Adjuvant Chemotherapy for Stage III Colon Cancer

Implications of Race/Ethnicity, Age, and Differentiation

J. Milburn Jessup, MD
Andrew Stewart, MS
Frederick L. Greene, MD
Bruce D. Minsky, MD

Context A 1990 National Institutes of Health Consensus Conference recommended that patients with stage III colon cancer receive adjuvant chemotherapy because survival was improved in clinical trials in patients who received a 5-fluorouracil–based regimen.

Objective To determine whether adjuvant chemotherapy is used in the community as a standard of practice that improves outcome and whether it failed to benefit any specific sets of patients.

Design, Setting, and Participants Prospective data from 85 934 patients with stage III colon cancer from 560 hospital cancer registries were entered into the National Cancer Data Base between 1990 and 2002 and included standard clinical, pathological, and first course of treatment variables.

Main Outcome Measures Prevalence of adjuvant chemotherapy usage and 5-year survival in patients treated in US hospitals.

Results Adjuvant chemotherapy use increased from 39% in 1991 to 64% in 2002 but was lower in black, female, and elderly patients. It improved 5-year survival from almost 8% in 1991 to more than 16% in 1997 compared with surgery alone. Adjuvant chemotherapy increases survival in elderly patients as much as it does in younger patients. However, the benefit of adjuvant chemotherapy in blacks and those with high-grade cancers is not as great.

Conclusions Adjuvant chemotherapy use has increased from 1990 to 2002 for patients with stage III colon cancer with an associated increase in 5-year survival of 16%. The benefit of adjuvant chemotherapy seems to be lower in black patients and high-grade cancers. Women have the same benefit but are less often treated. Elderly patients have the same benefit as younger patients but are less frequently treated. New options for adjuvant therapy in 2004-2005 may further improve the outcome of patients with stage III colon cancer.

JAMA. 2005;294:2703-2711 www.jama.com

THE RESULTS OF A NATIONAL INSTITUTES of Health Consensus Conference on the adjuvant therapy of colon and rectal cancer were published in 1990.[1] Two prospectively randomized phase 3 trials demonstrated that adjuvant chemotherapy with 5-fluorouracil and levamisole improved the survival of patients with stage III colon cancer compared with patients who received levamisole alone or who only underwent the surgical resection.[2,3] Thus, the conference recommended that adjuvant chemotherapy be given to all patients with stage III colon cancer who were not enrolled in a clinical trial.

However, as with most recommendations, it is not clear to what extent they are followed or contribute to outcome in the general population. The patients in Cooperative Oncology Group trials may be younger with less comorbid disease and may be able to tolerate more therapy than do older patients in the community. Second, the results from clinical trials may not be incorporated into the daily practice of physicians and surgeons who care for patients in the community. Thus, the results obtained in rigorously controlled clinical trials may not necessarily translate into better outcomes for the general population.

For editorial comment see p 2758.

Our purpose in the present study was to assess to what extent the 1990 Consensus Conference recommendation has been followed in the community and whether adjuvant chemotherapy has improved the 5-year survival of patients with stage III colon cancer. Our approach was to use the National Can-

Author Affiliations: Department of Oncology, Georgetown University Medical Center, Washington, DC (Dr Jessup); Cancer Diagnosis Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Rockville, Md (Dr Jessup); Cancer Department, American College of Surgeons, Chicago, Ill (Mr Stewart); Department of Surgery, Carolinas Medical Center, Charlotte, NC (Dr Greene); and Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY (Dr Minsky).
Corresponding Author: J. Milburn Jessup, MD, Cancer Diagnosis Program, Division of Cancer Treatment Diagnosis, National Cancer Institute, Executive Plaza N 6040, 6130 Executive Blvd, Rockville, MD 20892 (jessupj@mail.nih.gov).

Table 1. Characteristics of Patients With Stage III Colon Carcinoma in the National Cancer Data Base, 1990-2002*

Variables	No. (%) of Patients† 1990-1991 (n = 12 413)	2001-2002 (n = 14 187)
Sex		
Men	5956 (48.0)	6622 (46.7)
Women	6457 (52.0)	7565 (53.3)
Age, y		
<60	2619 (21.1)	3601 (25.4)
60-69	3098 (25.0)	3195 (22.5)
70-79	4103 (33.1)	4086 (28.8)
≥80	2593 (20.9)	3305 (23.3)
Race/ethnicity‡		
Non-Hispanic white	9577 (77.2)	10 692 (75.4)
Black	975 (7.9)	1529 (10.8)
Hispanic	283 (2.3)	429 (3.0)
Asian or Pacific Islander	227 (1.8)	386 (2.7)
Other or unknown	1351 (10.9)	1151 (8.1)

*Age and race/ethnicity definitions are described in the "Methods" section.
†Percentages may not sum to 100 due to rounding.
‡Over the periods studied there has not been an appreciable change in the distribution of sex but there has been in age and the percentage of blacks, as presented in Figure 1.

cer Data Base (NCDB), a hospital-based database of patients who are diagnosed with or receive treatment for cancer in 1430 US hospitals,[4-6] and analyze both the use and effect of adjuvant chemotherapy on the outcomes of patients with node-positive colon cancer in patients within the community.

METHODS

NCDB, Data Collection, and Handling

The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society and collects data prospectively on all forms of cancer diagnosed in the United States. Approximately 1430 hospitals participate in the approvals program and respond to the annual calls for data to be delivered to the NCDB. A total of 168 598 patients with stage III (node-positive) colon cancer were reported to the NCDB from a total of 1902 hospital registries between 1990 and 2002. However, only 560 hospital registries participated in every data submission for this period and entered a total of 85 934 stage III colon cancers, which are the basis of this report. The cohort reported herein was selected so that patients would be studied from the same facilities and with similar inherent distributions of treatment, clinical, and pathological variables. There was no more than a 1% difference in the prevalence of any characteristic or outcome in the subset presented herein and the larger data set (data not shown). Hospital cancer registrars abstracted each case according to a standardized set of data elements and definitions[4-6] based on information provided by both the patients and the hospital medical information systems. The NCDB data elements include patient characteristics: sex, age or date of birth, race/ethnicity; tumor characteristics: primary site, histology, grade, regional nodes positive or examined, American Joint Committee on Cancer (AJCC) stage group, and date, type, and site of recurrence; first course of treatment: surgery, radiation, chemotherapy, hormone, and other; and follow-up: last contact date, vital status, and tumor status at last follow-up. The information about the first course of treatment: does not include the chemotherapeutic agents, the dosages, or the duration of therapy. The data were transmitted to the NCDB following a standard data transfer protocol.[7-9] Diagnosis and treatment were analyzed by AJCC stage for all cases,[10] which includes the pathological (pAJCC) stage group augmented by the clinical (cAJCC) stage group when pathological stage is not recorded. Low grade is defined as grades I, differentiated or well differentiated, and grade II, moderately differentiated or moderately well differentiated, whereas high grade is grade III, poorly differentiated, and grade IV, undifferentiated, anaplastic. Because race/ethnicity may affect outcome, registrars classified each patient's race or ethnicity based on information supplied by the patients according to the NCDB data element descriptions.[4-6] The hospitals providing these data were: 146 (26.1%) community cancer centers, facilities that diagnose and/or treat 300 or fewer cancer cases annually; 280 (50%) comprehensive community cancer centers, facilities that diagnose and/or treat more than 300 cancer cases annually; and 134 (23.9%) teaching-research centers, facilities associated with university medical schools or designated as National Cancer Institute Comprehensive Cancer Care Programs. The 3 types of hospitals submitted 12 887 (15%), 47 401 (55.2%), and 25 646 (29.8%) cases, respectively.

The American College of Surgeons has executed a business associate agreement that includes a data-use agreement with each of its Commission on Cancer–approved hospitals. Data reported to the NCDB are deidentified. The Georgetown University Institutional Review Board gave this study (protocol 2005-395) an exemption waiver in September 2005.

Analysis

The change over time between 1990 and 2002 in the proportion of cases presenting, treated, or pathologically evaluated with specific characteristics was assessed using a χ^2-based test for conditional independence. Statistical significance was established at the $P<.001$ level.

Relative survival is the ratio of the observed survival rate to the aggregated expected survival rate of persons of the same sex, age, and racial or ethnic background. Observed survival was computed by the actuarial method, compounding survival in 1-month intervals from the date of diagnosis, with death from any cause as the end point.[11] Expected survival rates are then computed in single-year increments using the most recent life-expectancy tables published by the National Cancer Institute.[12] With this method, the relative survival rates are adjusted for risk within the demographic variability in patient populations and can be calculated in the absence of specific and reliable cause of death information for each patient. Since the data set is quite large for each group, the 95% confidence interval is less than 2%.

A multivariate Cox proportional hazards model[13] was fitted to these data for cases first diagnosed during 1991-

1997. The primary end point was date of death, measured from the date of first diagnosis. The Cox model included age; AJCC substage IIIA vs IIIB vs IIIC; race/ethnicity: non-Hispanic white, black, Asian Pacific Islander, and other or unknown because not specified; sex; site: right colon (the cecum and ascending colon), the transverse colon (including both flexures), and the left colon (the descending and sigmoid colon); and histological grade, low vs high. All analyses were conducted using SPSS for Windows Advanced Statistics, 9.0 (SPSS Inc, Chicago, Ill).

RESULTS

Characteristics of Patients

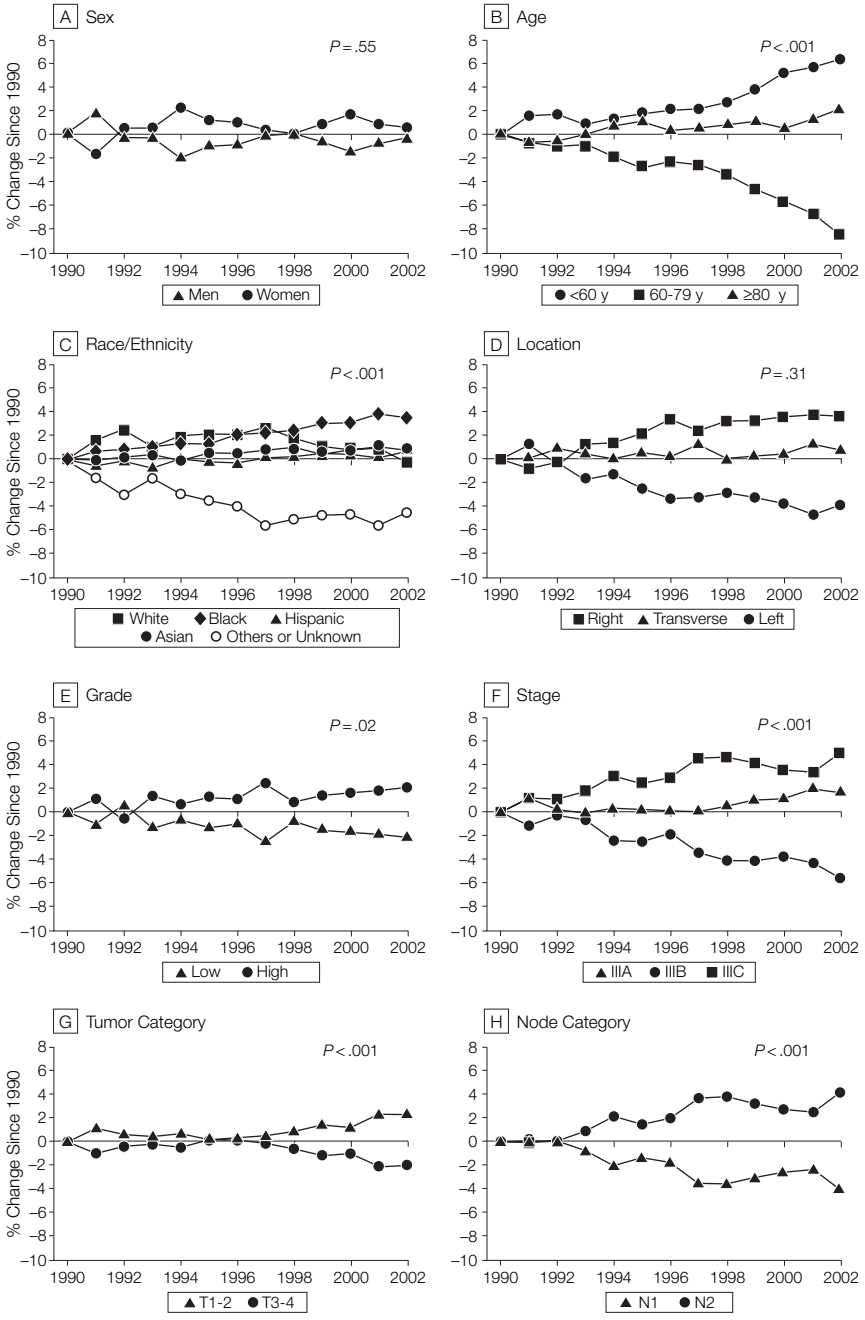
A total of 85 934 cases of stage III adenocarcinoma of the colon were reported to the NCDB from 1990 through 2002 by 560 hospitals. Slightly more than half of these patients were women, and approximately a quarter of the patients were 80 years or older at diagnosis (TABLE 1). The distribution of sex did not change appreciably over the period (FIGURE 1A). However, the distribution of age did change with increases in both the patients who were younger than 60 years at diagnosis and 80 years or older (Table 1, Figure 1B).

The percentage of blacks who had newly diagnosed stage III colon carcinoma also significantly increased by 3.4% from the 7.1% in 1990 to 10.5% in 2002. However, the percentage of colon cancer cases reported in Hispanics or Asian or Pacific Islanders remained stable while the percentage of patients whose ethnicity was not identified decreased from 10.9% in 1990 to 8.1% in 2002 (Table 1, Figure 1C). The US Census Statistical Abstract provides a crude measure of NCDB representativeness with regard to ethnicity in patients 65 years old or older. For all types of cancer in 1995-1996, the midpoint of this study, 9.9% of the patients were black in the NCDB vs 8.2% in the census, 2.6% Hispanic vs 4.9% in the census, and 1.8% Asian vs 2.1% in the census.[14] Thus, the NCDB has an ethnic distribution that is similar to that of the general population of the United States for blacks and non-Hispanic whites but slightly underrepresents Hispanics and Asians. Nevertheless, the patients in this analysis reflect the age, sex, and race/ethnicity of the majority of those who are treated within the community.

Characteristics of Stage III Colon Cancer

As has been true in previous reports, not only from the NCDB[15-17] but also from other sources, a trend toward right co-

Figure 1. Trends in Clinical and Pathologic Features, 1990-2002



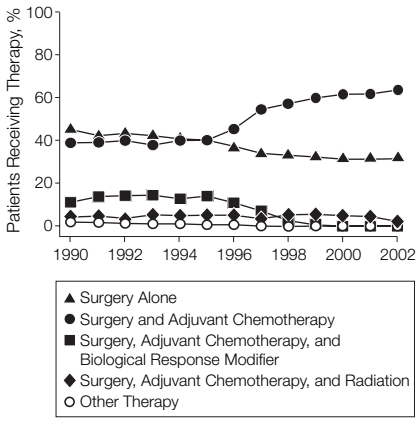
Changes in the distribution of clinical and pathologic characteristics from baseline year 1990 for sex, age, race/ethnicity, location of primary cancer, grade, substage of cancer, tumor category, and node category. *P* values reflect the significance of the changes, if any, in trends over the period of 1990 to 2002.

Table 2. Clinical and Pathologic Variables for Stage III Colon Cancer, 1990-2002

Location	No. (%) 1990-1991 (n = 12 413)	No. (%) 2001-2002 (n = 14 187)
Colon subsite*		
Right	7104 (56.3)	8830 (60.9)
Left	5309 (43.7)	5357 (39.1)
Pathologic tumor		
T1 or T2	1444 (11.6)	1857 (13.1)
T3 or T4	10 969 (88.4)	12 330 (86.9)
Pathologic node		
N1	8793 (70.8)	9603 (67.7)
N2	3620 (29.2)	4584 (32.3)
Cancer substage		
IIIA	1248 (10.1)	1599 (11.3)
IIIB	7545 (60.8)	8004 (56.4)
IIIC	3620 (29.2)	4584 (32.3)
Histological grade†		
Low	8546 (73.6)	9833 (71.9)
High	3070 (26.4)	3846 (28.1)

*Colon subsite is defined as either *right*, cecum, ascending and transverse colon with splenic flexure, or *left*, descending and sigmoid, colon.
†Histological grade is defined as either *low*, well and moderately differentiated malignant tumors, or *high*, poorly and undifferentiated malignant tumors. Not all tumors were graded

Figure 2. Use of Surgery and Other Therapies for Stage III Colon Cancer Between 1990 and 2002



Between 1990 and 2002, 85 934 patients were treated for stage III colon cancer. Patients received either surgery alone; surgery and chemotherapy, which includes all patients treated with a 5-fluorouracil–containing regimen other than the surgery and chemotherapy; and biological response modifier, which represents primarily the patients treated with adjuvant 5-fluorouracil and levamisole. Other therapy includes all other stage III colon cancers treated with various regimens that may include radiation, surgery, or both.

lon primary location was observed (Figure 1D, TABLE 2). The proportional distribution of diagnosed tumors in 1990 by substage and grade is 10.1%, stage IIIA; 60.8%, stage IIIB; and 29.2% stage IIIC with low grade occurring in about 73% of all stage III cancers (Table 2). In aggregate, this distribution is similar to previous reports from the NCDB.[17] Previous data from the NCDB have shown that histological grade is an independent covariant of outcome in both colon and rectal carcinoma.[17-19] However, the distribution of low-grade and high-grade cancers did not change significantly over the study period (Table 2, Figure 1E). In contrast, the substage of stage III colon cancers did change over the 1990-2002 period quite significantly (Figure 1F). There was a small increase in the relative proportion of pT1 and pT2 lesions from 11.6% in 1990 to 13.1% in 2002 (Table 2, Figure 1G). However, the frequency of N2 disease (≥4 regional nodes containing metastases) increased 3.1% that was significant ($P<.001$, Table 2, Figure 1H). Combined, these changes in T and N category caused an increase of more than 3% in the proportion of patients with stage IIIC disease and a decrease in stage IIIA disease (Figure 1F).

Use of Adjuvant Chemotherapy

An increase in the use of adjuvant chemotherapy was observed for all patients with stage III colon cancers from 39% of patients in 1990 to 64% in 2002 (FIGURE 2). These percentages include the use of both chemotherapy and a biological response modifier—primarily the use of 5-fluorouracil and levamisole and a small number of patients who received the BCG vaccine in the early 1990s. Adjuvant chemotherapy use remained constant until the mid 1990s when 5-fluorouracil and leucovorin was found to be as effective as 5-fluorouracil and levamisole[20-22] and then that 6 months of 5-fluorouracil and leucovorin were as effective as 12 months.[23] The use of 5-fluorouracil and leucovorin–based regimens then increased so that approximately 10% more patients received adjuvant chemotherapy in 2002 than in the mid 1990s (Figure 2).

However, use of adjuvant chemotherapy differed considerably by race/ethnicity, age group, and sex (FIGURE 3). Its usage was significantly less in blacks at the beginning and middle of the period but was not different from that of the other ethnic groups by 2002. Adjuvant chemotherapy usage increased in both sexes over the study period but, significantly, 3% fewer women received adjuvant chemotherapy after surgery than did men for each period analyzed. The proportion of patients receiving surgery and adjuvant chemotherapy declined significantly with age. In 2001-2002 adjuvant chemotherapy was used in 82% of patients younger than 60 years but declined to 77.2% of those aged 60 through 69 years, 69% of those aged 70 through 79 years, and only 39.2% in those 80 years or older.

When the use of adjuvant chemotherapy was analyzed by the substage at diagnosis, patients with substage IIIC were more likely to receive it than either those with substage IIIA or IIIB (data not shown), but the percentage of patients receiving adjuvant chemotherapy increased in all substages between 1990 and 2002 (data not shown).

Effect of Adjuvant Chemotherapy on Survival

The 5-year relative survival of patients who received adjuvant chemotherapy within 18 months of the National Institutes of Health Consensus Conference was 62% compared with 54% in patients who only received surgery (FIGURE 4). However, the 5-year survival of the group that received adjuvant chemotherapy after surgery in 1997 was 66%, a relative increase of 4% in the 5-year survival of these patients (Figure 4). The difference in relative survival increased from an 8% improvement in the 1991 subgroup to 16% in the 1997 subgroup that received adjuvant chemotherapy compared with surgery alone. The increase in difference in survival is not only associated with an increase in survival in the group treated with adjuvant chemotherapy but also with a decrease in the survival of patients treated with surgery only from 54% in 1991 to 50% in 1997. As described below, this change in survival may be associated partially with changes in the distribution of patients who receive adjuvant chemotherapy.

Effect of Adjuvant Chemotherapy on Survival in Various Subgroups

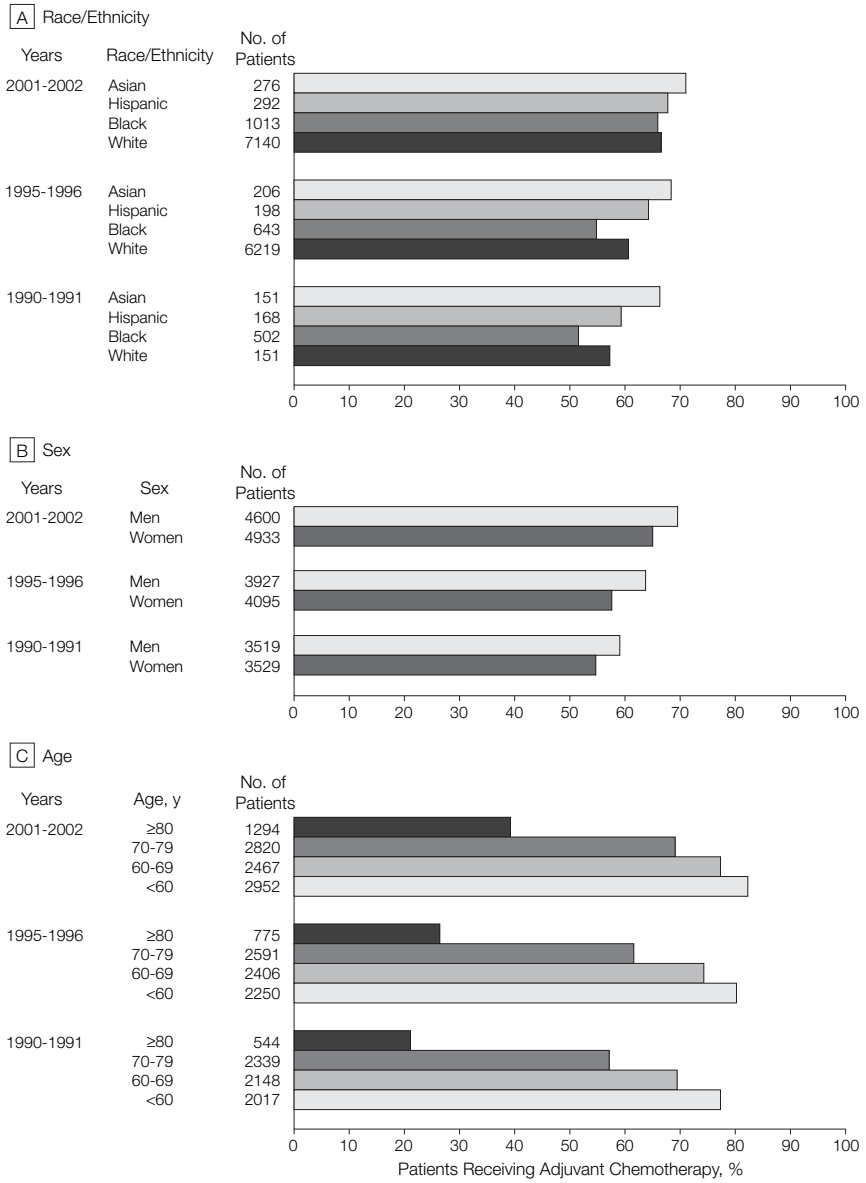
The present data confirm that patient race/ethnicity is associated with survival in colon cancer.[24] Blacks have an approximate 4% worse 5-year survival than non-Hispanic whites when they undergo surgery with or without adjuvant chemotherapy (FIGURE 5A). In contrast, the 5-year survival rates of women undergoing surgery with or without adjuvant chemotherapy is similar to that of men (Figure 5B). Age also affects survival after therapy. Patients 80 years or older who received adjuvant chemotherapy had 5-year survival similar to that of younger patients who received postoperative adjuvant chemotherapy and 19% better than patients 80 years or older who received surgery alone. The youngest cohort of patients had a 10% increase in 5-year survival with surgery plus adjuvant chemotherapy compared with surgery alone in the 1997 cohort (Figure 5C).

The association between tumor grade and the efficacy of adjuvant chemotherapy is also strong. In 1997 patients with low-grade cancers who received it after surgery had an almost 19% improvement in 5-year survival compared with patients who underwent surgery alone (Figure 5D). In contrast, the improvement in 5-year survival in patients with high-grade cancers who received adjuvant chemotherapy in the 1997 cohort was 13.5% better than the patients with high-grade cancers who did not receive it. The survival of patients with high-grade cancers who received adjuvant chemotherapy was still almost 3% lower than the survival of patients with low-grade cancers who did not receive it (Figure 5D). Thus, both grade and ethnicity influence survival and affect the efficacy of adjuvant chemotherapy while the 5-year survival of elderly patients is similar to younger age groups. Sex does not seem to influence survival in the cohorts presented in this series.

Independent Prognostic Factors

Because patient race/ethnicity and grade appear to be associated with survival, is it possible that stage or other factors contributed to this poor prognosis in specific subgroups? Greene et al[18] have shown previously that substage IIIC in the new 6th edition of the AJCC TNM staging system and grade have a worse prognosis than either IIIA-IIIB or low-grade cancers. A Cox proportional hazards analysis included demographic variables (race/ethnicity, age, sex), pathologic variables (histological grade, anatomic subsite, AJCC substage), and treatment variables (surgery, adjuvant chemo-

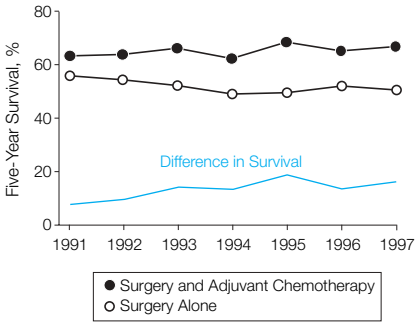
Figure 3. Percentage of Subgroups of Patients With Stage III Cancer Receiving Adjuvant Chemotherapy



A, The percentage of black patients with stage III colon cancer who received adjuvant chemotherapy was significantly lower than the percentage of whites in 1990-1991 and 1994-1995 ($P<.001$). This difference was no longer significant in 2001-2002. B, The percentage of women with stage III colon cancer who received adjuvant chemotherapy was significantly lower than the percentage of men in each period ($P<.001$). C, The percentage of patients 80 years or older with stage III colon cancer who received adjuvant chemotherapy was significantly lower than the percentage of patients younger than 60 years in each period ($P<.01$). *P* values were calculated by contingency table analysis with Bonferroni correction.

therapy) in the model. The significant independent cofactors identified were AJCC substage, the first course of therapy, the age of the patient, and the histological grade of the tumor but not race/ethnicity (TABLE 3). The 5-fluorouracil and leucovorin and 5-fluorouracil and levamisole treatments reduce the risk of death significantly (hazard ratio [HR], 0.64) while the risk of death is increased in substage IIIB (HR, 1.75) and IIIC (HR, 2.95) disease. Interestingly, blacks did not have an increased proportion of stage IIIC or high-grade lesions (data not shown). Similarly, patients 80 years or older tended to present less frequently with stage IIIC disease but more frequently with high-grade lesions (data not shown). Thus, the independent effect of age is similar to that of advanced substage, while high-grade cancers have a 40% increased risk of death from colon cancer.

Figure 4. Comparison of the 5-Year Relative Survival in Patients With Stage III Colon Cancer Treated by Surgery Alone vs Surgery and Adjuvant Chemotherapy



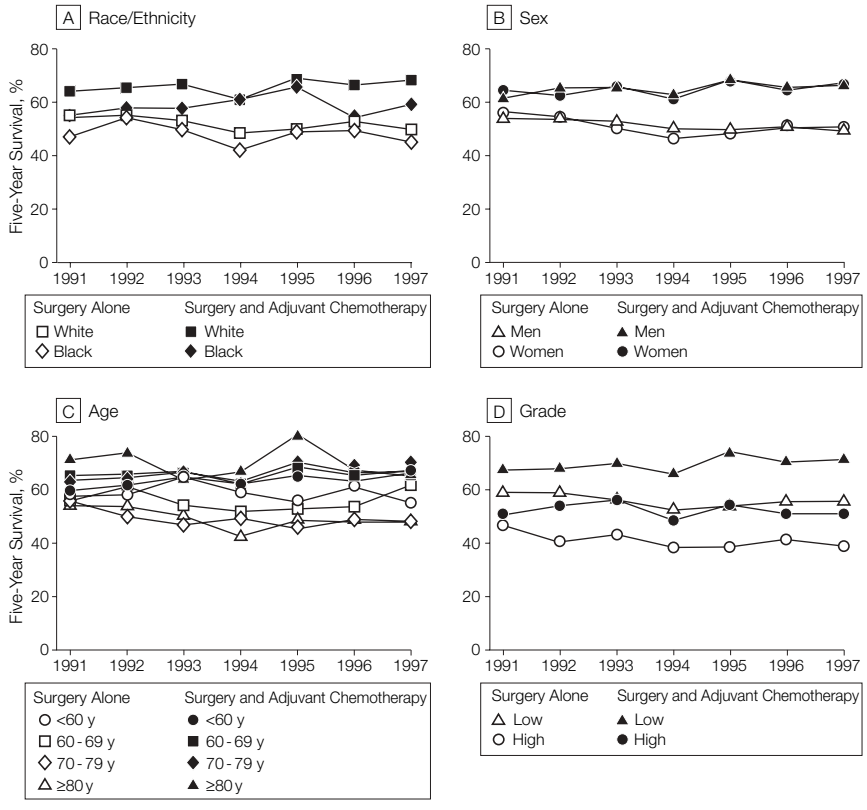
The relative 5-year survival of cohorts of patients treated from 1991 through 1997 is presented along with the difference in survival between the 2 groups.

COMMENT

The present data from the NCDB indicate that the 1990 NIH Consensus Conference on adjuvant therapy for colorectal cancer has had an impact on the usage of adjuvant chemotherapy in stage III colon cancer. Four years before the consensus conference less than 10% of eligible patients received adjuvant chemotherapy (data not shown). However, within 12 months of the conference more than a third of patients with stage III colon cancer received adjuvant chemotherapy. This pattern of use remained stable through the first half of the 1990s but then increased again when reports from prospective randomized clinical trials first demonstrated the efficacy of 5-fluorouracil and leucovorin regimens and especially then that 6 months of adjuvant 5-fluorouracil and leucovorin were as effective as 12 months of 5-fluorouracil and levamisole.[22,23] The original recommendation was based on the 2 randomized trials in which 12 months of 5-fluorouracil and levamisole improved the survival of patients with stage III colon cancer. Thus, the intent of the 1990 NIH Consensus Conference to translate information from prospective, randomized clinical trials to the community has been achieved. Since the use of adjuvant chemotherapy has continued to increase through the last cohort available for study, the recommendation is followed but a substantial fraction of patients are still not receiving adjuvant chemotherapy.

The exact regimen of adjuvant therapy, how much of the drug patients received, and the adverse effects cannot be assessed in the NCDB. Therefore, like the cooperative oncology group trials, the data are analyzed on an intention-to-treat basis and cannot assess whether patients received a full course of a particular adjuvant regimen. At the time of the NIH conference in 1990, the data suggested that 12 months of 5-fluorouracil and levamisole was the best regimen and produced approximately a 10% to 15% increase in overall survival at 5 years.[2,3] However, subsequent data[25] indicated that 6 months of 5-fluorouracil and levamisole provided a similar improvement in survival with fewer toxic effects and time for patients. Unfortunately, the NCDB does not currently contain information about which agents are used for chemotherapy in its core data set but may be able to do so in the future. In addition, analysis of NCDB data indicates that it

Figure 5. Interaction Between Select Clinical and Pathologic Variables and 5-Year Survival



is 98% accurate when it identifies patients receiving adjuvant therapy.[26] As reported by Schneider et al,[27] the NCDB does have a lag of at least 6 months before cases are abstracted and then another year and a half for data analysis and quality control. However, as also pointed out by Schneider et al, this is common to all registry data whether it be hospital- or population-based.

The present data suggest that patients with stage III colon cancer have a 16% benefit in relative survival compared with patients with stage III colon cancer who do not receive adjuvant therapy. This is important because further analysis suggests that the benefit occurs primarily in patients with well to moderately differentiated stage III colon cancer while the improvement in relative survival in higher grade stage III colon cancer is less (Figure 5). Also the improvement in survival appears to include both an improvement in survival associated with adjuvant chemotherapy as well as a decrease in the survival of patients who only receive surgery. The decrease in survival in the surgery-only group may result from redistribution of patients, such as the oldest subgroup who do not receive adjuvant chemotherapy whose survival is quite worse than that of younger subgroups that did not receive it. Gill et al[28] analyzed more than 3000 patients who were treated on randomized controlled trials for the efficacy of treatment in such demographic variables as age and sex as well as such clinicopathologic variables as T and N category, grade, and location. Adjuvant chemotherapy only provided a 1% improvement in 5-year overall survival in patients with high-grade lesions compared with surgery alone in patients with high-grade lesions while the benefit in low-grade lesions was greater with a difference of 9% associated with adjuvant chemotherapy. Thus, the effect of histological grade on therapeutic outcome may need to be further evaluated in other trials.

The NCDB is a hospital-based sample that reflects a wide range of race/ethnic, sex, and age diversity reflecting what occurs within the community. The data presented herein represent usage and practice in the community and are collected prospectively but are not randomized. These data represent an attempt to analyze the impact that randomized clinical trials have on community clinical practices through the NIH Consensus Conference mechanism. Therefore, these data are a large convenience sample that represents a large fraction of the underlying set of patients with stage III colon cancer. As a result, the analysis of these nonrandom patients can only be considered as a guide to interpretation of the trends in changing proportions of patients who receive and benefit from adjuvant chemotherapy.

Unfortunately, because comorbidity information is not available, there are no data on why subsets of patients did or did not receive adjuvant chemotherapy. The patients are older than the patients in cooperative group trials and age may have a large impact on patterns of treatment and survival outcome. We have previously shown that patients with colon[17] or rectal[19] cancer and who are older than 70 years are more frequently diagnosed at an earlier stage than younger patients, yet they have a worse stage-specific relative survival even using relative survival, which corrects for age-related mortality. The current data indicate that fewer patients older than 80 years who have stage III colon cancer receive adjuvant therapy—even though the survival of these older patients who receive adjuvant chemotherapy is similar to that of younger patients who also receive it.

Ayanian et al[29] examined the use of adjuvant therapy in a population-based study of patients treated between 1996 and 1997 in Northern California that included both stage III colon cancer as well as stage II and III rectal cancer. Patients older than 74 years with colon cancer also had reduced usage of adjuvant chemotherapy as did our cohorts. Because their study also described the use of adjuvant chemoradiotherapy for rectal cancer, the issues surrounding the lack of adjuvant therapy in elderly patients with colon cancer were somewhat limited but appeared to involve the presence of comorbid disease, patient refusal, and perhaps an inverse association between the use of adjuvant therapy and hospital size. Unfortunately, the NCDB data for our cohorts did not include information

Table 3. Significant Variables in a Cox Proportional Hazards Model of 43 126 Patients With Colon Carcinoma Diagnosed Between 1991 and 1997

Covariate	No. of Cases	Hazard Ratio (95% Confidence Interval)*	*P* Value
Cancer substage			
IIIA	4085	1	
IIIB	25 900	1.75 (1.65-1.87)	<.001
IIIC	13 123	2.95 (2.77-3.14)	<.001
First-course therapy			
Surgery alone	17 046	1	
Surgery and adjuvant chemotherapy†	18 403	0.64 (0.62-0.66)	<.001
Surgery and adjuvant chemotherapy BRM‡	5315	0.53 (0.50-0.56)	<.001
Other pharmaceutical treatment	2344	0.97 (0.92-1.03)	.34
Patient age, y			
<60	9027	1	
60-69	10 574	1.19 (1.14-1.25)	<.001
70-79	14 063	1.56 (1.49-1.62)	<.001
≥80	9444	2.24 (2.14-2.35)	<.001
Histological grade§			
Low	31 386	1	
High	11 740	1.41 (1.37-1.45)	<.001

Abbreviation: BRM, biological response modifier.
*The Cox proportional hazards model included all the demographic, clinicopathologic, and treatment variables described and then eliminated those in a forward step-wise manner that did not make a contribution at a significance level of .05 or less.
†5-Fluorouracil and leucovorin.
‡5-Fluorouracil and levamisole.
§Histological grade is defined as either *low*, well and moderately differentiated malignant tumors, or *high*, poorly and undifferentiated malignant tumors.

about the presence of comorbidities but neither did the data on which Ayanian et al based their analyses. Instead, they examined the perceptions of the treating physicians and surgeons who suggested that comorbidity was often a reason for not providing adjuvant chemotherapy to elderly patients with colon cancer. As Ayanian et al[29] suggested, more adjuvant chemotherapy could be given to this population.

Gill et al[28] commented that age did not adversely affect benefit from the treatment; however, their cutoff was age 60 years for their univariate analysis that was the age limit of the youngest cohort in the present study. Gill et al did establish a binning model that includes older patients and enables examination of the interaction between T and N category, as well as age with adjuvant chemotherapy. Sundararajan et al[30,31] and VanEenwyk et al[32] also found that patients older than 65 years with stage III colon cancer were significantly less likely through 1996 to receive adjuvant chemotherapy. Potosky et al[33] examined the use of adjuvant therapy in colon and rectal cancer in different Surveillance, Epidemiology, and End Results registries and found that in addition to disparities in the administration of adjuvant chemotherapy in stage III colon cancer for elderly patients there were similar disparities based on racial differences with blacks receiving it less often. Potosky et al[33] found that 88% of patients younger than 55 years, 65% of those between 55 and 74 years, and 41% of those 75 years and older received adjuvant chemotherapy, which is considerably higher than the oldest cohort in our community-based study although the divisions in age cohorts are somewhat different from ours. Nevertheless, it is clear that Potosky et al also demonstrate a decreased use of adjuvant chemotherapy in older patients and concluded that its use, even in older patients, may lead to improved survival. In a population-based study of stage III colon cancer patients treated between 1990 and 1996, Bouchardy et al[34] observed, as we did, that chemotherapy improved survival independent of age. Schrag et al[35] also studied the relationship between adjuvant chemotherapy usage and age in a large cohort of patients from population-based registries collected between 1991 and 1996 and found that its usage decreased dramatically in patients in their late 70s and 80s. Interestingly, Mahoney et al[36] attempted to define why elderly patients were less likely to receive adjuvant chemotherapy than younger patients and found that education of both patients and physicians would be appropriate to increase its usage in older patients.

A more recent review by Townsley et al[37] demonstrated that physicians were less likely to include elderly patients in trials than younger patients because they perceived that older patients required more time, effort, and expense to manage in trials than younger patients and that older patients were as interested in chemotherapy as younger patients but were not well educated about its potentials and risks. Our results confirm and extend theirs since we show that adjuvant chemotherapy usage decreases in the elderly and that those who receive it enjoy survival similar to that of younger patients. Although the expression of enzymes that metabolize commonly used agents may be altered in older patients and contribute to the toxic effects of agents, such as 5-fluorouracil,[38] and nearly half of the patients within the community are older than 79 years, any increase in the effective use of adjuvant chemotherapy may further enhance the survival of stage III colon cancer.

Race/ethnicity is another major factor for outcome in stage III colon cancer. Our data indicate that blacks received adjuvant chemotherapy less often than other ethnic groups in the early to mid 1990s but that disparity disappeared by 2002. Also the current data suggest that the 5-year relative survival is persistently lower in blacks than whites by at least 3% to 4% per cohort, despite their receipt of adjuvant chemotherapy. Dignam et al[39] studied the effect of race across National Surgical Adjuvant Breast and Bowel Project trials on survival and found that there was a significant decrement in survival for blacks compared with whites and that the decrease in overall survival was approximately 4% to 5%, which is similar to that observed in our study. Although Dignam et al argued that other factors may have contributed to this decreased survival, such as later diagnosis or comorbid disease, it is also possible that there are inherent genetic causes associated with ethnicity that may lead either to differences in response to adjuvant chemotherapy or the biological aggressiveness of colon cancer. For instance, certain polymorphisms in p53[40] and 5,10-methylenetetrahydrofolate reductase[41] are associated with race and may contribute to either resistance to a chemotherapeutic agent or to the biological aggressiveness of the cancer. In addition, racial differences may cause greater neutropenia and result in a decreased dose of chemotherapy.[42] However, McCollum et al[43] compared the survival of blacks treated in the randomized controlled Intergroup Trial 0089 to that of whites and found that there was no difference in survival based on race and, in fact, blacks had lower levels of toxic effects that were related to chemotherapy.

A criticism of this analysis is that race was not a stratification factor and when clinical variables were compared there were significant differences in several important variables between blacks and whites that may have contributed to the lack of any survival difference, particularly age, sex, location, and grade among others. Thus, although this prospective, randomized, controlled trial suggests that there is not a survival disadvantage for blacks, it must be interpreted with caution.

Also, it must be emphasized that the present data reflect patterns of care and survival in the community and are not the result of randomized, prospective trials. The NCDB data do not provide insight into why physicians may choose certain patients for therapy and not others. Because these patients were not randomized, selection bias is possible. It is likely that physicians recommend therapy based on a perceived balance between benefit and risk of the therapy as suggested by Sargent et al.[44] Thus, a relatively nontoxic therapy may be given to older patients more frequently than a

more toxic therapy. Unfortunately, the NCDB does not have the capacity to record specific agents, the dose, and schedule of chemotherapy received or the toxic effects experienced. Furthermore, the NCDB is an anonymized data set that does not contain personal identifiers. As a result, it is difficult to perform detailed analyses on randomly selected subsets of NCDB patients to define issues about how physicians recommend treatment.

In summary, 15 years after the NIH Consensus Conference, adjuvant chemotherapy use has increased to include nearly two thirds of patients with stage III colon cancer patients. Patients receiving adjuvant therapy for stage III colon cancer, especially low-grade cancer, have an increased survival benefit of 16%. The benefit of adjuvant chemotherapy seems to be lower in blacks and patients with high-grade cancers. Women have the same benefit but are less often treated. Elderly patients have the same benefit as younger patients but are also less frequently treated. Future studies are needed to identify whether newer agents such as irinotecan and oxaliplatin may be more effective in patients with high-grade cancers or in blacks than the 5-fluorouracil and leucovorin regimens that were dominant during the time that the cohorts reported herein were followed up for survival.

Author Contributions: Jessup 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: Jessup, Greene.
Acquisition of data: Jessup, Stewart.
Analysis and interpretation of data: Jessup, Stewart, Greene, Minsky.
Drafting of the manuscript: Jessup, Stewart, Greene, Minsky.
Critical revision of the manuscript for important intellectual content: Jessup, Stewart, Greene, Minsky.
Statistical analysis: Jessup, Stewart.
Administrative, technical, or material support: Stewart.
Study supervision: Jessup, Minsky.
Financial Disclosures: None reported.
Funding/Support: This study was supported in part by the American College of Surgeons and the American Cancer Society.
Role of the Sponsor: Mr Stewart is an employee of the American College of Surgeons and assisted with the collection, management, analysis, and initial interpretation of the data. In addition, the medical director of the cancer programs of the American College of Surgeons reviewed and approved the manuscript for submission.
Acknowledgment: We are grateful for the use of the National Cancer Data Base.

REFERENCES

1. NIH Consensus Conference. Adjuvant therapy for patients with colon and rectal cancer. *JAMA*. 1990;264:1444-1450.
2. Laurie JA, Moertel CG, Fleming TR, et al. Surgical adjuvant therapy of large-bowel carcinoma: an evaluation of levamisole and the combination of levamisole and fluorouracil. *J Clin Oncol*. 1989;7:1447-1456.
3. Moertel CG, Fleming TR, Macdonald JS, et al. Levamisole and fluorouracil for adjuvant therapy of recected colon carcinoma. *N Engl J Med*. 1990;322:352-358.
4. Menck HR, Cunningham MP, Jessup JM, et al. The growth and maturation of the National Cancer Data Base. *Cancer*. 1997;80:2296-2304.
5. Menck HR, Bland KI, Scott-Conner CEH, Eyre H, Murphy GP, Winchester DP. Regional diversity and breadth of the National Cancer Data Base. *Cancer*. 1998;83:2649-2658.
6. Fremgen AM, Bland KI, McGinnis LS, et al. Clinical highlights from the National Cancer Data Base, 1999. *CA Cancer J Clin*. 1999;49:145-158.
7. Gordon B, ed. *Data Exchange Standards and Record Description.* Sacramento, Calif: North American Association of Central Cancer Registries; 1994. *Standards for Cancer Registries*. Vol 1.
8. *Data Acquisition Manual.* Chicago, Ill: Commission on Cancer, American College of Surgeons; 1990.
9. *International Classification of Diseases for Oncology.* 2nd ed. Geneva, Switzerland: World Health Organization; 1992.
10. Greene FL, Page DL, Fleming ID, et al. *AJCC Cancer Staging Manual.* 6th ed. New York, NY: Springer; 2002:113-123.
11. Mettlin CJ, Menck HR, Winchester DP, Murphy GP. Comparison of breast, colorectal, lung, and prostate cancers in the National Cancer Data Base to the Surveillance, Epidemiology and End Results data. *Cancer*. 1997; 79:2052-2061.
12. Shambaugh E, Young JL, Zippin C, Lum D, Akers C, Weiss MA. *Statistics and Epidemiology for Cancer Registrars, Self-instructional Manual for Cancer Registrars, Book 7: Surveillance Epidemiology and End Results Program*. Bethesda, Md: National Institutes of Health; 1995.
13. Cox DR. Regression models and life tables (with discussion). *J R Stat Soc B*. 1972;34:187-220.
14. Statistical Abstract of the United States Web page. Table 22; 1996. Available at: http://www.census.gov/prod/www/statistical-abstract-us.html. Accessed February 4, 2005.
15. Steele GD. The National Cancer Data Base report on colorectal cancer. *Cancer*. 1994;74:1979-1989.
16. Beart RW, Steele GD, Menck HR, et al. Management and survival of patients with adenocarcinoma of the colon and rectum: a national survey of the Commission on Cancer. *J Am Coll Surg*. 1995;181:225-236.
17. Jessup JM, McGinnis LS, Steele GD, et al. The National Cancer Data Base Report on colon cancer. *Cancer*. 1996;78:918-926.
18. Greene FL, Stewart AK, Norton HJ. A new TNM staging strategy for node-positive (stage III) colon cancer: an analysis of 50,042 patients. *Ann Surg*. 2002;236:416-421.
19. Jessup JM, Stewart AK, Menck HR. The National Cancer Data Base report on patterns of care for adenocarcinoma of the rectum, 1985-95. *Cancer*. 1998;83:2408-2418.
20. Wolmark N, Rockette H, Fisher B, et al. The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer. *J Clin Oncol*. 1993;11:1879-1887.
21. Wolmark N, Rockette H, Mamounas EP, et al. The relative efficacy of 5FU + leucovorin (5-FU-LV), 5-FU + levamisole (LEV), and 5-FU+LV+LEV (5-FU-LV-LEV) in patients with Dukes' B and C carcinoma of the colon: first report of NSABP C-04. *Proc Am Soc Clin Oncol*. 1996;15:460.
22. Wolmark N, Rockette H, Mamounas E, et al. Clinical trial to assess the relative efficacy of fluorouracil and leucovorin, fluorouracil and levamisole, and fluorouracil, leucovorin, and levamisole in patients with Dukes' B and C carcinoma of the colon. *J Clin Oncol*. 1999;17:3553-3559.
23. Andre T, Colin P, Louvet C, et al. Semimonthly versus monthly regimen of fluorouracil and leucovorin administered for 24 or 36 weeks as adjuvant therapy in stage II and III colon cancer. *J Clin Oncol*. 2003;21:2896-2903.
24. Dayal H, Polissar L, Yang CY, Dahlberg S. Race, socioeconomic status, and other prognostic factors for survival from colo-rectal cancer. *J Chronic Dis*. 1987;40:857-864.
25. O'Connell MJ, Laurie JA, Kahn M, et al. Prospectively randomized trial of postoperative adjuvant chemotherapy in patients with high-risk colon cancer. *J Clin Oncol*. 1998;16:295-300.
26. Malin JL, Kahn KL, Adams J, et al. Validity of cancer registry data for measuring the quality of breast cancer care. *J Natl Cancer Inst*. 2002;94:835-844.
27. Schneider EC, Epstein AM, Malin JL, Kahn KL, Emanuel EJ. Developing a system to assess the quality of cancer care: ASCO's national initiative on cancer care quality. *J Clin Oncol*. 2004;22:2985-2991.
28. Gill S, Loprinzi CL, Sargent DJ, et al. Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III colon cancer. *J Clin Oncol*. 2004;22:1797-1806.
29. Ayanian JZ, Zaslavsky AM, Fuchs CS, et al. Use of adjuvant chemotherapy and radiation therapy for colorectal cancer in a population-based cohort. *J Clin Oncol*. 2003;21:1293-1300.
30. Sundararajan V, Mitra N, Jacobson JS, et al. Survival associated with 5-fluorouracil-based adjuvant chemotherapy among elderly patients with node-positive colon cancer. *Ann Intern Med*. 2002;136:349-357.
31. Sundararajan V, Grann VR, Jacobson JS, Ahsan H, Neugut AI. Variations in the use of adjuvant chemotherapy for node-positive colon cancer in the elderly. *Cancer J*. 2001;7:213-218.
32. VanEenwyk J, Campo JS, Ossiander EM. Socioeconomic and demographic disparities in treatment for carcinomas of the colon and rectum. *Cancer*. 2002;95:39-46.
33. Potosky AL, Harlan LC, Kaplan RS, Johnson KA, Lynch CF. Age, sex, and racial differences in the use of standard adjuvant therapy for colorectal cancer. *J Clin Oncol*. 2002;20:1192-1202.
34. Bouchardy C, Queneau PE, Fioretta G, et al. Adjuvant chemotherapy for colon carcinoma with positive lymph nodes. *Br J Cancer*. 2001;85:1251-1257.
35. Schrag D, Cramer LD, Bach PB, Begg CB. Age and adjuvant chemotherapy use after surgery for stage III colon cancer. *J Natl Cancer Inst*. 2001;93:850-857.
36. Mahoney T, Kuo YH, Topilow A, Davis JM. Stage III colon cancers: why adjuvant chemotherapy is not offered to elderly patients. *Arch Surg*. 2000;135:182-185.
37. Townsley CA, Selby R, Siu LL. Systematic review of barriers to the recruitment of older patients with cancer onto clinical trials. *J Clin Oncol*. 2005;23:3112-3124.
38. Milano G, Etienne MC, Pierrefite V, et al. Dihydropyrimidine dehydrogenase deficiency and fluorouracil-related toxicity. *Br J Cancer*. 1999;79:627-630.
39. Dignam JJ, Colangelo L, Tian W, et al. Outcomes among African-Americans and Caucasians in colon cancer adjuvant therapy trials. *J Natl Cancer Inst*. 1999;91:1933-1940.
40. Shepherd T, Tolbert D, Benedetti J, et al. Alterations in exon 4 of the p53 gene in gastric carcinoma. *Gastroenterology*. 2000;118:1039-1044.
41. Keku T, Millikan R, Worley K, et al. 5,10-Methylenetetrahydrofolate reductase codon 677 and 1298 polymorphisms and colon cancer in African Americans and whites. *Cancer Epidemiol Biomarkers Prev*. 2002;11:1611-1621.
42. Hershman D, Weinberg M, Rosner Z, et al. Ethnic neutropenia and treatment delay in African American women undergoing chemotherapy for early-stage breast cancer. *J Natl Cancer Inst*. 2003;95:1545-1548.
43. McCollum AD, Catalano PJ, Haller DG, et al. Outcomes and toxicity in African-American and Caucasian patients in a randomized adjuvant chemotherapy trial for colon cancer. *J Natl Cancer Inst*. 2002;94:1160-1167.
44. Sargent DJ, Goldberg RM, Jacobson SD, et al. A pooled analysis of adjuvant chemotherapy for resected colon cancer in elderly patients. *N Engl J Med*. 2001;345:1091-1097.