

Special Article

UNDERREPRESENTATION OF PATIENTS 65 YEARS OF AGE OR OLDER
IN CANCER-TREATMENT TRIALSLAURA F. HUTCHINS, M.D., JOSEPH M. UNGER, M.S., JOHN J. CROWLEY, PH.D., CHARLES A. COLTMAN, JR., M.D.,
AND KATHY S. ALBAIN, M.D.**ABSTRACT**

Background Studies have documented the underrepresentation of women and blacks in clinical trials, and their recruitment is now federally mandated. However, little is known about the level of participation of elderly patients. We determined the rates of enrollment of patients 65 years of age or older in trials of treatment for cancer.

Methods We analyzed data on 16,396 patients consecutively enrolled in 164 Southwest Oncology Group treatment trials between 1993 and 1996 according to sex, race (black or white), and age under 65 years or 65 or older. These rates were compared with the corresponding rates in the general population of patients with cancer, derived from the 1990 U.S. Census and from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program for the period from 1992 through 1994. Fifteen types of cancer were included in the analysis.

Results The overall proportions of women and blacks enrolled in Southwest Oncology Group trials were similar to or the same as the estimated proportions in the U.S. population of patients with cancer (women, 41 percent and 43 percent; blacks, 10 percent and 10 percent, respectively). In contrast, patients 65 years of age or older were underrepresented overall (25 percent vs. 63 percent, $P < 0.001$) and in trials involving all 15 types of cancer except lymphoma. The underrepresentation was particularly notable in trials of treatment for breast cancer (9 percent vs. 49 percent, $P < 0.001$). The findings were similar when data on patients who were 70 years of age or older were analyzed, when 15 trials that excluded older patients were eliminated from the analysis, and when community-based enrollment was analyzed separately from enrollment at academic centers.

Conclusions There is substantial underrepresentation of patients 65 years of age or older in studies of treatment for cancer. The reasons should be clarified, and policies adopted to correct this underrepresentation. (N Engl J Med 1999;341:2061-7.)

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IN the late 1980s and early 1990s, federal agencies established requirements that women and members of minority groups be adequately represented in clinical trials of treatment for cancer.¹⁻⁵ This mandate is crucial in oncology, because with many types of cancer, biologic, epidemiologic, prognostic, and outcome variables differ between the sexes, among racial groups, or both.⁶⁻¹¹ Moreover, the clinical applicability of the results of a treatment trial depends in large part on whether the sample of patients represents the entire spectrum of patients who have the type of cancer being studied.

For these reasons, investigators engaged in cooperative trials of cancer treatment sponsored by the National Cancer Institute have made concerted efforts to enroll women and members of minority groups.¹²⁻¹⁴ In contrast, the enrollment of patients 65 years of age or older has received little attention, despite the increasing number of older people in the population and the relatively high frequency of cancer, especially solid tumors, in this age group.^{2,15}

The Committee on Women and Special Populations of the Southwest Oncology Group (SWOG) analyzed the rates of enrollment of women, blacks, and patients 65 years of age or older, using the SWOG data base of consecutive cancer-treatment trials. These rates were compared with the estimated proportions of women, blacks, and persons 65 years of age or older in the U.S. population of patients with cancer.

METHODS**The SWOG Cohort**

The SWOG is a national cooperative group, funded by the National Cancer Institute, that conducts studies of treatment in adults with cancer. We analyzed data on all consecutive persons

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enrolled in SWOG treatment trials from 1993 through 1996. Enrollment data were examined for trials involving all major cancers (invasive disease only): cancer of the bladder, brain, breast, cervix, colon and rectum, head and neck, lung, ovary, pancreas, and prostate; lymphoma; melanoma; myeloma; leukemia; and soft-tissue sarcoma. For each type of cancer, the percentages of enrolled women, blacks, and patients 65 years of age or older were compared with the corresponding percentages in the U.S. population of patients with cancer. The number of trials restricted to premenopausal patients or to patients 65 years of age or younger or 70 years of age or younger was ascertained.

U.S. Population of Patients with Cancer

The numbers of patients with cancer in the U.S. population were estimated on the basis of 1990 U.S. Census data and data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program for the period from 1992 through 1994. Both sets of data represented the most recent information available at the time of the analysis. The nine SEER registry areas represented 9.5 percent of the U.S. population. Patients with *in situ* cancers were excluded.

A subgroup of interest was defined by each unique combination of age (in five-year intervals), sex, and designation as white or black. Three computations were performed for each type of cancer. First, the number of new cases of cancer in each subgroup of interest in the SEER area was divided by the population in that area for that subgroup (on the basis of the 1990 U.S. Census); the result of this calculation was the SEER incidence rate for each subgroup of interest. Second, the SEER incidence rate was multiplied by the total U.S. population for each subgroup of interest, yielding the estimated number of new cases of cancer nationally for that subgroup. Third, the national number of new cases of cancer for each subgroup of interest was divided by the total number of new cases of cancer; the result of this calculation was the estimated percentage corresponding to the subgroup (women, blacks, or patients 65 years of age or older) in the United States for each type of cancer.

Comparison of SWOG and National Rates

For analyses according to sex, enrollments of patients with cancers other than cancers of the breast, cervix, ovary, and prostate were included. Patients enrolled at military or Department of Veterans Affairs centers were compared with patients enrolled at all other centers to determine differences in the rates of enrollment of women. The military or Department of Veterans Affairs affiliation of each patient was determined on the basis of the method of payment for health care, information that since 1993 has been required at the time of enrollment. Therefore, the SWOG enrollment period from 1993 through 1996 was chosen as the period closest to the most recent SEER data (1992 through 1994).

The proportions of women, blacks, and patients 65 years of age or older in the SWOG data base and in the U.S. population of patients with cancer were compared for each type of cancer. The subgroup of blacks was chosen as the largest potentially underserved population. The age of 65 years was chosen as the cutoff point for the primary analysis because it is the age at which people become eligible for Medicare. Enrollment of patients 70 years of age or older was also analyzed.

SWOG enrollment rates according to age were analyzed according to whether enrollment was conducted at large, urban academic centers or community-based practices. The latter included both Community Clinical Oncology Programs (community services designated and funded by the National Cancer Institute) and Cooperative Group Outreach Programs (community-based networks of physicians affiliated with member institutions). To determine whether community-based practices were more or less likely than urban academic centers to enroll patients 65 years of age or older, rates of enrollment of older patients in community-based practices were compared with the corresponding rates for their urban academic counterparts.

TABLE 1. ENROLLMENT OF WOMEN, BLACKS, AND ELDERLY PATIENTS IN SOUTHWEST ONCOLOGY GROUP TREATMENT TRIALS FROM 1993 THROUGH 1996, ACCORDING TO THE TYPE OR SITE OF CANCER.

TYPE OR SITE OF CANCER	TOTAL ENROLLMENT	WOMEN*	BLACKS	ELDERLY (≥65 YR)
Bladder	277	58 (24)	17 (6)	154 (56)
Brain	604	269 (46)	45 (7)	113 (19)
Breast	5122	5122 (100)	505 (10)	486 (9)
Cervical	289	289 (100)	50 (17)	21 (7)
Colorectal	2047	817 (43)	170 (8)	829 (40)
Head and neck	388	71 (26)	83 (21)	93 (24)
Leukemia	1127	471 (44)	118 (10)	304 (27)
Lung	1627	524 (39)	215 (13)	638 (39)
Lymphoma	1380	517 (40)	101 (7)	197 (14)
Melanoma	1113	440 (41)	8 (1)	247 (22)
Myeloma	930	387 (45)	139 (15)	236 (25)
Ovarian	428	428 (100)	17 (4)	130 (30)
Pancreatic	85	41 (51)	9 (11)	32 (38)
Prostate	886	0	185 (21)	570 (64)
Soft-tissue sarcoma	93	42 (48)	12 (13)	27 (29)

*The numbers and percentages of women are based on enrollments at institutions without military or Department of Veterans Affairs affiliations (see the Methods section).

Statistical Analysis

The rates of cancer in the U.S. population were considered to be fixed in the comparisons with SWOG enrollment rates. One-sample binomial tests were used to compare the rates. To adjust for multiple comparisons, only two-tailed P values of 0.01 or less (rather than the standard 0.05) were considered to indicate statistical significance.

RESULTS

Table 1 shows the numbers of patients enrolled in SWOG treatment trials during the period from 1993 through 1996, according to the type of cancer. Overall, 16,396 patients were enrolled in 164 studies. Forty-one percent of the patients who did not have sex-specific cancers and who were enrolled at sites without military or Department of Veterans Affairs affiliations were women, 10 percent of all patients were black, and 25 percent of all patients were 65 years of age or older.

Enrollment of Women

A total of 9671 patients were enrolled in trials that did not involve sex-specific cancers, such as breast and prostate cancer. For every type of cancer, the proportion of women at military or Department of Veterans Affairs centers was substantially smaller than the proportion of women at other centers, as would be expected on the basis of the demographic characteristics of patients at military or Department of Veterans Affairs medical facilities (data not shown). Thus, 838 patients who were enrolled at these centers were

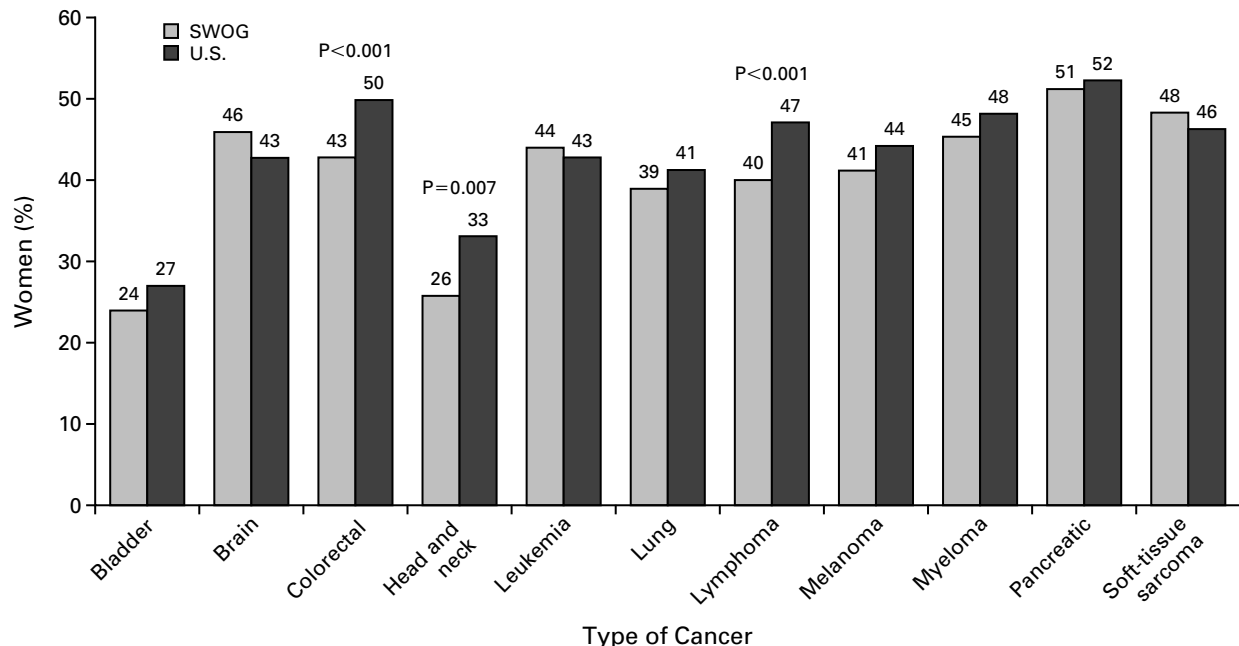


Figure 1. Proportion of Women Enrolled in Trials of the Southwest Oncology Group (SWOG) as Compared with the Proportion of Women in the U.S. Population of Patients with Cancer, According to the Type of Cancer.

All patients with sex-specific cancers and all patients enrolled at centers with military or Department of Veterans Affairs affiliations were excluded from the analysis according to sex.

excluded from all analyses according to sex (since they constituted a unique cohort with respect to the enrollment of women), for a total of 8833 patients.

The overall enrollment rate for women in the SWOG trials (41 percent) was similar to the proportion of women in the U.S. population of patients with cancer (43 percent). Figure 1 shows the proportions of women enrolled in SWOG trials and the proportions of women in the U.S. population of patients with cancer for 11 types of cancer. Differences between the two groups were significant only for colorectal cancer ($P<0.001$), head and neck cancer ($P=0.007$), and lymphoma ($P<0.001$), with a difference of only 7 percentage points for each type.

Enrollment of Blacks

All types of cancer and all types of treatment facilities were included in analyses of the enrollment of black patients. They represented 10 percent of the patients enrolled in SWOG trials, which is the same as the proportion of blacks in the U.S. population of patients with cancer. Figure 2 compares the enrollment of black patients in SWOG trials with the proportion of blacks in the U.S. population of patients with cancer for 15 types of cancer. Blacks were significantly underenrolled only in trials of treatment for lymphoma ($P<0.001$) and ovarian cancer ($P=0.002$), a difference of only 4 percentage points for each type. Conversely, black patients were significantly overrep-

resented in SWOG trials of treatment for head and neck cancer ($P<0.001$), leukemia ($P=0.001$), and prostate cancer ($P<0.001$).

Enrollment of Older Patients

All types of cancer and all types of treatment facilities were included in the analyses according to age. Overall, patients who were 65 years of age or older accounted for 25 percent of patients in SWOG trials, as compared with 63 percent in the U.S. population of patients with cancer ($P<0.001$). When the age cutoff was set at 70 years, the proportions of patients enrolled in SWOG trials and those in the U.S. population of patients with cancer were 13 percent and 47 percent, respectively ($P<0.001$). Thus, the proportions of patients who were 65 to 69 years old were 12 percent in the SWOG trials and 16 percent in the U.S. population of patients with cancer ($P<0.001$). These figures indicate that patients who were 70 years of age or older accounted for much of the shortfall in enrollment but not all of it.

The percentage of patients 65 years of age or older who were enrolled in the SWOG trials was significantly less than the percentage of such patients in the U.S. population of patients with cancer ($P<0.001$) for all types of cancer except lymphoma (Fig. 3). The difference persisted when the analysis was restricted to the 2127 patients who were 70 years of age or older (data not shown) and was unrelated to the type

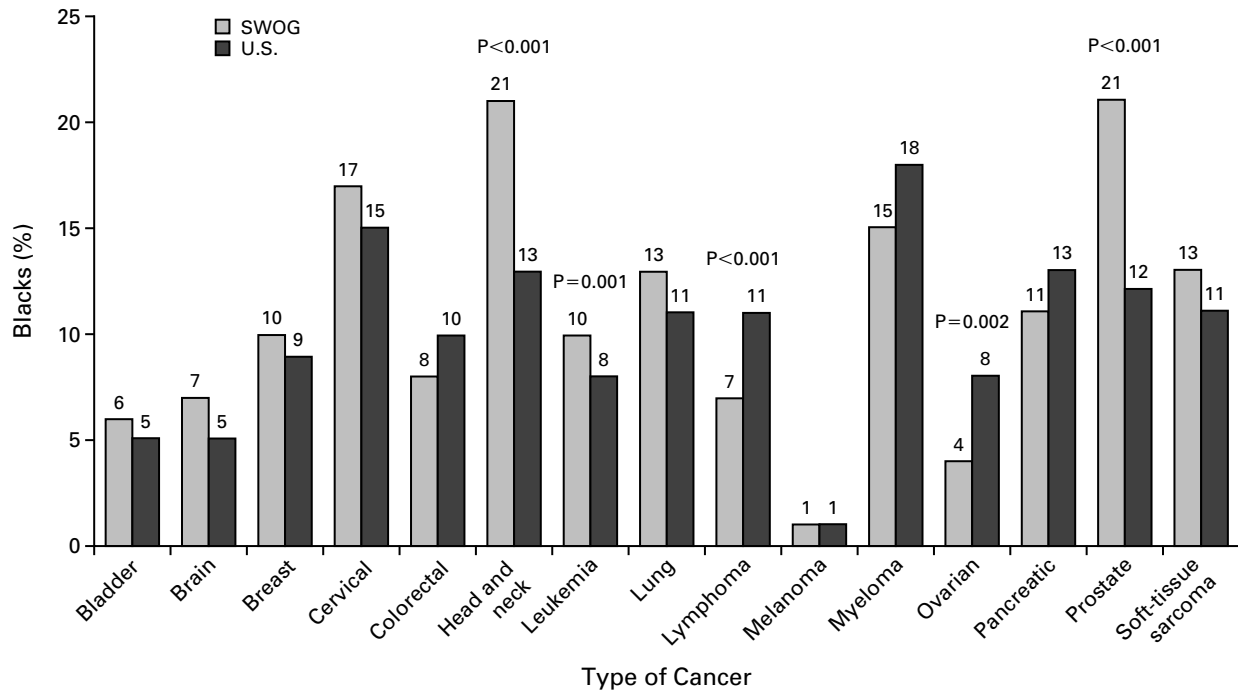


Figure 2. Proportion of Blacks Enrolled in Trials of the Southwest Oncology Group (SWOG) as Compared with the Proportion of Blacks in the U.S. Population of Patients with Cancer, According to the Type of Cancer.

of oncologic practice (patients in community-based practices, 27 percent; patients at urban academic centers, 22 percent).

Thirteen studies conducted by SWOG (involving 819 patients, or 5 percent of the total number) were restricted to patients who were 65 years old or younger or to women who were premenopausal, and 15 trials (involving 1043 patients, or 6 percent) were restricted to patients who were 70 years old or younger or to women who were premenopausal. With these studies excluded, the overall rate of enrollment of patients 65 years old or older was 27 percent (as compared with 25 percent for all the studies), and for patients who were 70 years old or older, the overall enrollment rate was 14 percent (as compared with 13 percent for all the studies). The SWOG enrollment rate for elderly patients with breast cancer changed from 9 percent to 10 percent when the 293 patients enrolled in trials restricted to premenopausal patients or to patients 65 years old or younger were excluded.

DISCUSSION

We found that the enrollment rates for women and blacks in SWOG trials of cancer treatment were similar to the proportions of women and blacks in the U.S. population of patients with cancer. In contrast, the enrollment rate for patients 65 years of age or older was unexpectedly low. Underenrollment of elderly patients was particularly striking in trials of

treatment for breast cancer, even after the exclusion of trials restricted to premenopausal women or to patients who were 65 years old or younger. In the U.S. population of patients with cancer, 49 percent of breast cancers occurred in patients who were 65 years old or older, whereas only 9 percent of patients enrolled in SWOG-sponsored studies of breast cancer were 65 or older.

Some studies have found age-related differences in the pharmacologic characteristics and toxicity of chemotherapeutic drugs in patients with breast cancer, whereas others have not.¹⁶⁻¹⁹ The results of two retrospective analyses of clinical trials involving patients with solid tumors suggest that older age does not diminish tolerance of or response to chemotherapy.^{20,21} These findings raise questions that can be answered definitively only by the prospective enrollment of larger numbers of elderly patients in clinical trials.

A representative sample of adults of all ages is necessary in phase 2 studies that assess the toxicity and pharmacologic properties of chemotherapeutic drugs. This policy has been inconsistently implemented in trials of new agents approved for the treatment of common solid tumors. Adequate enrollment of older patients is also required in phase 3 trials, especially because of the potential interactions between age and toxicity and because age is often an independent prognostic variable.

Why are the rates of enrollment of elderly patients

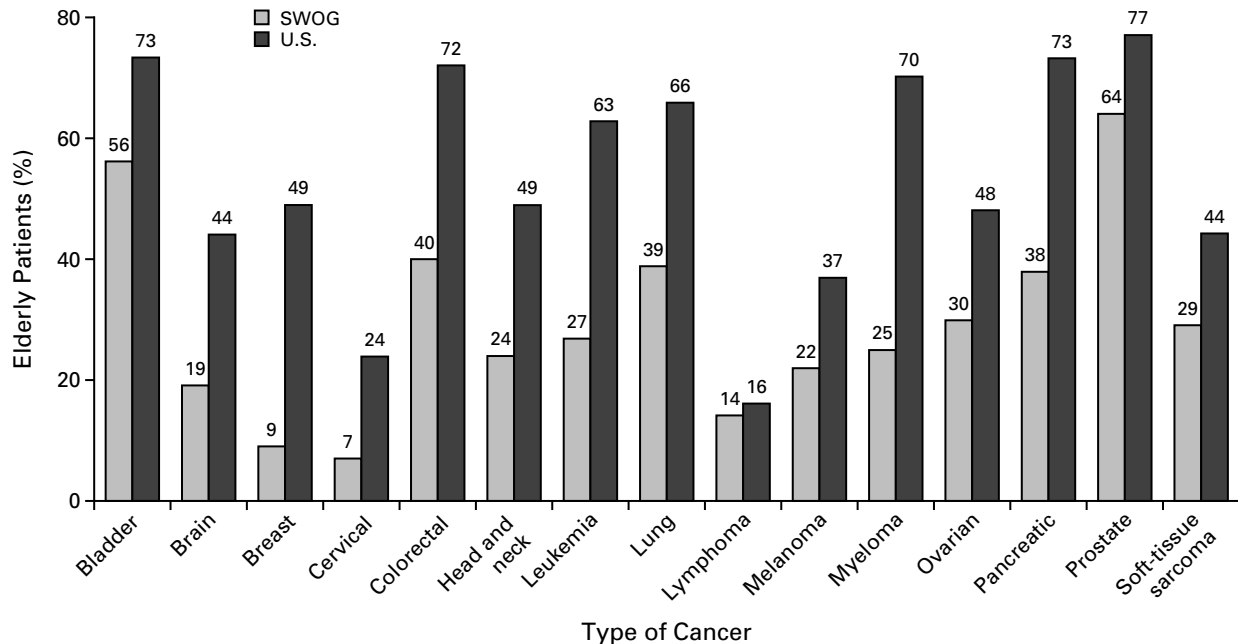


Figure 3. Proportion of Elderly Patients (65 Years of Age or Older) in Trials of the Southwest Oncology Group (SWOG) as Compared with the Proportion of Elderly Patients in the U.S. Population of Patients with Cancer, According to the Type of Cancer. The differences between the two groups were significant ($P < 0.001$) for all types of cancer except lymphoma.

in trials of treatment for cancer disproportionately low? The reasons include misconceptions about the benefits of enrollment in clinical trials for older patients on the part of the patients themselves, their family members, or their physicians; stringent eligibility criteria; coexisting medical conditions; and logistic barriers.^{14,15,22}

Clinicians and patients and their families may assume that older patients with cancer are not likely to tolerate or benefit from treatment in clinical trials. They may consider these studies too “experimental” or the treatments too toxic or otherwise inappropriate for older patients.^{22,23} In a survey of American oncologists, 80 percent of the respondents agreed with published data showing that patients have better outcomes when they receive treatment in clinical trials, but 50 percent indicated that they declare patients unsuitable for clinical trials on the basis of age alone.²²

There are few data supporting the notion that fit older patients cannot tolerate or benefit from treatment in clinical trials, especially studies that test standard drugs for common solid tumors. Most clinical trials do not enroll enough older patients to permit an analysis of treatment and outcome end points in this age group. However, the first cooperative group studies designed specifically for older patients have recently been completed.^{24,25} Other, ongoing trials are analyzing toxicity, pharmacologic factors, and outcomes in subgroups of older patients.

Data from studies of leukemia in older patients

highlight the importance of designing studies specifically for elderly patients with cancer. Older patients with leukemia do not tolerate intensive treatment well and have poor outcomes,²⁶⁻²⁸ often because of coexisting medical conditions and age-related end-organ or immune dysfunction. Recent studies show that the poor outcome in older patients with leukemia is also related to specific biologic characteristics: a high frequency of unfavorable cytogenetic factors, increased expression of the MDR1 protein, and functional efflux of chemotherapeutic drugs from the leukemic cells.²⁹ Cooperative groups are now conducting trials designed to modulate these biologic abnormalities in older patients with leukemia. Similar studies are needed to determine whether there are age-related biologic characteristics of common solid tumors.

Stringent eligibility criteria that prevent the enrollment of many patients in clinical trials are important safeguards against excessive treatment-related morbidity and mortality. Older patients often do not meet the eligibility criteria because of organ impairment or coexisting medical conditions. These conditions may increase the risk of excessive treatment-related toxicity, thus influencing the results of the trial.³⁰ Because of these stringent restrictions, little is known about whether older patients with normal age-related organ impairment or those with coexisting diseases that may not interact with the treatment under study can tolerate the treatment and benefit from it.³¹

The accessibility of medical care is particularly im-

portant in the case of older patients with cancer. Since transportation costs are not covered by Medicare, traveling to the study site may be an insurmountable barrier. Such logistical factors may also influence physicians' decisions about recommending participation in clinical trials.¹⁹ Financial barriers to participation in trials of cancer treatment may be greater for older patients than for younger patients. Medicare does not provide reimbursement for most of the outpatient prescription drugs needed to control the side effects of chemotherapy. Clinical trials are often considered experimental by Medicare, and billing for investigational treatments is not permitted. However, these financial barriers are not the only explanation for the underrepresentation of older patients. The National Cancer Institute of Canada Clinical Trials Group reported a markedly decreased rate of enrollment of older patients in Canadian trials of cancer treatment, even though the Canadian national health program provides reimbursement for all health care costs, including those associated with participation in a clinical trial.³²

Our retrospective analysis is limited in providing reasons for the low rate of enrollment of older patients. The SWOG data base does not contain data for all patients referred to each institution; it contains data only for enrolled patients. For this reason, the low rate of enrollment of patients 65 years of age or older may be due to a low rate of enrollment of older patients at each center or to a low rate of referral of older patients to the center. Our analysis can eliminate two explanations: study-imposed age restrictions (because overall rates increased only slightly when trials with upper-age restrictions were excluded from the analysis) and the type of center (since older patients were underrepresented at both urban academic centers and community-based practices).

Our findings have implications for federal policies concerning clinical trials. By 2030, the number of persons in the United States over the age of 65 years will have doubled, and the number of persons over the age of 85 years will have quadrupled. Because of the relatively high risk of cancer in these populations, we predict a high prevalence of cases of cancer in older members of the U.S. population in the future. It may not be premature to implement prospective trials in order to determine why the rates of enrollment of elderly patients in cancer trials are low, to study and modulate the biologic features of cancer in older patients, and to design therapy for otherwise fit older patients with cancer.

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