breast cancer. By eliminating the need to know axillary nodal status in order to make decisions regarding the use of systemic therapy, the importance of that procedure is diminished. Because tumor characteristics, such as size, S-phase fraction, and nuclear grade, are also predictors of patient outcome and because there is no firm evidence to indicate that axillary dissection results in improved patient outcome *(15)*, a rationale for its universal use is, at present, becoming increasingly more tenuous. Another implication of the findings relates to the use of preoperative therapy. One of the concerns about the use of such therapy is that patients with pathologically negative nodes may needlessly receive the same regimens reserved for patients with positive nodes. The findings from B-20, which demonstrate a benefit from chemotherapy in all patient cohorts, diminish that concern. However, should there still be a question regarding the propriety of using chemotherapy in addition to tamoxifen in certain cohorts of patients (e.g., women aged 50 years or more whose tumors are ER positive), other considerations, such as tumor size (i.e., large tumors with cells having a high S-phase fraction and/or poor nuclear grade), may provide justification for the administration of chemotherapy. These findings remove rigid barriers in thinking regarding differences in the management of patients with negative nodes and patients with positive nodes.

The findings demonstrating a benefit from MFT and CMFT evoke consideration regarding decision making relative to which regimen should be used when there are no significant differences in outcome parameters resulting from their administration. Such a situation was encountered in the NSABP B-19 trial. Although findings from that study clearly demonstrated an advantage from CMF over MF with regard to disease-free survival and survival in patients aged 49 years or less, it was less clear which regimen was most effective in women aged 50 years or more. At that time it was considered that differences in the toxic effects encountered might be of significance in deciding which regimen to use. The same situation prevails with regard to the findings from B-20, where a concordance in outcome between the regimens is demonstrated in certain patient cohorts. Of particular interest is the remarkable similarity in findings from the 1089 MF- and CMF-treated patients with toxicity data in the B-19 study and the 1557 MFT- and CMFT-treated patients in the B-20 trial *(4)*. Aside from the somewhat increased frequency of serious toxic effects, such as grade 3 leukopenia, septic episodes, infection, and alopecia in the CMFT group, other toxic effects were similar in the two groups. Although the incidence of thromboembolic events was similar in the MFT- and CMFT-treated groups in the B-20 trial, the incidence in both was greater than that encountered when tamoxifen was administered without chemotherapy. In our previous reports on the B-14 study *(3,8)*, we and other investigators noted that thromboembolic events were more frequent in tamoxifen-treated patients than in women who received placebo; this was particularly evident in women aged 50 years or more. The approximately threefold increase in such events observed in women who received chemotherapy plus tamoxifen in B-20 is in keeping with similar findings observed by others *(16,17)*. Of particular interest was our finding that a pulmonary embolism occurred during or shortly after chemotherapy in 10 of the 17 patients in the MFT- and CMFT-treated groups, in one patient who withdrew from the study after the first course of therapy, and in six women a relatively long time after they had completed therapy (12–57 months after study entry). There was a slightly greater incidence of diarrhea during MFT than during CMFT therapy. Thus, it is difficult to define which of the chemotherapy regimens is preferable on the basis of findings related to drug compliance and toxicity alone. As we noted in a previous study *(4)*, although there is little information on which to base a conclusion, the somewhat lower incidence of severe toxicity following MFT therapy may make its use appropriate for patients with comorbid conditions.

Because, in the B-20 trial, statistical analyses failed to identify a subgroup of patients with negative nodes and ER-positive tumors who failed to benefit from either MFT or CMFT therapy, two questions arise: 1) Should *all* patients with negative nodes and ER-positive tumors be treated with tamoxifen plus chemotherapy? and 2) Is the benefit received adequate to justify such treatment? The first question requires a measured response. Because only 20% of the patients enrolled in B-20 had tumors 1 cm or less in size and because the number of events that occurred in these patients were relatively few, it remains unclear whether the use of tamoxifen in conjunction with chemotherapy is appropriate at this time in such patients. Additional follow-up time and further studies will be required to clarify this issue. As has previously been pointed out *(2,3)*, the answer to the second question depends on individual value judgments on the part of physicians and their patients. There are no absolute criteria for deciding the magnitude of the benefit received from a therapy before it can be judged appropriate for general use. Finally, when considered in conjunction with findings noted in other NSABP studies, the results from B-20 permit us to conclude that

patients who meet NSABP protocol criteria, regardless of their age, nodal status, or tumor ER status, should be candidates for chemotherapy.

Appendix Table 1. Institutions contributing more than 15 patients to National Surgical Adjuvant Breast and Bowel Project B-20*

Institution	Investigator
Baptist Regional Cancer Institute, Jacksonville, FL	Neil Abramson
Baystate Medical Center, Springfield, MA	Donald J. Higby
Boston Medical Center, Boston, MA	Maureen T. Kavanah
CCOP, Allegheny, Pittsburgh, PA	Reginald Pugh
CCOP, Alton Ochsner Medical Foundation, New Orleans, LA	Carl G. Kardinal
CCOP, Central Illinois, Springfield, IL	James L. Wade III
CCOP, Columbia River Oncology Program, Portland, OR	Keith S. Lanier
CCOP, Marshfield Clinic, Marshfield, WI	James L. Hoehn
CCOP, Mt. Sinai Medical Center, Miami Beach, FL	Enrique Davila
CCOP, Southeast Cancer Control Consortium, Winston-Salem, NC	James N. Atkins
CCOP, Spartanburg, SC	James D. Bearden III
Credit Valley Hospital, Mississauga, ON, Canada	Leonard Kaizer
Cross Cancer Institute, Edmonton, AB, Canada	Alan W. Lees
Dana-Farber Cancer Institute, Boston, MA	Charles Shapiro
Hartford Hospital, Hartford, CT	Patricia A. DeFusco
Jewish General Hospital, Montreal, PQ, Canada	Richard G. Margolese
Kaiser Permanente, Portland, OR (CGOP)	Andrew G. Glass
Lehigh Valley Hospital and Health Network, Allentown, PA	David Prager
Manitoba Cancer Foundation, Manitoba, MB, Canada (CGOP)	David M. Bowman
Michigan State University, East Lansing, MI	Nikolay V. Dimitrov
Montreal General Hospital, Montreal, PQ, Canada	Michael P. Thirlwell
Mt. Sinai Medical Center, Cleveland, OH	Terry Mamounas
N.E. Ontario Regional Cancer Center, Sudbury, ON, Canada	Stephen Gluck
Pennsylvania Hospital, Philadelphia, PA	Harvey J. Lerner
Rockford Clinic, Rockford, IL	William R. Edwards
Royal Victoria Hospital, Montreal, PQ, Canada	Henry Shibata
Rush Presbyterian–St. Luke's Medical Center, Chicago, IL	Janet Wolter
St. Mary's Hospital Center, Montreal, PQ, Canada	Donna Stern
St. Sacrement Hospital, Quebec, PQ, Canada	Luc Deschenes
Tom Baker Cancer Centre, Calgary, AB, Canada	Alexander H. G. Paterson
University of California, Davis, CA	Frederick J. Meyers
University of Cincinnati, Cincinnati, OH	David Hyams
University of Hawaii, Honolulu, HI	Robert Oishi
University of Kentucky, Lexington, KY	Edward H. Romond
University of Louisville, Louisville, KY	John T. Hamm
University of Montreal Hospital Group, Montreal, PQ, Canada	Andre Robidoux
University of Pittsburgh, Pittsburgh, PA	Victor Gerald Vogel III

*CCOP = Community Clinical Oncology Program; CGOP = Cooperative Group Outreach Program.

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Notes

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