Adjuvant Chemotherapy in Older and Younger Women With Lymph Node–Positive Breast Cancer

Hyman B. Muss, MD
Susan Woolf, BS
Donald Berry, PhD
Constance Cirrincione, MS
Raymond B. Weiss, MD
Daniel Budman, MD
William C. Wood, MD
I. Craig Henderson, MD
Clifford Hudis, MD
Eric Winer, MD
Harvey Cohen, MD
Judith Wheeler, BA, MPH
Larry Norton, MD
for the Cancer and Leukemia Group B

Context Adjuvant chemotherapy improves survival for patients with local-regional breast cancer, but healthy older patients at high risk of recurrence are frequently not offered adjuvant chemotherapy, and the benefit of adjuvant chemotherapy in older patients is uncertain.

Objective To compare the benefits and toxic effects of adjuvant chemotherapy among breast cancer patients in age groups of 50 years or younger, 51 to 64 years, and 65 years or older.

Design and Setting Retrospective review of data from 4 randomized trials that accrued patients from academic and community medical centers between 1975 and 1999. Median follow-up for all patients was 9.6 years. All trials randomized patients to different regimens, doses, schedules, and durations of chemotherapy and all had a treatment arm with doses or schedules that were regarded to be "high" and potentially more toxic.

Patients A total of 6487 women with lymph node–positive breast cancer; 542 (8%) patients were 65 years or older and 159 (2%) were 70 years or older.

Main Outcome Measure Comparison of disease-free survival, overall survival, and treatment-related mortality among different age groups.

Results Multivariate analysis showed that smaller tumor size, fewer positive lymph nodes, more chemotherapy, and tamoxifen use were all significantly ($P<.001$) related to longer disease-free and overall survival. There was no association between age and disease-free survival. Overall survival was significantly ($P<.001$) worse for patients aged 65 or older because of death from causes other than breast cancer. Thirty-three deaths (0.5% of all patients) were attributed to treatment, and older women had higher treatment-related mortality. Older women and younger women derived similar reductions in breast cancer mortality and recurrence from regimens containing more chemotherapy.

Conclusion Age alone should not be a contraindication to the use of optimal chemotherapy regimens in older women who are in good general health.

JAMA. 2005;293:1073-1081 www.jama.com

THE INCIDENCE OF BREAST CANcer increases with increasing age, and almost half of all new breast cancers in the United States now occur in women 65 years of age or older.[1] Systemic adjuvant chemotherapy in women with early-stage breast cancer significantly improves both relapse-free and overall survival for women aged 50 to 69 years old, but data are lacking for women aged 70 years or older.[2] Nevertheless, available data suggest that systemic adjuvant chemotherapy may be significantly underused in older patients,[3] even though for many patients in this setting, chemotherapy may improve survival. Moreover, even when chemo-

For editorial comment see p 1118.

Author Affiliations: Vermont Cancer Center, Burlington (Dr Muss); Cancer and Leukemia Group B Statistical Center (Mss Woolf, Cirrincione, and Wheeler) and Duke University and Veterans Administration Medical Centers (Dr Cohen), Durham, NC; M. D. Anderson Cancer Center, Houston, Tex (Dr Berry); Georgetown University Medical Center, Washington, DC (Dr Weiss); North Shore University Hospital–New York University, Manhasset, NY (Dr Budman); Massachusetts General Hospital (Dr Wood) and Dana Farber Cancer Institute (Dr Winer), Boston; Emory University School of Medicine, Atlanta, Ga (Dr Wood); University of California, San Francisco (Dr Henderson); and Memorial Sloan-Kettering Cancer Center, New York, NY (Drs Hudis and Norton).
Cancer and Leukemia Group B Investigators are listed at the end of this article.
Corresponding Author: Hyman B. Muss, MD, Fletcher Allen Health Care, Vermont Cancer Center, UHC Campus, St Joseph 3400, 1 S Prospect St, Burlington, VT 05401 (hyman.muss@uvm.edu).

Table 1. Trial Characteristics

Characteristics	Years Open to Accrual				Total
	CALGB 7581 (1975-1981)	CALGB 8082* (1980-1984)	CALGB 8541 (1985-1991)	CALGB 9344 (1994-1999)	
Regimens					
More chemotherapy	CMF+VP	CMF+VP; VATH	High-dose CAF	AC+T	
Less chemotherapy	CMF+MER	CMF+VP	Mid-/low-dose CAF	AC	
Follow-up, median (range), y	23.5 (0-27.9)	19.0 (2.5-22.5)	14.0 (1.8-18.2)	6.0 (0.23-8.9)	9.6 (0.23-27.9)
Total No. accrued	906	945	1572	3170	6593
Total No. treated	884	933	1549	3121	6487
Age at enrollment, y, No. (%)					
≤50	405 (46)	411 (44)	806 (52)	1884 (60)	3506 (54)
51-64	394 (44)	394 (42)	595 (38)	1056 (34)	2439 (38)
≥65	85 (10)	128 (14)	148 (10)	181 (6)	542 (8)

Abbreviations: AC, doxorubicin and cyclophosphamide; AC+T, doxorubicin and cyclophosphamide followed by paclitaxel; CAF, cyclophosphamide, doxorubicin, and fluorouracil; CALGB, Cancer and Leukemia Group B; CMF, cyclophosphamide, methotrexate, and fluorouracil; CMF+VP, CMF plus vincristine and prednisone; CMF+MER, CMF plus the methanol extraction residue of bacillus Calmette-Guérin; VATH, vinblastine, doxorubicin, thiotepa, and fluoxymesterone (Halotestin).
*Excluding patients aged 70 years or older.

therapy is administered to older patients, inappropriate dose reductions are frequently made that may decrease effectiveness.[4]

The potential for increased chemotherapy-related toxic effects in older patients leads to important concerns. For instance, renal function and marrow reserve decrease with age and can increase the risk of toxic effects from treatment regimens that include myelosuppressive agents or agents such as methotrexate that are renally excreted.[5] Dose modification using creatinine clearance values can minimize toxic effects.[6] Also, data from small trials and retrospective analyses of larger trials suggest that older women in good health tolerate chemotherapy, including anthracycline-based regimens, with toxic effects profiles similar to those of younger patients.[7-10]

Recently, randomized clinical trials of combination chemotherapy regimens in the adjuvant setting have shown that dose-intensive chemotherapy regimens and regimens incorporating newer antineoplastics, such as taxanes, are associated with significant improvements in both relapse-free and overall survival when compared with older, more established treatments. These more effective regimens have often included anthracyclines and include trials comparing anthracyclines with nonanthracycline regimens,[11] larger vs smaller doses of anthracyclines,[12] anthracyclines with vs without the inclusion of taxanes,[13] and dose-dense regimens that give the same doses of chemotherapy in a shorter time.[14] The benefits and risks of these more toxic regimens have not been adequately explored in older patients because older patients have been underrepresented in clinical trials.[15,16] To determine how older patients fared with more aggressive systemic adjuvant chemotherapy regimens, the Cancer and Leukemia Group B (CALGB) retrospectively reviewed 4 randomized clinical trials of treatments for lymph node–positive breast cancer that accrued patients from 1975 to 1999. These trials compared more aggressive with less aggressive chemotherapy regimens.

METHODS

Patient Selection

Data were obtained from 4 CALGB randomized trials designed for patients with node-positive breast cancer. All trials compared at least 2 chemotherapy regimens that differed by dose level, dose intensity, or regimen (TABLE 1). All trials required informed consent based on federal, state, and institutional guidelines. The CALGB 7581 trial randomly assigned patients to receive cyclophosphamide, methotrexate, and fluorouracil (CMF), CMF plus vincristine and prednisone (CMF+VP), or CMF plus the methanol extraction residue of bacillus Calmette-Guérin (CMF+MER). Details concerning this trial have been previously published.[17] In a multivariate proportional hazards model, CMF+VP was significantly superior to the other 2 arms combined (CMF and CMF+MER) in improving disease-free survival ($P=.009$); overall survival was not significantly different among the groups. Endocrine therapy was not addressed in this trial and it is unlikely that any of these patients received adjuvant tamoxifen.

The CALGB 8082 trial was a randomized trial that compared CMF+VP or CMF+VP followed by a doxorubicin-based regimen: vinblastine, doxorubicin, thiotepa, and fluoxymesterone (Halotestin) (VATH). All patients were given a 6-week induction course of CMF+VP and then were randomly assigned to receive 1 of 2 CMF+VP consolidation regimens. One consisted of 6 months of conventional 2-week blocks of CMF+VP therapy separated by 2-week rest periods, and the second consisted of 2 additional 6-week blocks separated by 6-week rest periods. At the end of the first 8 months of CMF+VP therapy, patients were again randomly assigned to continue CMF+VP for 6 more months or to receive 6 cycles of escalating doses of VATH. The results of this trial have been previously published.[18] There was no statistical difference in disease-free survival between the 2 CMF+VP con-

solidations regimens. Compared with continuing CMF+VP, VATH intensification was associated with significantly improved disease-free survival ($P=.004$) and overall survival ($P=.04$). Endocrine therapy was not addressed in this trial but it is unlikely that any of these patients received adjuvant tamoxifen.

In the CALGB 8541 trial, patients were randomly assigned to receive 1 of 3 regimens of cyclophosphamide, doxorubicin, and fluorouracil (CAF) that differed in dose duration and dose intensity. The high-dose group received cyclophosphamide at 600 mg/m^2, doxorubicin at 60 mg/m^2, and fluorouracil at 600 mg/m^2, every 4 weeks for 4 cycles, with fluorouracil repeated on day 8 of each cycle. The moderate-dose group received 400 mg/m^2 of cyclophosphamide, 40 mg/m^2 of doxorubicin, and 400 mg/m^2 of fluorouracil in the same schedule as the high-dose group but for 6 cycles. The low-dose group received exactly half the doses of the high-dose group, on the same schedule. Details of this trial have been previously published.[19] Patients treated with moderate- or higher-dose intensity of CAF had significantly longer disease-free survival ($P<.001$) and overall survival ($P=.004$) compared with those treated with lower doses. There were no differences in disease-free survival or overall survival between the moderate- and high-dose groups, but a subsequent analysis showed that patients whose tumors were human epidermal growth factor receptor 2 (*ERBB2*; formerly HER-2 or HER-2/neu)–positive had significantly improved disease-free survival and overall survival when treated with the high-dose regimen compared with the moderate- and lower-dose regimens.[20] For patients who were *ERBB2*-negative, there were no differences in disease-free and overall survival among the 3 different treatment arms. In 1998, an addendum to the protocol required the addition of tamoxifen after CAF in patients who were perimenopausal or postmenopausal and who had estrogen receptor–positive tumors. Patients already participating in this study who met these criteria could be given tamoxifen at a time decided by their treating physician. All subsequent accruals, however, were required to begin tamoxifen therapy. Tamoxifen was given to 18% of patients aged 50 years or younger, 47% of patients aged 51 to 64 years, and 50% of patients aged 65 years or older.

The CALGB 9344 trial (Intergroup Trial 0148) used a 3×2 factorial design in which patients were randomly assigned first to 1 of 3 dose levels of doxorubicin (60, 75, or 90 mg/m^2) and a fixed dose of cyclophosphamide (600 mg/m^2). Both agents were administered every 3 weeks for 4 cycles (AC). Subsequently, all patients were randomly assigned to either receive or not receive paclitaxel (175 mg/m^2), given every 3 weeks for 4 cycles. Patients with estrogen receptor–positive tumors in this trial were required to take tamoxifen, 20 mg/d for 5 years. Details of this trial have been previously published.[13] There were no differences in outcome among patients randomized to the 3 different dose levels of doxorubicin. Patients randomized to paclitaxel, however, had significantly improved 5-year disease-free survival ($P=.002$) and 5-year overall survival ($P=.006$).

A total of 6593 patients were accrued to these trials. Of these, 6489 received protocol therapy; data for 2 patients were missing date of birth and therefore are not evaluable for age. The resulting sample of 6487 patients is the basis of the results reported herein.

Statistical Analysis

Disease-free survival was defined as the time from study entry until first recurrence of breast cancer or death due to breast cancer; therefore, a treatment failure refers to locoregional or distant recurrence or death from breast cancer. Patients who died of causes other than breast cancer and without recurrence were censored at their date of death, and patients still alive without recurrence were censored at the last date that they were known to be disease-free. Overall survival was defined as the time from study entry until death due to any cause. Surviving patients were censored at the last date they were known to be alive. Age refers to patient age at study enrollment.

Proportional hazards regressions with Wald χ^2 tests were used to multivariately model and assess the relationship between disease-free survival (or overall survival) and treatment (more or less chemotherapy), standard clinical variables (ie, age at study entry [≤50, 51-64, or ≥65 years], number of positive nodes, tumor size, estrogen receptor status [negative or positive], tamoxifen use [yes or no], and treatment study [CALGB 7581, 8082, 8541, or 9344]). We also assessed whether there was any differential benefit of chemotherapy by age (a chemotherapy-age interaction term). Time-to-event distributions were calculated using the Kaplan-Meier product-limit method. Proportions were compared using contingency table analysis; their 95% confidence intervals (CIs) used exact binomial methods. All *P* values are 2-sided and $P<.05$ was considered statistically significant. Analyses were carried out using SAS statistical software, version 8.02 (SAS Institute Inc, Cary, NC).

RESULTS

Trial and Patient Characteristics

Trial characteristics and age distribution of the study sample are presented in Table 1. The 4 trials spanned a 24-year period and included a total of 6593 patients initially accrued and 6487 patients comprising the study sample. Median follow-up time ranged from 6.0 years (CALGB 9344) to 23.5 years (CALGB 7581), with an overall median of 9.6 years. Patients aged 65 years or older comprised 8% (542 patients) of the study sample, and 2% (159 patients) were at least 70 years old.

Clinical characteristics by age are presented in TABLE 2. Tumor sizes were similar across the age groups; however, the proportions of patients with 10 or more positive lymph nodes at the time of entry were significantly differ-

ent. Twenty-five percent of patients aged 65 years or older had 10 or more positive nodes compared with 17% of patients aged 51 to 64 years and 11% of patients aged 50 years or younger. Estrogen receptor status was similar among age groups; progesterone receptor data were missing for 30% of patients, precluding meaningful comparisons among age groups. Tamoxifen data were missing for 28% of patients; at the time that CALGB 7581 and 8082 were accruing patients (1975-1984), tamoxifen was not considered standard therapy for patients with estrogen receptor– or progesterone receptor–positive tumors and no recommendations were made for its use in either of these trials, nor were data pertaining to tamoxifen use collected. In CALGB 8541, 97% of patients had estrogen receptor status recorded and estrogen receptor–positive patients included 61% of those aged 50 years or younger, 66% of those aged 51 to 64 years, and 62% of those aged 65 years or older. Tamoxifen use in these 3 age groups was 18%, 47%, and 50%, respectively, and these data were available for 99% of patients. In CALGB 9344, 98% of patients had estrogen receptor status recorded and estrogen receptor–positive patients included 57% of those aged 50 years or younger, 62% of those aged 51 to 64 years, and 62% of those aged 65 years or older. Tamoxifen use in these 3 age groups was 67%, 72%, and 71%, respectively.

Table 2. Clinical Characteristics by Patient Age*

Characteristics	Age, y ≤50 (n = 3506)	51-64 (n = 2439)	≥65 (n = 542)	Total (n = 6487)
Tumor size				
T1	1178 (34)	807 (33)	170 (31)	2155 (33)
T2	1846 (53)	1337 (55)	295 (54)	3478 (54)
T3	410 (12)	211 (9)	57 (11)	678 (10)
Missing	72 (2)	84 (3)	20 (4)	176 (3)
Positive nodes, No.				
1-3	1818 (52)	1091 (45)	207 (38)	3116 (48)
4-9	1276 (36)	908 (37)	194 (36)	2378 (37)
≥10	388 (11)	409 (17)	135 (25)	932 (14)
Missing	24 (1)	31 (1)	6 (1)	61 (1)
Estrogen receptor status				
Negative	1346 (38)	768 (31)	172 (32)	2286 (35)
Positive	1860 (53)	1387 (57)	312 (58)	3559 (55)
Missing	300 (9)	284 (12)	58 (11)	642 (10)
Progesterone receptor status†				
Negative	1095 (31)	751 (31)	159 (29)	2005 (31)
Positive	1532 (44)	868 (36)	166 (31)	2566 (40)
Missing	879 (25)	820 (34)	217 (40)	1916 (30)
Menopausal status				
Premenopausal	3055 (87)	297 (12)	0	3352 (52)
Postmenopausal	423 (12)	2109 (86)	542 (100)	3074 (47)
Missing	28 (1)	33 (1)	0	61 (1)
Tamoxifen use†				
No	1267 (36)	601 (25)	124 (23)	1992 (31)
Yes	1417 (40)	1047 (43)	203 (37)	2667 (41)
Missing	822 (23)	791 (32)	215 (40)	1828 (28)

*All data are expressed as No. (%).
†Available only for Cancer and Leukemia Group B 8541 and 9344 trials.

Table 3. Incidence and Causes of Treatment-Related Death

	Age, y ≤50 (n = 3506)	51-64 (n = 2439)	≥65 (n = 542)	Total (n = 6487)
Death due to treatment, No. (%) [95% CI]	8 (0.2) [0.1-0.5]	17 (0.7) [0.4-1.1]	8 (1.5) [0.6-2.9]	33 (0.5) [0.4-0.7]
Specific cause of death, No.				
Cardiac toxicity	4	2	1	7
Thromboembolism	1	3	2	6
AML/MDS	0	4	1	5
Infection	2	2	1	5
Other/unknown	1	6	3	10

Abbreviations: AML, acute myelogenous leukemia; CI, confidence interval; MDS; myelodysplastic syndrome.

Treatment-Related Mortality

TABLE 3 shows treatment-related mortality by age. The overall treatment-related mortality was 0.5% (95% CI, 0.4%-0.7%). There was a significant relationship between age and death due to protocol therapy. Older patients had higher chemotherapy-related mortality, and the incidence of treatment-related mortality increased linearly with increasing age: 0.2% (≤50 years), 0.7% (51-64 years), and 1.5% (≥65 years) ($P<.001$).

Disease-free and Overall Survival

TABLE 4 shows the multivariate proportional hazards regression model, which relates patient age and degree of chemotherapy to disease-free and overall survival after adjustment for standard clinical variables and treatment study. There was no interaction of chemotherapy and age for either disease-free survival or overall survival. The standard prognostic variables were statistically significant for both disease-free and overall survival. More positive nodes, larger tumor size, no tamoxifen use, and having an estrogen receptor–negative tumor were prognosticators of shortened disease-free and overall survival. There was a greater risk of treatment failure and shorter survival for patients entered in studies other than CALGB 9344.

Degree of chemotherapy significantly related to disease-free survival and overall survival ($P<.001$). The ob-

served reduction in hazard of failure of relapse was 22% for patients who received more chemotherapy vs those who received less chemotherapy (hazard ratio, 0.78; 95% CI, 0.72-0.85). Patient age did not relate to disease-free survival. FIGURE 1 shows the effects of chemotherapy on disease-free survival by age group. Regardless of age, those who received more chemotherapy consistently had longer disease-free survival. The reduction in hazard of failure attributed to more chemotherapy compared with less chemotherapy was 18% (95% CI, 9%-27%) for women aged 50 years or younger, 20% (95% CI, 8%-30%) for women aged 51 to 64 years, and 42% (95% CI, 22%-56%) for women aged 65 years or older (TABLE 5).

More chemotherapy, after adjustment for standard clinical variables, was related to significantly longer overall survival ($P<.001$). More chemotherapy was associated with a hazard of death that was 18% lower than that of less chemotherapy (Table 4). FIGURE 2 shows the concomitant relationship between degree of chemotherapy and patient age with overall survival. Specifically, regardless of age, those who received more chemotherapy had better overall survival; regardless of degree of chemotherapy, younger age was associated with better overall survival. The reduction in hazard of death due to more chemotherapy compared with less chemotherapy was 17% (95% CI, 6%-27%) for women aged 50 years or younger, 16% (95% CI, 4%-27%) for women aged 51 to 64 years, and 27% (95% CI, 5%-44%) for women aged 65 years or older. Survival and disease status by age is presented in Table 5. Older patients were more likely to have died of either breast cancer– or non–breast cancer–related causes. The reduction in the hazard ratios for patients receiving more compared with less chemotherapy was similar among all age groups.

COMMENT

This study showed that older patients in reasonably good health who met the rigorous eligibility criteria needed for inclusion into these randomized trials derived similar benefits from more chemotherapy treatment as did younger patients. Older patients in these trials were at higher risk for breast cancer recurrence, as evidenced by the higher percentage of older patients with involvement of 10 or more lymph nodes. This finding, as well as the fact that only 8% of patients entered in these trials were aged 65 years or older, underscore what is probably substantial age bias when offering patients clinical trials. Kemeny and colleagues[21] have shown that age bias remains a significant independent cause of oncologists' reluctance to offer participation in clinical trials to older patients; only 34% of women aged 65 years or older with stage II breast cancer[22] and eligible for a clinical trial in their institution were offered participation, compared with 68% of women younger than 65 years.

Not all older patients with node-positive breast cancer are good candidates for chemotherapy, and such treatment may be inappropriate for older patients with frailty or significant comorbidity. Comorbidity increases with age and can have a profound effect on the survival of patients with breast cancer.[23,24] Among 1312 patients aged 55 years or older with breast cancer, Yancik et al[23] found 1 or more major comorbidities in approximately 14% of those aged 55 to 59 years, in about 30% of those aged 65 to 69 years, and in about 48% of those aged 75 to 79 years. Nevertheless, it appears almost cer-

Table 4. Disease-Free and Overall Survival in Multivariate Proportional Hazards Model*

Comparison, Lower vs Higher Risk	Degrees of Freedom	HR (95% CI)	*P* Value
Disease-free survival			
More vs less chemotherapy	1	0.78 (0.72-0.85)	<.001
Age , y†			
≥65 vs ≤50	2	0.97 (0.90-1.20)	.90
≥65 vs 51-64		0.97 (0.89-1.19)	
Age × chemotherapy interaction†	2	. . .	.16
1 vs 10 positive lymph nodes‡	1	0.43 (0.40-0.46)	<.001
Tumor size, 2 cm vs 5 cm§	1	0.83 (0.79-0.87)	<.001
Estrogen receptor positive vs negative	1	0.90 (0.81-0.99)	.03
Tamoxifen use vs no use	1	0.59 (0.52-0.67)	<.001
CALGB trial†			
9344 vs 7581	3	0.79 (0.67-0.93)	.002
9344 vs 8082		0.96 (0.83-1.11)	
9344 vs 8541		0.84 (0.75-0.94)	
Overall survival			
More vs less chemotherapy	1	0.82 (0.75-0.90)	<.001
Age, y†			
≤50 vs ≥65	2	0.72 (0.63-0.83)	<.001
51-64 vs ≥65		0.84 (0.73-0.96)	
Age × chemotherapy interaction†	2	. . .	.72
1 vs 10 positive lymph nodes‡	1	0.46 (0.43-0.50)	<.001
Tumor size, 2 cm vs 5 cm§	1	0.87 (0.83-0.91)	<.001
Estrogen receptor positive vs negative	1	0.75 (0.68-0.83)	<.001
Tamoxifen use vs no use	1	0.58 (0.51-0.66)	<.001
CALGB trial†			
9344 vs 7581	3	0.97 (0.82-1.15)	.007
9344 vs 8082		0.81 (0.70-0.95)	
9344 vs 8541		0.90 (0.80-1.01)	

Abbreviations: CALGB, Cancer and Leukemia Group B; CI, confidence interval; HR, hazard ratio. Ellipses indicate data not applicable.
*Based on n = 5742; 41% were treatment failures and 38% were deaths.
†Dummy coding used.
‡Square-root transformation used.
§Linear scale used.

tain that for many older patients seen during the period that the trials analyzed in this study encompassed, age bias played a major role in whether trial participation was offered. At present, women aged 65, 75, and 85 years in generally good health can expect to live, on average, an additional 20, 12, and 6 years, respectively[25]; if they were to

Figure 1. Disease-Free Survival for All Patients by Chemotherapy Intensity and Age Group

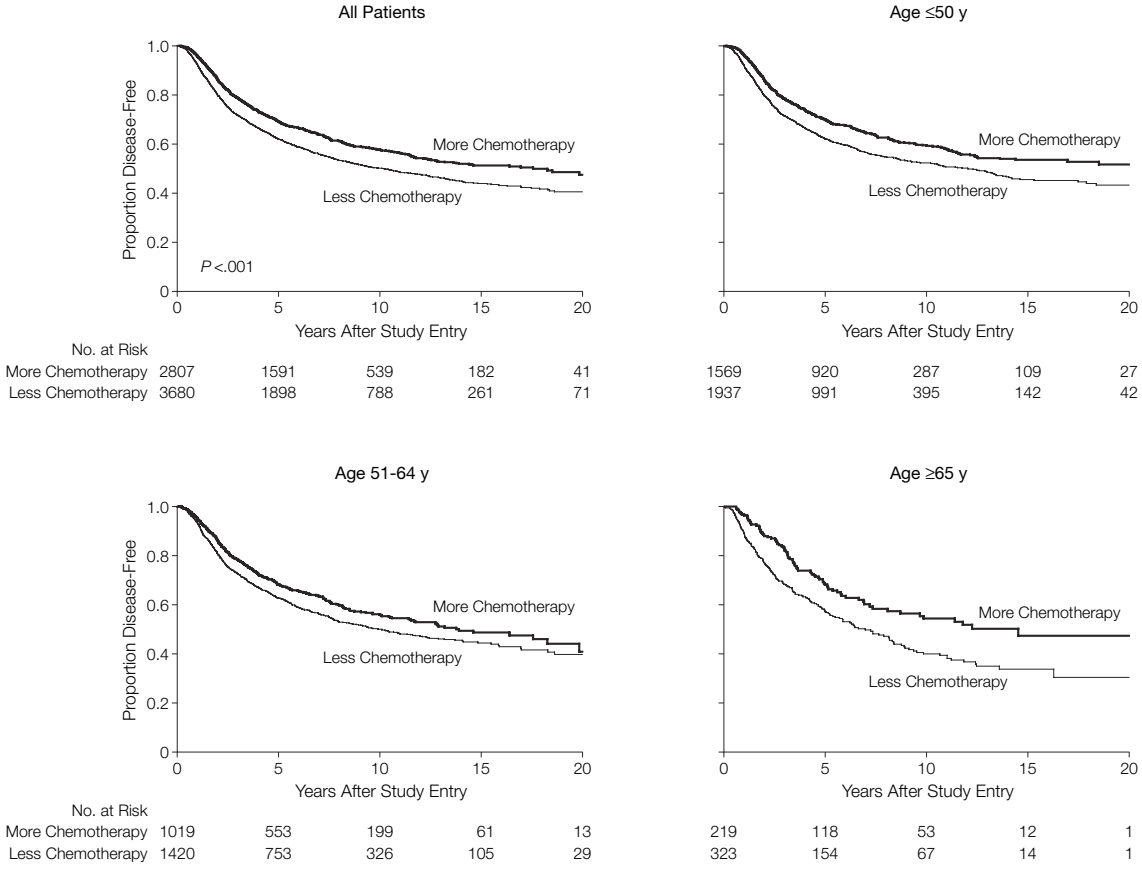
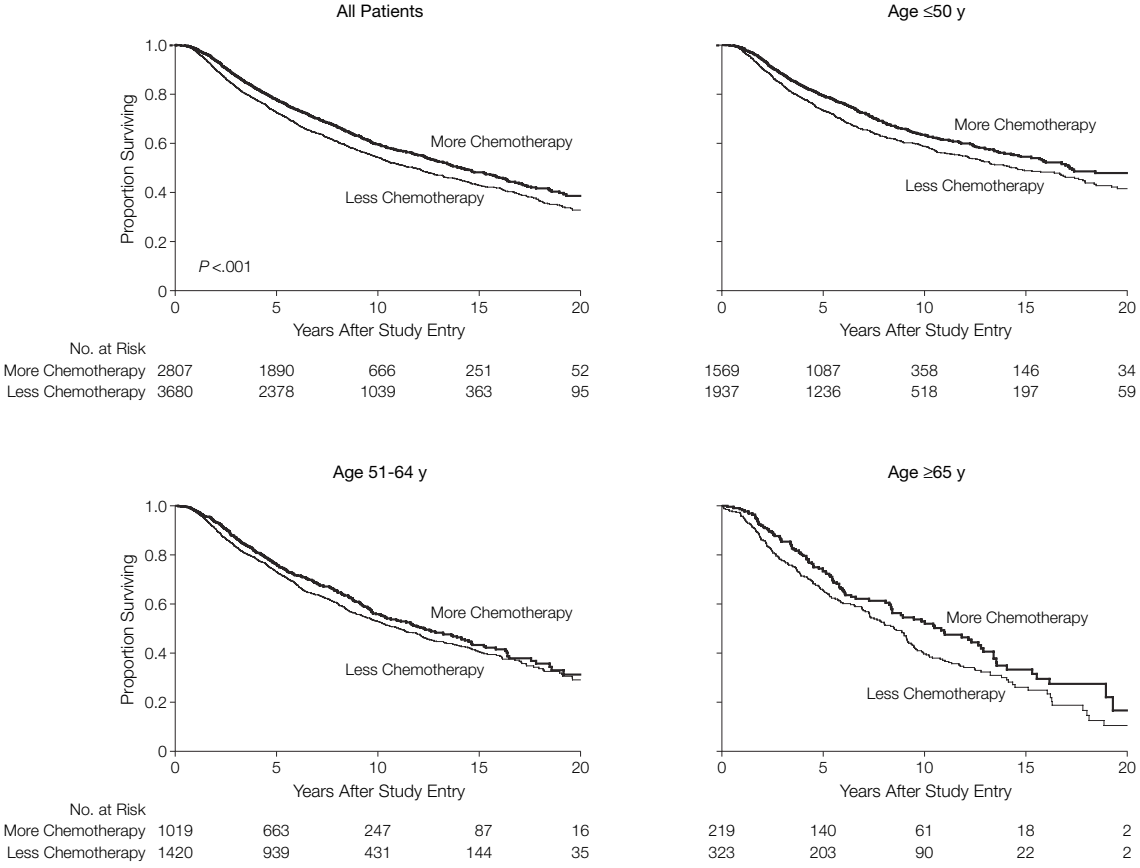


Table 5. Survival and Disease Status by Age

Characteristics	Age, y ≤50 (n = 3506)	51-64 (n = 2439)	≥65 (n = 542)	Total (n = 6487)
Survival status, No. (%)				
Alive	2249 (64)	1354 (56)	228 (42)	3831 (59)
No evidence of breast cancer recurrence	1986 (57)	1205 (49)	202 (37)	3393 (52)
Breast cancer recurrence	263 (8)	149 (6)	26 (5)	438 (7)
Died	1257 (36)	1085 (44)	314 (58)	2656 (41)
Breast cancer	1133 (32)	871 (36)	228 (42)	2232 (34)
Treatment	8 (<1)	17 (1)	8 (1)	33 (1)
Neither breast cancer nor treatment	73 (2)	139 (6)	59 (11)	271 (4)
Unknown cause	43 (1)	58 (2)	19 (4)	120 (2)
Median survival time, y				
Overall	16.0	11.4	9.0	12.7
Disease-free	13.8	11.6	8.3	12.4
Reduction in hazard due to more chemotherapy, % (95% confidence interval)				
Overall survival	17 (6-27)	16 (4-27)	27 (5-44)	18 (10-25)
Disease-free survival	18 (9-27)	20 (8-30)	42 (22-56)	22 (15-28)

Figure 2. Overall Survival for All Patients by Chemotherapy Intensity and Age Group



develop high-risk breast cancer, many of these women would likely derive major benefits from adjuvant chemotherapy.

In this study, older patients experienced a higher treatment-related mortality of 1.5% compared with younger patients (0.2%-0.7%). This increase in chemotherapy-associated toxic effects with older age has been noted by others.[26] Hospitalizations resulting from chemotherapy toxic effects in 35 060 women with stage I to IV breast cancer aged 65 years or older were analyzed by Du and colleagues.[27] Neutropenia, fever, thrombocytopenia, and other adverse effects of treatment resulted in hospitalizations for 6.3% of patients with stage I and 8.1% with stage II breast cancer. The hospitalization rate increased with increasing comorbidity and the use of anthracyclines but was not associated with age. Crivellari and colleagues[26] noted that older patients were much more likely to have grade 3 treatment-related toxic effects with a CMF adjuvant therapy regimen, but they noted no grade 4 toxic effects.

The overall risk reduction in breast cancer relapse in this analysis was 22% lower for patients treated with higher-dose regimens. These data reflect the results of the individual trials themselves. Although these trials did not stratify patients by age, the older cohort of patients showed a hazard reduction due to more chemotherapy that was similar to that in younger patients. This study was complicated by the fact that tamoxifen was not used in the 2 early trials but was used in the 2 later trials (CALGB 8541 and 9344) However, even in these 2 later trials, in which data on tamoxifen use were available, the more intensive chemotherapy regimen was still a significant factor in decreasing the risk of relapse in our multivariate analysis. This indicates that there is added value to receiving higher-dose chemotherapy regimens, even in patients receiving tamoxifen. Considerable uncertainty still exists concerning the added value of chemotherapy in older, node-positive, postmenopausal, hormone receptor–positive patients given tamoxifen. Data from the overview analysis, however, show a significant improvement in disease-free and overall survival for patients treated with tamoxifen and chemotherapy compared with those treated with tamoxifen alone.[28] The added value of chemotherapy in older women who receive tamoxifen is influenced greatly by comorbidity and life expectancy. Extermann and colleagues[29] have developed models for estimating the benefits of chemotherapy in hormone receptor–positive older

women and have demonstrated that high risks of recurrence are needed to achieve even small survival benefits for adjuvant chemotherapy. For example, to reduce mortality risk at 10 years by 1% with chemotherapy, the risk of breast recurrence at 10 years had to be at least 25% for a 75-year-old in average health, a recurrence risk that may not be exceeded by all node-positive women. These data suggest that chemotherapy for older women with hormone receptor–positive breast cancer should be offered only to node-positive patients who are in reasonable health, with a high risk of recurrence and a life expectancy of more than 5 years. Results of the current study suggest that higher-dose chemotherapy regimens as used in younger patients are worthy of consideration in the older patient population. Older node-negative patients are unlikely to benefit from chemotherapy unless they have large hormone receptor–positive tumors with adverse pathologic characteristics (lymphovascular invasion or high tumor grade) or hormone receptor–negative tumors larger than 2 cm.[30] A model that incorporates age, health status, and tumor characteristics can be helpful in estimating the benefit of adjuvant chemotherapy in older patients (for example, see http://www.adjuvantonline.com). Our data also show a significant survival benefit for more intensive chemotherapy in healthy older patients that met the stringent eligibility criteria for these trials. Older patients in this study more frequently died of non–breast cancer causes than younger patients, but even in the older age group, 73% of deaths were due to breast cancer. Nevertheless, only 2% of patients in this study were aged 70 years or older, and caution should be exercised in extrapolating these data to patients aged 75 years or older, who have shorter life expectancies and more comorbidities than patients aged 66 to 70 years.

Our study adds to the increasing number of trials that suggest that older patients in fair to good health tolerate standard chemotherapy regimens, and even more intensive regimens, almost as well as younger patients.[31] Moreover, and more importantly, this study suggests that the added value gained from more intensive chemotherapy regimens commonly used in the adjuvant setting might be shared by older patients and not limited to younger age groups. A sobering finding from this analysis is the observation that only 8% of patients entered in the trials analyzed in this study were aged 65 years or older; about 50% of new breast cancer diagnoses occur in women in this older age group. Although good clinical judgment likely played a role in limiting the offering of these trials to many older patients, it is likely that age bias remained a major factor for offering older women clinical trial participation. For example, older patients entered in these 4 CALGB trials had a significantly higher number of positive lymph nodes than younger patients, suggesting that physicians were wary of offering these trials to lower-risk, node-positive older patients.

The majority of current chemotherapy trials for patients with node-positive cancer build on previous gains and include dose-dense regimens, new chemotherapeutic agents or biologics, or schedules of drug administration that many clinicians will perceive as being too toxic for older patients. The data from this study should help to encourage clinicians to offer healthy older patients participation in newer trials, because healthy older patients are likely to derive similar treatment benefits as younger patients. However, depending on the specific research question, older patients need to be carefully counseled about a higher risk of treatment-related toxicity. Trials exploring new approaches to adjuvant chemotherapy for older patients are now in progress. Older patients with high-risk early breast cancer who are in otherwise good health should be offered participation in ongoing clinical trials of adjuvant chemotherapy.

Author Contributions: Dr Muss had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Muss, Berry, Hudis, Winer, Norton.
Acquisition of data: Weiss, Wheeler, Norton.
Analysis and interpretation of data: Muss, Woolf, Berry, Cirrincione, Budman, Wood, Henderson, Hudis, Cohen, Norton.
Drafting of the manuscript: Muss, Berry, Cirrincione, Hudis, Cohen, Wheeler.
Critical revision of the manuscript for important intellectual content: Muss, Woolf, Cirrincione, Weiss, Budman, Wood, Henderson, Hudis, Winer, Cohen, Norton.
Statistical analysis: Woolf, Berry, Cirrincione, Wheeler.
Obtained funding: Henderson.
Administrative, technical, or material support: Wood, Hudis, Cohen, Norton.
Study supervision: Muss, Budman, Hudis, Norton.
Financial Disclosures: Dr Wood has received financial support from Aventis and Genomic Health. All other authors reported no disclosures.
Cancer and Leukemia Group B Investigators and Funding/Support: This CALGB research was supported in part by grant CA31946 from the National Cancer Institute to the Cancer and Leukemia Group B (Richard L. Schilsky, MD, chairman). The following institutions participated in the study: Baptist Cancer Institute CCOP, Memphis, Tenn, Lee S. Schwartzberg, MD, supported by grant CA71323; CALGB Statistical Center, Durham, NC, Stephen George, PhD, supported by grant CA33601; Christiana Care Health Services Inc, CCOP, Wilmington, Del, Stephen Grubbs, MD, supported by grant CA45418; Columbia Presbyterian Medical Center, New York, NY, supported by grant CA12011; Community Hospital–Syracuse CCOP, Syracuse, NY, Jeffrey Kirshner, MD, supported by grant CA45389; Dana Farber Cancer Institute, Boston, Mass, George P Canellos, MD, supported by grant CA32291; Dartmouth Medical School–Norris Cotton Cancer Center, Lebanon, NH, Marc S. Ernstoff, MD, supported by grant CA04326; Duke University Medical Center, Durham, NC, Jeffrey Crawford, MD, supported by grant CA47577; Eastern Cooperative Oncology Group, Philadelphia, Pa, Robert L. Comis, MD, chairman, supported by grant CA21115; Finsen Institute, Copenhagen, Denmark, Nis I. Nissen, MD, PhD; Georgetown University Medical Center, Washington, DC, Edward Gelmann, MD, supported by grant CA77597; Green Mountain Oncology Group CCOP, Bennington, Vt, H. James Wallace, Jr, MD, supported by grant CA35091; H. F. Verwoerd Hospital, Pretoria, South Africa; Hospital St-Louis, Paris, France; Johns Hopkins University, Baltimore, Md; Kaiser Permanente CCOP, San Diego, Calif, Jonathan A. Polikoff, MD, supported by grant CA45374; Long Island Jewish Medical Center, Lake Success, NY, Marc Citron, MD, supported by grant CA11028; Massachusetts General Hospital, Boston, Michael L. Grossbard, MD, supported by grant CA12449; McGill Department of Oncology, Montreal, Quebec, supported by grant CA31809; Medical Center of Delaware, Newark, supported by grant CA45418; Memorial Sloan-Kettering Cancer Center, New York, NY, supported by grant CA77651; Mount Sinai Medical Center CCOP Miami, Miami Beach, Fla, Rogerio Lilenbaum, MD, supported by grant CA45564; Mount Sinai School of Medicine, New York, NY, Lewis R. Silverman, MD, supported by grant CA04457; New York Hospital, New York, NY, supported by grant CA07968; North Central Cancer Treatment Group, Rochester, Minn, Michael J. O'Connell, MD, chairman, supported by grant CA25224; North Shore–Long Island Jewish Health Systems, Manhasset, NY, Daniel R. Budman, MD, supported by grant CA35279; Ochsner Clinic, New Orleans, La; Rhode Island Hospital, Providence, William Sikov, MD, supported by grant CA08025; Roswell Park Cancer Institute, Buffalo, NY, Ellis Levine, MD, supported by grant CA02599; South New Jersey CCOP, Camden, NJ, Jack Goldberg, MD, supported by grant CA54697; Southeast Cancer Control Consortium Inc

CCOP, Goldsboro, NC, James N. Atkins, MD, supported by grant CA45808; Southern Nevada Cancer Research Foundation CCOP, Las Vegas, NV, John Ellerton, MD, supported by grant CA35421; Southwest Oncology Group, San Antonio, Tex, Charles Coltman, MD, chairman, supported by grant CA32102; St Michael's Medical Center Tri-County CCOP, Paterson, NJ, Arnold D. Rubin, MD, supported by grant CA60247; State University of New York Upstate Medical University, Syracuse, NY, Stephen L. Graziano, MD, supported by grant CA21060; Swiss Group Hospitals, Basel, Bern, and Tessin/Bellinzona, Switzerland; Syracuse Hematology-Oncology Association CCOP, Syracuse, NY, Jeffrey Kirshner, MD, supported by grant CA45389; Mayo Clinic, Rochester, Minn; University of Alabama, Birmingham, Robert Diasio, MD, supported by grant CA47545; University of California, San Diego, Stephen Seagren, MD, supported by grant CA11789; University of California, San Francisco, Alan P. Venook, MD, supported by grant CA60138; University of Chicago Medical Center, Chicago, Ill, Gini Fleming, MD, supported by grant CA41287; University of Cincinnati, Cincinnati, Ohio, supported by grant CA47515; University of Illinois at Chicago, Lawrence E. Feldman, MD, supported by grant CA74811; University of Iowa Hospitals, Iowa City, Gerald H. Clamon, MD, supported by grant CA47642; University of Maryland Cancer Center, Baltimore, Martin Edelman, MD, supported by grant CA31983; University of Massachusetts Medical Center, Worcester, Pankaj Bhargava, MD, supported by grant CA37135; University of Minnesota, Minneapolis, Bruce A. Peterson, MD, supported by grant CA16450; University of Missouri/Ellis Fischel Cancer Center, Columbia, Mo, Michael C Perry, MD, supported by grant CA12046; University of Nebraska Medical Center, Omaha, Anne Kessinger, MD, supported by grant CA77298; University of North Carolina at Chapel Hill, Thomas C. Shea, MD, supported by grant CA47559; University of Tennessee, Memphis, Harvey B. Niell, MD, supported by grant CA47555; Vermont Cancer Center, Burlington, Hyman B. Muss, MD, supported by grant CA77406; Virginia Commonwealth University MB CCOP, Richmond, John D. Roberts, MD, supported by grant CA52784; Virginia Mason Medical Clinic CCOP, Seattle, Wash; Wake Forest University School of Medicine, Winston-Salem, NC, David D. Hurd, MD, supported by grant CA03927; Walter Reed Army Medical Center, Washington, DC, Joseph J. Drabeck, MD, supported by grant CA26806; Washington University School of Medicine, St Louis, Mo, Nancy L. Bartlett, MD, supported by grant CA77440; Weill Medical College of Cornell University, New York, NY, Scott Wadler, MD, supported by grant CA07968; West Virgina University Medical Center CCOP, Morgantown, supported by grant CA28652.

Role of the Sponsor: The funding agency had no role in the design and conduct of the study; the collection, analysis, and review of the data; or the preparation, review, or approval of the manuscript.

Disclaimer: The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

REFERENCES

1. Yancik R, Ries LA. Aging and cancer in America: demographic and epidemiologic perspectives. *Hematol Oncol Clin North Am*. 2000;14:17-23.

2. Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomised trials. *Lancet*. 1998;352:930-942.

3. Du XL, Key CR, Osborne C, Mahnken JD, Goodwin JS. Discrepancy between consensus recommendations and actual community use of adjuvant chemotherapy in women with breast cancer. *Ann Intern Med*. 2003;138:90-97.

4. Lyman GH, Dale DC, Crawford J. Incidence and predictors of low dose-intensity in adjuvant breast cancer chemotherapy: a nationwide study of community practices. *J Clin Oncol*. 2003;21:4524-4531.

5. Lichtman SM, Skirvin JA. Pharmacology of antineoplastic agents in older cancer patients. *Oncology (Huntingt)*. 2000;14:1743-1755.

6. Gelman RS, Taylor SG. Cyclophosphamide, methotrexate, and 5-fluorouracil chemotherapy in women more than 65 years old with advanced breast cancer: the elimination of age trends in toxicity by using doses based on creatinine clearance. *J Clin Oncol*. 1984;2:1404-1413.

7. Begg CB, Cohen JL, Ellerton J. Are the elderly predisposed to toxicity from cancer chemotherapy? an investigation using data from the Eastern Cooperative Oncology Group. *Cancer Clin Trials*. 1980;3:369-374.

8. Dees EC, O'Reilly S, Goodman SN, et al. A prospective pharmacologic evaluation of age-related toxicity of adjuvant chemotherapy in women with breast cancer. *Cancer Invest*. 2000;18:521-529.

9. Ibrahim NK, Frye DK, Buzdar AU, Walters RS, Hortobagyi GN. Doxorubicin-based chemotherapy in elderly patients with metastatic breast cancer: tolerance and outcome. *Arch Intern Med*. 1996;156:882-888.

10. Christman K, Muss HB, Case LD, Stanley V. Chemotherapy of metastatic breast cancer in the elderly: the Piedmont Oncology Association experience. *JAMA*. 1992;268:57-62.

11. Levine MN, Bramwell VH, Pritchard KI, et al; National Cancer Institute of Canada Clinical Trials Group. Randomized trial of intensive cyclophosphamide, epirubicin, and fluorouracil chemotherapy compared with cyclophosphamide, methotrexate, and fluorouracil in premenopausal women with node-positive breast cancer. *J Clin Oncol*. 1998;16:2651-2658.

12. Bonneterre JM, Roche H, Kerbrat P, et al. Long-term cardiac follow-up in free of disease patients (pts) after receiving 6 FEC 50 vs 6 FEC 100 (FASG-05 Trial) as adjuvant chemotherapy (CT) for node-positive (N+) breast cancer (BC). *Proc Am Soc Clin Oncol*. 2002;21:39a.

13. Henderson IC, Berry DA, Demetri GD, et al. Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. *J Clin Oncol*. 2003;21:976-983.

14. Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. *J Clin Oncol*. 2003;21:1431-1439.

15. Hutchins LF, Unger JM, Crowley JJ, Coltman CA Jr, Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. *N Engl J Med*. 1999;341:2061-2067.

16. Sateren WB, Trimble EL, Abrams J, et al. How sociodemographics, presence of oncology specialists, and hospital cancer programs affect accrual to cancer treatment trials. *J Clin Oncol*. 2002;20:2109-2117.

17. Weiss RB, Woolf SH, Demakos E, et al. Natural history of more than 20 years of node-positive primary breast carcinoma treated with cyclophosphamide, methotrexate, and fluorouracil-based adjuvant chemotherapy: a study by the Cancer and Leukemia Group B. *J Clin Oncol*. 2003;21:1825-1835.

18. Perloff M, Norton L, Korzun AH, et al. Postsurgical adjuvant chemotherapy of stage II breast carcinoma with or without crossover to a non-cross-resistant regimen: a Cancer and Leukemia Group B study. *J Clin Oncol*. 1996;14:1589-1598.

19. Budman DR, Berry DA, Cirrincione CT, et al; Cancer and Leukemia Group B. Dose and dose intensity as determinants of outcome in the adjuvant treatment of breast cancer. *J Natl Cancer Inst*. 1998;90:1205-1211.

20. Thor AD, Berry DA, Budman DR, et al. erbB-2, p53, and efficacy of adjuvant therapy in lymph node-positive breast cancer. *J Natl Cancer Inst*. 1998;90:1346-1360.

21. Kemeny MM, Peterson BL, Kornblith AB, et al. Barriers to clinical trial participation by older women with breast cancer. *J Clin Oncol*. 2003;21:2268-2275.

22. American Joint Committee on Cancer. *Cancer Staging Manual*. 5th ed. Philadelphia, Pa: Lippincott Raven; 1997.

23. Yancik R, Wesley MN, Ries LA, Havlik RJ, Edwards BK, Yates JW. Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. *JAMA*. 2001;285:885-892.

24. Satariano WA, Ragland DR. The effect of comorbidity on 3-year survival of women with primary breast cancer. *Ann Intern Med*. 1994;120:104-110.

25. Holmes CE, Muss HB. Diagnosis and treatment of breast cancer in the elderly. *CA Cancer J Clin*. 2003;53:227-244.

26. Crivellari D, Bonetti M, Castiglione-Gertsch M, et al. Burdens and benefits of adjuvant cyclophosphamide, methotrexate, and fluorouracil and tamoxifen for elderly patients with breast cancer: the International Breast Cancer Study Group Trial VII. *J Clin Oncol*. 2000;18:1412-1422.

27. Du XL, Osborne C, Goodwin JS. Population-based assessment of hospitalizations for toxicity from chemotherapy in older women with breast cancer. *J Clin Oncol*. 2002;20:4636-4642.

28. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet*. 1998;351:1451-1467.

29. Extermann M, Balducci L, Lyman GH. What threshold for adjuvant therapy in older breast cancer patients? *J Clin Oncol*. 2000;18:1709-1717.

30. Desch CE, Hillner BE, Smith TJ, Retchin SM. Should the elderly receive chemotherapy for node-negative breast cancer? a cost-effectiveness analysis examining total and active life-expectancy outcomes. *J Clin Oncol*. 1993;11:777-782.

31. Kimmick GG, Muss HB. Systemic therapy for older women with breast cancer. *Oncology (Huntingt)*. 2001;15:280-291.