Clinical Trial Enrollment of Rural Patients with Cancer

**PURPOSE:** The goal of this study was to examine the effect of a rural community clinical oncology program-based cancer-care intervention program that was launched to increase the number of rural patients with cancer enrolled in clinical trials.

**DESCRIPTION OF STUDY:** Five rural counties in eastern North Carolina served as intervention communities, and five rural counties in South Carolina served as the comparison region. The intervention counties used a rapid tumor-reporting system, a nurse facilitator who identified and prompted oncologists to enter patients into clinical trials, a quarterly newsletter to primary-care physicians about cancer treatment and clinical trials, and a health educator who focused on community-wide education regarding cancer prevention, treatment, and clinical trial information. Outcomes included changes in knowledge and attitudes about clinical trials among the primary-care providers who were surveyed and enrollment in clinical treatment trials for breast and colorectal cancer, as analyzed by comparing practice pattern data from before and after the intervention.

**RESULTS:** The results indicate that the intervention was not effective. The proportion of primary-care physicians who were aware of clinical trials for their patients with cancer rose slightly in comparison counties (26% to 34%) but remained constant (41% to 43%) in intervention counties. Perceived patient and actual physician barriers toward clinical trial participation were reported by the physicians. A minority of potentially eligible patients with breast or colon cancer in both North Carolina and South Carolina were enrolled in clinical trials.

**CLINICAL IMPLICATIONS:** These data suggest that different types of interventions may be needed to improve accrual to cancer treatment trials in rural communities. In addition, the role that primary-care providers play in encouraging patients with cancer to participate in clinical treatment trials needs further exploration.

**KEY TERMS:** Breast cancer; Cancer treatment; Clinical trials; Colorectal cancer; Recruitment

Vast improvements have been made in the treatment of cancer over the last several decades. These advancements are due mainly to clinical trials that test the effectiveness of new treatment regimens and agents. The proportion of patients with cancer who participate in clinical treatment trials, however, represents only 3% to 5% of those who have received diagnoses of cancer. In 1983, the National Cancer Institute (NCI) established the Community Clinical Oncology Program (CCOP) with the idea of extending specialized cancer care to communities at a distance.
from tertiary-care centers and research institutions, to allow community-based physicians to enter patients into clinical trials.\textsuperscript{3–5} A major focus of the CCOP initiative was to improve cancer care and participation in clinical trials among patients in rural areas.\textsuperscript{5}

The problem of differential access to cancer care for rural versus urban populations has been recognized widely. Studies have identified differences in disease stage at diagnosis, with rural patients with cancer receiving diagnoses significantly later than urban patients with cancer.\textsuperscript{6–8} This finding has been replicated over time, despite there being little conclusive evidence that there are consistent mortality differences between urban and rural areas for all cancers.\textsuperscript{9} There have been analyses of the differences in the management of cancer between urban and rural areas,\textsuperscript{9–11} and studies comparing the attitudes of clinicians toward cancer care.\textsuperscript{12–14} The general conclusions of the literature are that rural areas lack adequate access to cancer-care services and that there are potential, if not real, negative effects on the health of rural persons. To address this, various programs that attempted to reach out to rural communities and link rural providers with more sophisticated and effective services were developed and fielded in rural areas.\textsuperscript{9,15,16} These outreach programs often attempted to bring “state-of-the-art” care to the outlying communities and to involve rural clinicians and patients in clinical trials or to treat patients according to the most recent NCI recommendations.\textsuperscript{9} Despite the generally positive outcomes of the CCOP and case studies of rural cancer outreach programs involving hospitals, nursing center interventions, or lay health-worker involvement, there is no clear evidence that these programs significantly changed either public or provider behavior in a comprehensive fashion to improve overall cancer care.

The viewpoints of both primary-care and referring physicians are of importance in ensuring that patients with cancer receive adequate care, due to the integral role they play in the access to cancer control and treatment services.\textsuperscript{17–19} First, they are responsible for providing cancer prevention and early detection services, such as smoking cessation counseling, clinical breast examinations, and Pap smears.\textsuperscript{9,15,17} When primary-care physicians actually provide the services, they often determine when a patient should be referred for screening, and they participate in the interpretation of the results.\textsuperscript{15} When a malignancy is suspected or detected, the primary-care physician may even have substantial influence over diagnostic procedures, enrollment in clinical trials, and other treatment decisions through his or her referrals to surgeons, oncologists, and other specialists.\textsuperscript{13,15} In rural areas, the influence of the primary-care doctor may be even more significant.\textsuperscript{15}

In 1992, the NCI funded a series of projects intended to improve rural cancer care. One of these projects, Reaching Communities for Cancer Care (REACH), which was conducted in rural North Carolina and South Carolina, was an intervention program aimed at improving state-of-the-art cancer diagnosis and management in rural areas and at increasing the number of rural patients with cancer who are enrolled in cancer clinical trials. This article reports on the knowledge and attitudes of rural primary-care physicians regarding cancer clinical trials and accrual to clinical treatment trials among rural patients with cancer.

### Methods

#### Overview of Reaching Communities for Cancer Care Program

The REACH intervention took place in Wayne County, NC, and its five contiguous counties. Greenwood County, SC, and five adjacent counties served as the comparison region and did not receive any intervention components. Both areas had active CCOP physicians. The study began in 1992 and was completed in 1998. The REACH project intervention components, conducted from 1993 through 1996, included the following:

- The installation of a rapid tumor-reporting system in the intervention area to improve the quality of data about rural patients with cancer and to expedite the process at which the state cancer registry obtained this information;
- A nurse facilitator who was responsible for alerting physicians about clinical trials that might be appropriate for their patients;
- A quarterly newsletter mailed to physicians regarding cancer treatment and clinical trials;
- A health educator who provided community-based education about cancer screening and treatment and who also trained lay health educators in the intervention communities.

The evaluation focused on before-and-after comparisons of change in primary-care physician knowledge, beliefs, and cancer-care practice patterns between the intervention and the comparison communities. These data were obtained from surveys of primary-care physicians and hospital record data. The study design can be classified as a nonequivalent groups design with separate, but not independent, preintervention and postintervention samples. The REACH study was reviewed by the Institutional Review Board at the Wake Forest University School of Medicine. Informed consent was obtained from all participants before the surveys were administered.

#### Data Collection

The physician survey was used to assess knowledge, attitudes, and reported practices among primary-care physicians regarding cancer treatment, prevention, control, and knowledge and attitudes related to clinical trials. The survey was administered to primary-care physicians in the intervention and comparison regions at the outset of the project (1993; n = 196) and 3 years later (1996; n = 168), allowing preintervention and postintervention comparisons of physician survey responses.

The survey instrument was based upon the 1989-to-1990 National Physician Survey that was used in the NCI CCOP-II evaluation, which was conducted by the University of Illinois Survey Research Laboratory and the Cecil G. Sheps Center for Health Services Research at the University of North Carolina at Chapel Hill.\textsuperscript{5} Physicians were queried regarding their attitudes toward cancer clinical trials, the
degree to which they participate or encourage patient participation in clinical trials, and their familiarity with clinical trials. Those respondents who were aware of clinical trials were asked about their sources of information about clinical trials and about their experience in referring or enrolling patients in clinical trials. Questions were added to the 1996 survey to explore physician-related and patient-related factors that might inhibit clinical trial enrollment.

Preintervention and postintervention surveys were administered in both the intervention and comparison areas. The sample consisted of all community primary-care physicians in active practice. These included family physicians, general practitioners, internists, gynecologists, obstetrician/gynecologists, dermatologists, and general surgeons. Names, addresses, and specialties of active physicians were obtained from the North Carolina Medical Board and the South Carolina Office of Budget and Control, which maintains an inventory of physicians in that state.

In 1993, the survey instrument was initially mailed to all the physicians included in the sampling frame. The follow-up consisted of three rounds of phone calls and subsequent mailings to nonresponders. In 1996, three rounds of mailings and two rounds of follow-up phone calls were completed. In place of a third round of phone calls, reminders were sent by facsimile to those physicians for whom fax numbers were released by the practices. Additionally, the physician serving as co-principal investigator on the project attempted to contact directly those physicians in the NC sample who had failed to respond to the survey. Treatment data from patient medical records, which were collected at the outset of the study and 5 years later, were intended to address several questions, including the assessment of cancer patients’ clinical trial participation. A practice pattern analysis was used for the main analyses. The results of these analyses have been published elsewhere.20,21

Analysis

The results were analyzed using computer software (SAS, version 6.0 for Windows, SAS Institute, Cary, NC). Univariate statistics were computed, with frequencies computed for all categorical variables and means calculated for continuous variables. Cross-tabulations were calculated to test for significant differences in frequencies across different levels of control variables and for the stratification levels of state and year. The comparisons of differences between states were accomplished using chi-square tests of differences in values for 1996 and 1993 within each state.

Results

Physician Survey

In the 1993 survey, 196 of 388 primary-care physicians responded (response rate 51%), and 168 of 380 primary-care physicians responded in 1996 (response rate 44%). Because the response rate for the physician survey was lower than anticipated, a special analysis was completed to compare responders with nonresponders in the 1996 Physician Survey. This was done using supplementary data provided by the North Carolina Health Professions Data System, which includes the complete listing of all licensed physicians in North Carolina. The group of responders was similar to the population of physicians according to several measures, including specialty distribution, gender, race, average age, average years in practice, and having had experience treating a cancer case in the past year. This comparison indicates that the respondents in the two areas are representative of all primary-care physicians in those areas.

Table 1 indicates that respondents were primarily men in both states and both periods, with an average age slightly higher in the NC sample. In both years, the proportion of respondents in solo practice was greater in North Carolina, with South Carolina seeing a marked decline in solo practitioners between the two periods. The proportion of NC respondents who were members of a medical school teaching or clinical facility doubled during the time period, reaching 28% in 1996. That proportion increased between the two periods only slightly in South Carolina, reaching 18%. A quarter of SC respondents in both periods reported being a preceptor in a residency training program, while that proportion in North Carolina rose to only 13% in 1996. The majority of respondents in the 1993 survey were in single-specialty practices with fee-for-service payment structures. This question was not asked in the 1996 survey. Managed-care penetration was minimal in both states and in both periods. In North Carolina and South Carolina, the proportion of respondents participating in cancer research or in professional or volunteer associations rose slightly between the two periods, while the proportion of respondents who had completed oncology-related continuing medical education (CME) courses or seminars in the preceding two periods approximately doubled. In 1996, only 24% of the responding family practitioners and 32% of internists had received oncology-related CME, but 74% (14/19) of the surgeons had completed such training in the previous 2 years.

Physicians who had treated a patient who had received a diagnosis of cancer were asked whether they were aware of any formal clinical trials that were applicable to those patients. As shown in Figure 1, the proportion of respondents who were aware of such trials rose from 26% to 34% in South Carolina, while holding steady (41% to 43%) in North Carolina. There was a significant association between participation in oncology-related CME and familiarity with clinical trials that were relevant to one’s patients among the 1996 respondents. While only 22% of respondents who had not received CME were familiar with research studies, 58% of respondents who had received CME were familiar with trials that were applicable to their patients ($P < .05$). Between 1993 and 1996, the proportion of respondents who had had at least one patient with cancer in the past year referred or enrolled in a clinical trial significantly increased from 8% to 25% in North Carolina but increased only from 4% to 11% in South Carolina ($P < .05$ [North Carolina vs South Carolina]).

The 1996 survey examined the factors that might inhibit enrollment in clinical trials. First, physicians were asked about their perceptions of patient concerns that
might inhibit them from enrolling in clinical trials. Figure 2 shows the proportion of respondents considering each factor to be “strongly influential” in inhibiting patients’ enrollment in clinical trials. The most widely recognized barriers were patients’ unwillingness or inability to travel outside their communities for care, followed closely by their lack of knowledge about clinical trials. More SC respondents than NC respondents indicated that concerns over traveling outside one’s community were “strongly influential” in inhibiting patients from enrolling in clinical trials. About one third of respondents in both states considered the following factors to be strongly influential in inhibiting clinical trial enrollment from the patient perspective: distrust toward investigational medicine; concern about increased discomfort or prolonged suffering; and concern about the cost of care or insurance coverage. Only about 20% of respondents believed that patient resistance to being treated by an unfamiliar physician was a strongly influential barrier. Similar proportions (48% versus 61%) of respondents felt that problems associated with travel to the clinic to participate in the clinical trial and patient lack of knowledge about clinical trials were significant barriers to participation.

Survey participants also were asked about concerns that might prevent physicians from enrolling patients in clinical trials. These results (Fig 3) indicate that just over one third of respondents in both states reported that two factors—high treatment risks with uncertain benefits and excessive logistical burden for a busy practice—were strongly influential in inhibiting the enrollment of patients into clinical trials. More than one third of SC respondents also identified two other factors as being strongly influential: the likely financial costs to the patients; and well-
established referral patterns to physicians who do not participate in clinical trials. Significantly more respondents in South Carolina than North Carolina (36% vs 20%, respectively) stated that physicians’ concerns over the likely costs to patients is “influential” in inhibiting clinical trial enrollment \((P = .028)\). Sixty percent of NC respondents and 57% of SC respondents indicated that the low probability of patient eligibility was somewhat influential in inhibiting enrollment (data not shown). Only 10% of NC respondents and 17% of SC respondents viewed the high treatment risks with uncertain benefits as “not a factor” in keeping physicians from discussing clinical trial enrollment with their patients (data not shown).

**Clinical Trial Enrollment**

**Breast Cancer.** Medical record data were obtained on 486 breast cancer cases for the practice patterns analysis. Substantially more cases in the practice patterns data came from North Carolina than South Carolina in both 1991 and 1996 \((P < .001)\). In both locations, the majority of patients with breast cancer in both years were White (75% in 1991; and 74% in 1996). The balance of the patients with breast cancer in both years were African American. Most patients with breast cancer in both years were married (60%). Approximately 5% of women in both time periods had no health insurance. The remaining 95% had some form of health insurance, which was most commonly Medicare (almost 50% of women in both years). The overall mean age of patients with breast cancer was 66 years (range: 29–100), and the mean age was 68 years in 1991 and 62 years in 1996. The majority of patients were not enrolled in clinical trials, in either 1991 or 1996. Overall, 24 (15%) breast cancer patients from North Carolina in 1991 had been enrolled in a clinical trial, while 6 (6%) breast cancer patients from South Carolina had been enrolled. During 1996, 14 (6%) breast cancer patients were enrolled in a clinical trial in
North Carolina and 16 (50%) were enrolled in a clinical trial in South Carolina.

Colorectal Cancer. There were 228 colorectal cancer cases in 1991 and 128 in 1996 in North Carolina and South Carolina. Of the total of 343 colorectal cancers that were staged, 9% (n = 31) were stage 0, 27% (n = 91) were stage I, 25% (n = 85) were stage II, 27% (n = 93) were stage III, and 13% (n = 45) were stage IV. More than half of colorectal cancer cases in both years were men, 55% in 1991 and 58% in 1996. White patients comprised the majority of cases of colorectal cancer, with 75% of the cases in both years falling into this group. The remainder of the patients were African American. Most of the patients had some form of health insurance (92%), which most often was Medicare. The mean age of patients with colon cancer was 75 years in 1991 (range 30–102) and 71 years in 1996 (range 31–97). Clinical trial enrollment of colon cancer patients was low in both states over both years. In 1991, 5% of colorectal cancer patients in South Carolina were enrolled in clinical trials, compared with 4% of cases in North Carolina. In 1996, no colorectal cancer patients in South Carolina were enrolled in clinical trials, compared with 4% of cases in North Carolina. In 1996, no colorectal cancer patients in South Carolina were enrolled in clinical trials, but 5% of patients in North Carolina were enrolled.

Discussion and Clinical Implications

The overall goal of the REACH study was to test the effect of a multicomponent community-based intervention on improving enrollment into clinical trials among patients with cancer in rural communities. In this study, which is one of the few to be conducted in a rural setting, oncology offices, primary-care physicians, patients with cancer, and the public were targeted to receive components of the intervention program. The evaluation of the program used data from surveys of primary-care physicians and clinical trial enrollment rates. According to physician self-reports, there was a greater increase in the proportion of physicians in North Carolina who had referred or enrolled at least one patient with cancer into a clinical trial compared with South Carolina respondents. A slightly greater proportion of SC respondents reported that potential participant barriers were "strongly influential" in inhibiting clinical trial enrollment, compared with NC respondents. Clinical trial enrollment data indicated that no clear patterns of improvement in clinical trial participation in either state were evident.

The rates of enrollment into clinical treatment trials did not improve significantly in the intervention communities. It is important to remember that in South Carolina in 1996, incomplete data on all breast cancer cases were obtained, thus necessitating caution in making any comparisons across time in South Carolina. Other limitations of the study include the low response rate for the physician survey, potentially affecting the generalizability of the results, and the inability to prevent contamination in the comparison region. The results also suggest that the intervention itself was not targeted toward specifically improving clinical trial enrollment.

Although these rates may seem low, nationally only 2% to 3% of patients with cancer are enrolled in clinical trials. In the past, the reasons for low enrollment in clinical treatment trials have been categorized as patient issues, provider issues, or protocol issues, which is similar to what the physicians in this study reported. Patient (or participant issues) include economic barriers such as the following: 1) access to trial information, physicians who offer trials, and insurance carriers who will cover treatments; and 2) costs of participation in terms of risk, expenses of examinations, transportation, time lost from work, childcare or eldercare versus the rewards for participation (including examinations, incentives, and monitoring of health). Personal and cultural barriers also have been identified for individual participation in clinical trials. These include the following: 1) problems with consent forms (too long, complicated language, or only available in English); 2) unknown benefits of trial participation for the individual or the community; 3) lack of interest in the clinical reasons for the study; 4) access to the clinical center (e.g., scheduling or transportation problems); 5) lack of ownership of the study (relevance of

Figure 3 Physicians indicating that the selected physician factor is strongly influential in inhibiting clinical trial enrollment. Significantly more respondents in South Carolina than in North Carolina responded that the cost to patients was strongly influential in inhibiting clinical trial enrollment (P = .028).
the disease under study to the community; 6) no personal relationship with the physician; and 7) the time commitment required for study participation and follow-up. Many lay persons do not understand clinical trials, and randomization is often a difficult concept to grasp. In general, there has been little or no history of clinical trial results that have been made available to the general population, and images of “guinea pigs” still exist due to reports of previously conducted studies (such as Tuskegee) or experiences with persons who die of cancer, rather than are cured of cancer.

In contrast, the reasons that trial participants give for joining studies include: 1) a desire to help others, including their own family members; 2) access to “free” medical care; 3) trust in community spokespersons; 4) interaction with a medical team that has similar beliefs; and 5) some sort of compensation for participation, whether tangible (money or gifts) or intangible (study results). These factors can be used to motivate participation, however, in the present study, these factors were not mentioned.

Provider (ie, physician, nurse, or recruitment team) barriers to recruiting patients to clinical trials include the following: 1) perceptions of lack of trust of participants, the community, or referring physicians; 2) time constraints that limit the ability to explain the study, answer questions, or get to know the participant; 3) lack of appropriate resources, for example, staff, space, incentives, or community outreach; 4) inadequate knowledge about the community or the people in the community; 5) bias in terms of selecting who would be a “better” trial participant; and 6) trial design criteria (eg, too complicated or excessive eligibility criteria). Trial design barriers consist of the following: 1) study design features (eg, exclusion criteria, questionnaires, and consent forms); 2) recruitment issues, especially without adequate funding to implement a variety of strategies; 3) operational issues, including the implementation of study procedures and communication; and 4) dissemination strategies (eg, trial results). This issue could be especially relevant to this study as the number of cardiovascular disease is decreasing while more patients are receiving diagnoses at earlier stages.

Provider barriers can be reduced by using reminders to discuss studies (eg, chart reminders, posters, and brochures), allowing adequate time to discuss the study with potential participants, and having flexibility in clinic locations and scheduling. Trial design barriers can be addressed by developing more protocols for a variety of cancers, using less restrictive eligibility criteria and easily read consent forms/questionnaires, providing additional funding for recruitment, and sharing “results” with participants and the community. Some, but not all, of these interventions were included in the REACH program.

The REACH project, one of the few rural cancer care studies, provides a unique assessment of both primary-care physician knowledge and attitudes toward cancer care, and actual cancer treatment patterns. Therefore, the clinical implications of the research are significant, particularly for future research focused on highly innovative interventions with, and for, providers. For instance, the results indicate that accrual rates to clinical treatment trials among rural populations were low and were unaffected by the interventions implemented. In addition, information from rural providers about barriers to participation did not differ from the barriers reported in other studies conducted among nonrural populations. Thus, future studies that examine other types of interventions, including the implementation of community-based, multifaceted, small-scale models, to improve accrual to clinical treatment trials are needed. Second, ways to assess accrual rates accurately need to be explored. Efforts in this area, paired with a commitment to the community in terms of time, relationship building, and funding are essential to improve clinical trial participation among all segments of the population and ultimately to deliver state-of-the-art cancer care to all patients with cancer.

References

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