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Significant numbers of breast cancer patients will experience a recurrence of their disease. Breast cancer recurrence is a time of enormous crisis, with significant distress, depression, and symptomatology, and few effective coping strategies. Targeted support services are currently unavailable.

This study tests the hypothesis that patients experience greater well-being by participating in an intervention designed for breast cancer patients experiencing a first recurrence. Following pilot study phase, 300 breast cancer patients will be enrolled within 6 weeks post-recurrence. All participants are Southwest Oncology Group (SWOG) institutions. The women will be randomly assigned to a control group or an intervention to be carried out by Y-Me, a national breast cancer support and advocacy organization. The intervention consists of 4 to 8 structures sessions providing information and peer support delivered by breast cancer survivors via telephone over a 4 week period. Endpoints are assessed at baseline and 3 and 6 months later through validated quality of life and depression questionnaires.

This study provides information about improving well-being during a little studied portion of the breast cancer trajectory. The intervention is delivered by individuals who are well-qualified to provide support: women who themselves have experienced breast cancer recurrence. The project utilizes a cost-effective approach with the potential for widescale dissemination.

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Enhancing Well-Being During Breast Cancer Recurrence

INTRODUCTION

A. Subject and Purpose of the Research

This project uses a two phase implementation process to determine whether patients will experience greater levels of well-being as a function of participating in an intervention designed for breast cancer patients experiencing a first recurrence.

A Pilot Study was conducted in selected Southwest Oncology Group institutions to: refine intervention protocol materials; develop operating procedures to ensure coordination and communication between the Principal Investigator, Southwest Oncology Group Operations Office, the Study Coordinator, the Southwest Oncology Group Statistical Center, Y-ME, and the institutions accruing patients; develop a training program for the breast cancer survivors who will provide the intervention; finalize assessment questionnaires and examine length and ease of administration by telephone, especially with respect to burden for institution staff; and examine participation and attrition.

The Main Study is currently open to all Southwest Oncology Group institutions. A randomized, two group design is used to evaluate the impact of a telephone intervention delivered by breast cancer survivors on well-being in patients experiencing a first recurrence of breast cancer versus written information. The primary objective of the main study is: to assess the effectiveness of a telephone intervention delivered by breast cancer survivors on well-being in patients experiencing a first recurrence of breast cancer versus written information delivered by mail.

The secondary research objectives of the full trial are: to examine the impact of sociodemographic, clinical, and psychosocial predictors of well-being in patients experiencing a first recurrence of breast cancer; and to examine changes in well-being over time since recurrence.

B. Background of Previous Work

<u>The Psychosocial Impact of Breast Cancer Recurrence</u>

Despite significant increases in five-year breast cancer survival rates, mortality curves for these patients have remained largely unchanged for many years. While many breast cancer patients, especially women diagnosed with Stage I disease, can realistically expect to be cured of their disease, significant numbers of patients will experience a recurrence of their breast cancer at some point following diagnosis, treatment, or a disease-free period. Although this statistic is not generally emphasized, when all stages of breast cancer are considered, as many as 50% of patients will experience recurrence.

Recurrence marks a significant change in the breast cancer care continuum, since it brings home the limits of current knowledge in oncology. The cancer care team must acknowledge that the treatment did not work: that all of the optimism, faith in medicine, and careful compliance with treatment were not enough to forestall disease progression. The patient and family may question whether all of the suffering that they have gone through was really worth it, and they may have a sense of failure: not only about treatment, but about themselves. They must deal with a new reality: that the patient is experiencing pain and other symptoms of her recurrence, that chances for cure have been reduced, and that once again, treatment decisions need to be made.

What is a woman's experience when the worst happens – that is, when breast cancer returns? Surprisingly, very little attention has been given to this issue in the literature: only nine studies have been reported about recurrence of any cancer during the past 15 years (1). We do know that the patients identify the threat of recurrence as one of the most feared possible outcomes of cancer. The fear of recurrence repeatedly emerges as an important psychosocial theme in breast cancer patients who are newly-diagnosed (2, 3), attending follow-up visits (4), and among long-term survivors (5).

The largest study based on data from patients actually experiencing a recurrence is Worden's cross-sectional study of 102 individuals with recurrences of various cancers (6, 7). Worden found that distress levels of the patients with recurrence were high and equivalent to levels in newly-diagnosed patients. Compared to newly-diagnosed patients, the individuals in this study were less willing to participate in interventions focused solely on psychosocial counseling and more concerned about their medical problems and existential concerns. Among the factors that predicted higher distress were more symptoms, lack of social support, less hope, and being younger. Cella, Mahon, and colleagues (8, 9) also assessed adjustment in 40 patients within one month of recurrence; the patients represented a variety of cancer sites, and 27 were experiencing a first recurrence. Patients in this study experienced high levels of distress: they "almost universally agree that recurrence is more upsetting than initial diagnosis" (8, p. 20). There was a suggestion that having anticipated the possibility of recurrence aided adjustment: patients who reported that they were "completely surprised" by the recurrence fared the worst.

Several studies have focused on breast cancer recurrence. Silberfarb et al. (10) compared psychosocial status in groups of breast cancer patients during initial diagnosis (N=50), first recurrence (N=52), and metastatic disease (N=44). The findings indicated that the stage of first recurrence clearly was the most emotionally stressful time in their samples (10, p. 454). Significantly, only one woman out of the 52 could identify a single coping strategy she had found helpful, in marked contrast to the other two groups. In addition, the findings of this study illustrate how recurrence is often marked by physical impairment as well: 81% of the women in the recurrence group reported pain, the highest percentage of any group. Jenkins et al. (11) evaluated 22 women with newly-diagnosed breast cancer recurrence, and found that 45% experienced depression and anxiety at the level of psychiatric diagnosis; previous psychiatric illness was a significant predictor of recurrence distress. A recent study by Lewis and Deal (1) further described problems in 15 married couples in which the wife was diagnosed with a recurrence of breast cancer. A number of problems in marital adjustment were reported, as well as depression experienced by 40% of the women; the recurrence had been diagnosed a median of 10 months previously, indicating the long-lasting psychosocial impact of breast cancer recurrence and the potential that intervention could provide a real benefit for these patients.

Interventions to Reduce Psychosocial Distress

No intervention directed at the needs of patients experiencing a recurrence of breast cancer (or any other cancer) has been reported. However, several reviews (12-14), including a recent meta-analysis (15), have concluded that psychosocial interventions have a positive impact on the well-being of patients across the spectrum of disease stages and sites. To date, research has not established whether one kind of intervention is more effective than another, or more appropriate for certain patients. A variety of intervention types (e.g., informational, psychological, behavioral, social support) and formats (e.g., group, individual, telephone) have demonstrated beneficial effects. Effects have been demonstrated for quality of life, symptom management, and psychological functioning. The optimal point to evaluate the impact of psychosocial interventions has not been firmly established; most studies assess outcomes at one or more intervals during the first year post-intervention (12-14), although impacts may be long-lasting, even extending to ultimate survival (e.g., 16).

This study draws on an approach which has been found effective by a number of investigators: a brief, time-limited intervention combining information and support delivered by telephone. The telephone is

frequently used in providing information regarding cancer treatment and counseling (17-22). In particular, the telephone may make services available to individuals for whom traveling would pose difficulties because of geography, health, or access to transportation. The telephone-directed intervention approach is especially well-suited to the Southwest Oncology Group setting, given the potential of providing standardized assessment across participating institutions at a relatively low cost. Other cooperative groups, including the Eastern Cooperative Oncology Group and the Cancer and Leukemia Group B, are currently conducting research protocols utilizing telephone-delivered interventions, although no other group has focused on patients with recurrence. In fact, patients with recurrence appear to have recourse to few specialized resources; although resource and support programs frequently offer assistance to newly diagnosed patients, hospice patients, and (increasingly) to survivors, patients going through a recurrence seem to "fall between the cracks."

The Use of Lay Organizations to Provide Support to Breast Cancer Patients

The intervention will be provided by women who are particularly well-qualified to provide support and information: breast cancer survivors who have themselves experienced recurrence. A distinctive feature of this study is its delivery of the intervention through an established national breast cancer advocacy and support organization, Y-ME. Although Y-ME has provided telephone hotline services (using a toll-free 800 number) since 1987, the impact of the service has not been systematically assessed. This is also true for other lay programs for breast cancer patients, such as the American Cancer Society's Reach-to-Recovery program (23). This study will utilize breast cancer survivors within the context of a structured protocol, as well as standardized and validated outcome measures. If the program proves effective, it can become part of Y-ME's program and be delivered on a standard basis. The use of a voluntary organization staffed with non-health professionals represents a cost-effective approach to providing support. Y-ME has participated in a Southwest Oncology Group Lay Advisors/Advocates Steering Committee for the past two years. The lay advisors (who include representatives of national organizations and volunteers selected through a nationwide search) are special members of the Group, serve as members of Disease and other Committees (including the Committee on Women and Special Populations and the Breast Cancer Committee), and attend semi-annual Group meetings. The lay advisors contributed to the development and design of this protocol.

This study will provide information about how to improve well-being during a portion of the breast cancer trajectory where little attention has been focused. The project utilizes a cost-effective approach to intervention with demonstrated usefulness in cancer patients. The intervention will be delivered by individuals who are especially well-qualified to provide support: women who themselves have experienced breast cancer recurrence. This project represents one of the first formal research collaborations between a clinical cooperative research group and a lay breast cancer organization. The project reflects the overriding motivation of both groups: to provide the best possible care and support to cancer patients.

BODY

A. Experimental Methods

Overview

The Pilot Study involved 30 women meeting the eligibility criteria who all participated in the intervention and completed the outcome assessment questionnaires. The Main Study utilizes a two arm randomized design with repeated measures at three time points. Three hundred breast cancer patients commence participation following a first recurrence of breast cancer. At that time, the participants complete a battery of instruments, including baseline measures of well-being. Participants are stratified by age (< 50 years vs. ≥ 50 years), time since diagnosis (< 2 years vs. ≥ 2 years), and recurrence site (soft tissue/bone vs.

visceral) and randomly assigned to intervention group (intervention vs. control). Participants in the intervention group complete an intervention completed within a four-week period; the intervention will cover four discrete content areas and will be carried out in four to eight telephone calls. Assessments of well-being are collected at approximately three months post-baseline, and again 6 months post-baseline. The primary outcome is well-being, including quality of life (as measured by the Cancer Rehabilitation Evaluation System-Short Form (CARES-SF) [24-30]) and depression (as measured by the Center for Epidemiologic Studies-Depression scale (CES-D) [31-32]).

Eligibility Criteria

Eligibility criteria include: having received definitive surgical treatment for Stage I, II, or IIIa breast cancer and being diagnosed with a first recurrence of breast cancer in the past 42 days (pilot study) or 56 days (main study); being female; no current psychiatric diagnosis affecting ability to participate in the intervention; ability to read and understand English. In the first eight months the pilot study was open, patients must have had no previous enrollment or plans to enroll on a Southwest Oncology Group treatment protocol; this restriction was eliminated for the last portion of the pilot study and for the main study. All patients must complete baseline questionnaires to participate. Institutional Review Board approval must have been received prior to patient registration.

Procedures

Pilot Study: All women completed baseline questionnaires and received a questionnaire packet to complete and return by mail in six weeks. All women were provided with a basic information packet including a copy of the Y-ME booklet "I Still Buy Green Bananas" and a list of agencies which provide cancer-related information. All participating institutions compiled materials about resources available in their catchment area. Project staff compiled information on national organizations such as Y-ME, the Cancer Information Service (1-800-4-CANCER), and the American Cancer Society as part of the information packet. All women in the pilot study received the four session telephone intervention from Y-ME peer counselors.

Main Study: All women complete the baseline questionnaires and are provided with basic information (as above). Women in the *control group* receive no additional intervention. They are mailed self-administered assessment questionnaires to complete 3 months and 6 months later. After completing the final assessment, they are given the same packet of materials provided earlier to the women in the intervention group. Patients in the *intervention group* are provided with an intervention consisting of four to eight counseling/information sessions delivered by Y-ME counselors by telephone over a one-month period.

A standardized intervention protocol is used, and calls should require no longer than 45 minutes to complete. Each call focuses on different problem areas from the group below. The modules reflect psychosocial, physical, and existential concerns. Each woman is given a choice about the order in which the sessions are presented. Each call provides basic information and the opportunity for the patients to discuss individual concerns. The general format is to provide information in specified areas, active listening when the women discuss their concerns, assistance in problem-solving, and information about resources that may be helpful.

The intervention is not designed to provide psychotherapy. Instead, the Y-ME peer counselors provide information, peer support, and referrals to community organizations. Procedures currently in place at Y-ME are used if serious psychological disturbance is detected during a telephone session. In such cases, patients are asked if the Y-ME peer counselor can contact the Southwest Oncology Group physician who enrolled her on the study. Following the first session, the patients are sent a packet of written materials.

Study Endpoints

The primary endpoint in this study is well-being (CARES-SF psychosocial functioning and depression) three months post-enrollment in the study. A CARES-SF Psychosocial score of .615 or greater will designate impaired psychosocial functioning. This cut-off has been found to correctly classify breast cancer patients "at risk" for psychosocial distress, as identified in a comprehensive clinical interview by a social worker; the estimated probability of classifying women in the high risk group was .81 in a recursive partitioning model (30). Depression will be indicated by a score of 16 or above on the Center for Epidemiological Studies – Depression (CES-D) scale (31-32).

Longer-term well-being will also be examined at 6 months post-study entry. The intervention will also be evaluated through a standardized "Telephone Counseling Evaluation Form." A "Psychosocial Predictors Form" will be used to examine possible predictors of well-being. These include: social support (measured by Reynolds et al.'s four-item scale [33]); optimism-pessimism (measured using the total score on the Life Orientation Test (LOT) [34-35]); surprisingness of the recurrence (8); and, Sense of Coherence Scale (SOC) (36-38). A "Current Cancer Treatment" form will ascertain treatments being received at baseline, 3 and 6 months.

Analysis

Anticipated total accrual for the Pilot Study was 30 patients. Sample size for the Main Study is 300 patients, with 255 patients expected to be available at the three-month assessment point. Power calculations indicate that a sample size of 255 is sufficient to test intervention vs. control group differences for the two primary endpoints (CARES-SF Psychosocial cutoff score and CES-D cut-off score); with a power of .90 and a one-tailed alpha-level of .025, the study will be able to detect differences in proportions of women who score "at risk" of 20% between the intervention and control groups. Secondary analyses will utilize logistic and least squares regression analyses.

B. Results/Progress to Date

Current Status. The protocol for the pilot study was activated by the Southwest Oncology Group on June 1, 1997. The target sample size of 30 patients was reached in July 1998. The Main Study opened Group-wide on July 15, 1998 for activation by all Southwest Oncology Group institutions. The first patient was accrued to the protocol in September 1998. As of June 21, 2001, 225 patients had been entered on the study. Accrual has been steady over the 2001 calendar year. The accrual has been stable at approximately 7-10 per month for the past year.

During the past year, the following activities have been completed:

1. Recruitment and training of additional peer counselors (Y-ME) (due to disease progression and death in one of the original counselors, and desire to take a break from counseling by another counselor).

2. Continuation of continuing education and provision of feedback and reinforcement for Y-ME peer counselors by Dr. Taylor and Ms. Perotti.

3. Periodic communications from Dr. Gotay to the Project Team, Principal Investigators and Data Managers at participating institutions to encourage their participation, and communicate new information. The Southwest Oncology Group Operations Office has set up a listserve to enable communication with all institutions that have activated the study to facilitate regular e-mail messages.

4. As Study Coordinator, Dr. Gotay continues to respond to numerous telephone calls and e-mails regarding eligibility and other aspects of the protocol. These calls have come primarily from individuals at Southwest Oncology Group institutions and women across the country who learn about the study from the Y-ME newsletter or internet home page, where the study is listed. It is somewhat surprising that some institutions are still activating the study; Dr. Gotay answered questions posed by an institutional Institutional Review Board evaluating the study for initial approval in June 2001.

5. Regular communications were maintained between Dr. Gotay and the Project Team (including the Southwest Oncology Group Statistical Center, Southwest Oncology Group Operations Office, Y-ME, and the consultants). Monthly telephone conferences are scheduled between Dr. Taylor at Y-ME, and weekly or more frequent e-mail or telephone communication with the Southwest Oncology Group Statistical Center (Drs. Green and Moinpour).

6. Two project group meetings were held in conjunction with Southwest Oncology Group meetings in New Orleans, LA (October 2000) and San Francisco, CA (April 2001).

7. Presentations about the study were made at the October 2000 and April 2001 Breast Cancer Committee and Cancer Control Research Committee Meetings (C. Gotay).

8. The Southwest Oncology Group Statistical Center has continued to send reminders to let institutional personnel know about upcoming questionnaire completion dates for women registered at their institutions. This information is computer-generated and is transmitted to each institution on a monthly basis in the same way as is done for treatment studies.

9. The Southwest Oncology Group Statistical Center continues to analyze numbers of cases of missing questionnaires (either baseline, 3 month, or 6 months) by institution. There are few missing questionnaires overall.

10. Dr. Gotay and her staff continue to send mailed materials to institutions who have women who are in the control condition. The institutions distribute these materials to the women after they complete their final questionnaires. They also send materials to women who inquire about the study but do not meet eligibility criteria. These breast cancer survivors seem to appreciate receiving the materials a great deal.

11. Drs. Gotay and Moinpour developed a form to abstract data from the counselor's notes to provide an indication of "intensity of the intervention." This form tracks the number of calls, number of minutes, and module areas covered during the counselor telephone calls. This information will be abstracted from the counselor logs and added to the database.

12. A manuscript entitled "Behavioral science research in the cooperative group setting: the Southwest Oncology Group experience" was published in October 2000 (Gotay, CC, Moinpour, CM, Moody-Thomas, S, Gritz, ER, Albain, KS, DeAntoni, E, Hansen, L, Ganz, PA. (2000). *Journal of the National Cancer Institute92*:1381-7). It includes discussion of this project and the support of the Department of Defense is acknowledged.

13. Dr. Gotay and the research team are preparing a manuscript based on the baseline data from study participants.

KEY RESEARCH ACCOMPLISHMENTS

None, the project is not completed.

REPORTABLE OUTCOMES

A copy of the paper, "Behavioral science research in the cooperative group setting: the Southwest Oncology Group experience," is appended.

CONCLUSIONS

After a slower-than-expected start, the protocol continues to accrue at a steady rate. There is considerable enthusiasm for the research in the Group among behavioral scientists and clinicians alike, and women participating in the protocol have been highly supportive. Continued vigilance is needed to keep the protocol salient in the minds of physicians, nurses, and data managers so that referrals will be maintained until study completion. Dr. Gotay and the project team will maintain efforts at publicizing the study, providing communications with Southwest Oncology Group institutions, and making presentations at the Group meetings to ensure that the study continues to have a high profile within the Group. We recognize that sustained effort is needed to make certain that this study meets its accrual goals. Since there are still no studies elsewhere in the country that we are aware of addressing the needs of this population of breast cancer patients, we are convinced that our project will make a significant contribution when it is completed.

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APPENDIX

Behavioral science research in the cooperative group setting: the Southwest Oncology Group experience. CC Gotay, CM Moinpour, S Moody-Thomas, ER Gritz, KS Albain, E DeAntoni, L Hansen, PA Ganz. Journal of the National Cancer Institute 92(17):1381-1387, 2000.

COMMENTARY

Behavioral Science Research in the Cooperative Group Setting: the Southwest Oncology Group Experience

Carolyn Cook Gotay, Carol M. Moinpour, Sarah Moody-Thomas, Ellen R. Gritz, Kathy S. Albain, Edward DeAntoni, Lisa Hansen, Patricia A. Ganz

Background

Cancer prevention, detection, treatment, and continuing care require individuals to behave in specified ways, whether abstaining from certain behaviors (e.g., sun exposure) or adopting others (e.g., following recommendations for state-of-the-art treatment). Thus, behavior is one of the keys to controlling cancer. Much progress in cancer control has stemmed from behavioral research and interventions. For example, reductions in tobacco use are largely responsible for lower rates of lung cancer *(1)*, and increased use of mammography has led to decreases in breast cancer mortality *(2)*. Moreover, a recent meta-analysis of psychosocial interventions in adult cancer patients *(3)* concluded that such interventions have a positive effect on emotional, physical, and social outcomes. According to Dr. Richard Klausner *(4)*, Director of the National Cancer Institute (NCI), Bethesda, MD, "behavioral research is fundamental to the mission of [NCI] and the broader social goal of reducing cancer incidence, morbidity, and mortality."

Clinical cooperative groups represent a rich potential resource to promote and support behavioral research in cancer. Each year, more than 20 000 new patients participate in cooperative group clinical trials, most of which test cancer therapies, that are conducted under the auspices of the NCI's Division of Cancer Therapy and Diagnosis. In addition, most cooperative groups also sponsor behavioral research studies, although this emphasis is relatively new.

In this commentary, we illustrate the distinct contributions and challenges that behavioral studies pose within the cooperative group setting, drawing on our experiences over the past 10 years as members of the Southwest Oncology Group (SWOG).

Behavioral Research in the SWOG

Outcome Assessment Research

The first formalized behavioral science research activities in the SWOG focused on developing methods for outcome assessment: specifically, incorporating quality-of-life (QOL) end points within clinical trials of cancer therapy. The SWOG has provided an ideal environment for examining QOL outcomes in the context of cancer treatment for several reasons: QOL data can be collected at the same time and location that treatment is provided, QOL data can be obtained by the same personnel who collect treatment data, and most QOL data have been based on self-administered questionnaires for which administration does not greatly interfere with other clinic activities. QOL assessment within clinical trials also provides information of interest to oncologists. For example, QOL data may serve to characterize how the treatment affects the patient's daily life, suggest ways in which treatment regimens may be modified to improve the patient's well-being, and guide development of supportive interventions for patients undergoing treatment and after treatment has been completed *(5–9)*.

SWOG behavioral scientists have made important contributions to this area of research through advocating the importance of QOL outcomes and their incorporation in clinical protocols and developing rigorous methodology for assessing so-called "soft end points," such as QOL. Following an initial experience in which poor QOL questionnaire-submission rates forced the closure of one QOL companion study *(10)*, specific SWOG policies for QOL studies have been developed *(5)* and revised. These policies provide guidance to SWOG investigators who are considering whether QOL end points are appropriate in a given trial and, if so, the design of the portions of the protocol that relate to QOL.

Table 1 provides a list of studies in the SWOG over the past 10-year period that include QOL end points *(11–16)*. The results of these protocols have demonstrated how QOL data can enhance understanding of treatment effects. For example, one trial examined the effects of combined androgen-ablation treatment in patients with advanced prostate cancer. Patients were randomly assigned to receive either orchiectomy plus an antiandrogen (flutamide) or orchiectomy plus a placebo. Whereas the findings for survival and toxicity indicated no differences between the two arms *(17)*, analysis of the QOL data revealed that patients who received combined androgen-ablation treatment had worse emotional functioning than patients who received orchiectomy alone *(13)*. This difference in psychological well-being was not totally explained by symptom status, as was originally hypothesized, and its origin deserves exploration in future research on the therapeutic effects and mechanisms of action of antiandrogens. This study, thus, demonstrates the importance of including comprehensive QOL assessment instead of relying solely on symptom measurement. Had the trial used only a measure of symptom status to assess differences in the QOL effects

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See "Notes" following "References."

Table 1. Southwest Oncology Group (SWOG)-coordinated studies with quality-of-life (QOL) end points, 1990–1999*

Study (reference No.)	Phase	Disease and site	Date		Accural	
			Open	Closed	Now	Goal
SWOG-8994†	III	Stage C prostate cancer	February 1990	January 1997	219	400
SWOG-9021‡,§ *(11)*	II	Brain metastases	July 1991	December 1994	54	216
SWOG-9039† *(12,13)*	III	Stage D_2 prostate cancer	October 1990	September 1994	739	500
SWOG-9045†	III	Advanced-stage colorectal cancer	March 1991	December 1993	289	280
SWOG-9208†	III	Early-stage Hodgkin's disease	April 1994	May 2000	263	288
SWOG-9217§	III	Prostate cancer	October 1993	December 1996	18 882	18 000
SWOG-9235§ *(14)*	II	Advanced-stage prostate cancer	December 1993	June 1994	52	40
SWOG-9248§ *(15,16)*	II	Metastatic breast cancer	May 1993	February 1994	115	120
SWOG-9324§	II	Relapsed ovarian cancer	March 1995	July 1997	77	80
SWOG-9346§	III	Stage D_2 prostate cancer	May 1995	Still open	302	1512
SWOG-9509§	III	Stage IV/IIIB non-small-cell lung cancer	May 1997	January 1998	222	280
SWOG-9916§	III	Stage D_1 prostate cancer	October 1999	Still open	137	620

*As of June 23, 2000.
†Comparison study to therapeutic protocol.
‡Therapeutic trial closed early because of accrual problems.
§Single protocol incorporating QOL study.

of the two treatments, the strong and provocative effect of antiandrogen treatment on psychological well-being would not have been detected.

Intervention Research

SWOG behavioral research has extended beyond QOL outcome assessment into research on behavioral interventions in primary prevention (i.e., reducing cancer incidence), secondary prevention (i.e., detecting cancer earlier), and tertiary prevention (i.e., addressing the impacts of cancer management). Current and past behavioral intervention protocols are listed in Table 2 and will be briefly described below.

Primary Prevention

Lung cancer. Cancer patients who continue to smoke during and after treatment, as many do, are at increased risk for negative outcomes, including developing additional primary cancers *(18)*. More effective approaches to long-term smoking cessation in cancer patients are required, particularly for patients with lung cancer and other smoking-related cancers. Activation is pending for an SWOG protocol for patients with newly diagnosed stage I or II non-small-cell lung cancer. This trial builds on previous research that has established the effectiveness of a number of approaches, used alone and in combination, for smoking cessation, including self-help materials, physician or nurse advice, nicotine replacement (patch or gum) *(19)*, and the antidepressant drug bupropion *(20)*. In particular, attempts to change smoking behavior have been shown to be more successful if both the biologic and the behavioral aspects of tobacco addiction are addressed.

The two-arm SWOG study will, therefore, compare the effectiveness of a combined pharmacotherapy (active bupropion and nicotine patch) plus a behavioral intervention with that of

Table 2. Behavioral studies conducted or pending in the Southwest Oncology Group (SWOG)*

Study	Title	Phase	Disease site	Date		Accrual	
				Open	Closed	Now	Goal
SWOG-8807	Three interventions to increase breast self-examination	III	Breast	May 1989	December 1993	2235†	3200
SWOG-9418	Training of "Promotoras"‡ to increase breast and cervical cancer screening among Hispanic women	Pilot	Breast, cervix	May 1994	January 1996	Promotoras 5	6
						Women contacted 123	141
						Women screened 42	50
SWOG-9632	Psychosocial intervention (telephone) for women with first recurrence of breast cancer	Pilot	Breast	June 1997	August 1998	30	30
SWOG-9832	Psychosocial intervention (telephone) for women with first recurrence of breast cancer	III	Breast	July 1998	Still open	137	300
SWOG-0002	Smoking cessation intervention: behavioral + patch + drug versus behavioral + patch + placebo	III	Lung	Not yet open			442

*As of June 23, 2000.
†Number eligible for analysis.
‡Promotoras are lay health workers in the Hispanic community.

"placebo bupropion," nicotine patch, and the behavioral intervention. The behavioral intervention includes physician and oncology nurse messages, tailored self-help materials, and reminder telephone calls conducted by an oncology nurse or clinical research associate. The cessation advice and materials incorporate two established aspects of effective health-promotion messages: 1) They are delivered by trusted, respected individuals; and 2) they build individual confidence to make behavior changes. Outcomes are assessed at randomization, at the end of 11 weeks of pharmacologic treatment, and 6 and 12 months later, and they include self-report of smoking status measured behaviorally and validated via cotinine levels in saliva, as well as QOL (including mood and symptoms). Survival, recurrence, and the incidence of second primary cancers will be tracked as exploratory outcomes.

Prostate cancer prevention. The Prostate Cancer Prevention Trial (PCPT) is a randomized, double-blind, placebo-controlled study of the efficacy of finasteride in preventing prostate cancer, ascertained through a prostate biopsy at the end of the study *(21,22)*. The trial enrolled nearly 25 000 men for a 3-month run-in period, during which all participants were given placebo to test adherence to the study drug. At the end of the run-in period, men who met basic trial requirements and had pill-taking adherence rates between 80% and 120% (n = 18 882) were randomly assigned to take a daily pill for 7 years. Currently, participants have four contacts with the PCPT staff each year: two visits to the clinic and two telephone calls. QOL (including symptoms) is assessed at study entry, at 6 months, and then yearly for 7 years. An additional measure of symptoms only is collected at randomization.

Behavioral science expertise has been crucial in developing strategies to enhance trial recruitment and adherence in this trial. For example, a single-institution pilot study tested the feasibility of an intensive intervention to enhance compliance with the prostate biopsy. The intervention included one-on-one and small-group sessions and printed materials about the biopsy procedure, in conjunction with a video that provided information about what to expect during a prostate biopsy. Measures of intention to have a prostate biopsy were obtained before and after exposure to the intervention; results are still being analyzed.

The pilot study also included a questionnaire to identify factors associated with intention. The content of the questionnaire was derived directly from previous behavioral research on factors that affect individuals' likelihood of adhering to medical regimens *(23)*. It included items to measure knowledge, social support, self-efficacy (e.g., the degree to which the individual believed that he would able to handle the trial requirements), and the perceived benefit of the biopsy (e.g., in terms of answering the study question and providing definitive diagnostic information for the participant). The questionnaire findings will indicate whether these individual participant characteristics are associated with differential success of the pilot study intervention. This knowledge will guide the development of approaches for the full trial that are targeted to specific groups and/or tailored to individual characteristics to enhance adherence with the end-of-study prostate biopsy requirement.

Screening/Secondary Prevention

Breast self-examination. During the period from 1989 through 1993, the SWOG enrolled 2233 women (the majority from Community Clinical Oncology Programs [CCOPs]) in a trial that compared the impact of three interventions on the performance of breast self-examination (BSE). The interventions were based on several behavior-change models, including adoption theory *(24)* (e.g., raising awareness of the need to change behavior through a physician message), self-efficacy (i.e., confidence that one can successfully perform the target behavior, BSE), and behavioral reinforcement (e.g., personalized reminders to continue performing BSE).

Women were randomly assigned to one of three approaches to encourage BSE: 1) physician message about the value of BSE; 2) physician message plus participation in a class teaching BSE technique; or 3) physician message, participation in a BSE class, and reinforcement by regular reminders (telephone calls and postcards) to do BSE regularly. BSE compliance (i.e., self-report of performing BSE five or more times in a 6-month period) and accuracy (as determined by nurse ratings of five aspects of BSE performance [at intake and 6 months] or by responses to eight telephone interview questions [at 12 months]) were assessed at randomization and 6 months and 1 year later. The findings *(25)* indicated that compliance was statistically significantly higher (78%) for women in the most intensive intervention arm at 1 year as compared with women in the message-only and message-plus-training class arms (59% and 62%, respectively). In all three arms, compliance improved significantly from the time of randomization at both follow-up points. Moreover, comparison of the two less intensive arms showed that adding the training class to the physician message alone improved accuracy at both follow-up points.

Cancer screening in Hispanic women. In 1994, the SWOG implemented a pilot study to evaluate the feasibility of recruiting and training lay educators ("promotoras") to increase cervical and breast cancer screenings among Hispanic women (Hansen L: unpublished data). Previous behavioral theory and research *(26,27)* had suggested that the involvement of Hispanic women who were already recognized as trusted and credible sources of information could increase the use of screening mammography and Pap smears in their communities. The pilot project was conducted through a minority-based community clinical oncology program (MBCCOP) in San Antonio, TX. Five Hispanic women, four of whom were breast cancer survivors, participated in a 12-week training course led by two bilingual health educators. The curriculum included information about risk factors, screening tests, and breast and cervical cancer treatment, as well as an overview of educational principles, community screening resources, and specific strategies to encourage screening in the community. The course incorporated didactic presentations, videotapes, and visits to community facilities. The promotoras then documented their efforts to encourage screening in female relatives and friends, and procedures to monitor subsequent screening behaviors were thus established. This project demonstrated the feasibility of recruiting and training lay health educators to deliver health education to special populations within the SWOG structure.

Tertiary Prevention

Enhancing well-being in women experiencing breast cancer recurrence. An ongoing SWOG study tests the hypothesis that participating in an intervention designed for breast cancer patients experiencing a first recurrence will enhance well-being *(28)*. Three hundred breast cancer patients from SWOG institu-

tions are being entered in the study within 8 weeks after disease recurrence. The women are randomly assigned to either an intervention or a control group. In the intervention, which is carried out by Y-ME, a national breast cancer support and advocacy organization, breast cancer survivors—most of whom have themselves experienced a recurrence of their disease—provide information and peer support via telephone. Four to eight telephone calls are conducted over a 1-month period. Well-being end points are assessed at entry in the study and 3 and 6 months later through validated questionnaires measuring QOL and depression. A pilot phase of this protocol has been completed, with 30 patients enrolled from eight institutions. Eighty-six percent of the patients in the pilot phase found the intervention helpful, while 14% did not. Qualitative responses indicated the convenience of telephone support, and having an opportunity to talk to someone who had been through the same experience contributed to its success *(28)*. This study is one of the few research projects anywhere to focus on improving well-being during cancer recurrence, and to our knowledge, it is among the first research partnerships between a cooperative group and a lay survivor organization.

Conducting Behavioral Research in a Cooperative Group: Benefits and Challenges

There are both benefits and challenges associated with conducting behavioral research in a cooperative group such as the SWOG.

Benefits

Access to a Large and Varied Cancer Patient Population

SWOG's nationwide accrual, further broadened through the mechanism of intergroup trials, makes available a group of patients and other potential participants for behavioral studies that far exceeds the numbers and diversity in any single institution. A total of 216 SWOG institutions contributed 4391 patients to therapeutic and nontherapeutic trials in 1998 (not counting the PCPT). Participating organizations included 23 CCOPs, 128 Community Group Oncology Programs, and 22 Urologic Clinical Oncology Programs. The CCOP participants included three MBCCOPs (organizations based in communities with large minority populations). SWOG-affiliated MBCCOPs provide access to African-Americans, Hispanics, Native Americans, and Asians and Pacific Islanders.

Thus, the patient population in SWOG trials includes registrations from community-based oncologists from many communities, not just patients seen at tertiary referral centers. The large numbers of SWOG participants enhance the likelihood of timely study completion, a particularly important consideration in rare diseases. Studies can be tailored to specific populations (e.g., specific disease sites, therapies, or demographics). Given the variety of organizations that belong to the group, there is also the potential to study institutional and organizational variations. Of course, the opportunities afforded by these patient and institutional resources are not limited to behavioral research.

Access to a Large and Varied Patient and Physician Base

Through cancer-control projects such as the PCPT, the SWOG has demonstrated that a cooperative group can go beyond its traditional patient and physician base. This is particularly important for prevention research, where behavioral change (and, thus, behavioral research) may be the focus of attention. The two largest cooperative group prevention trials to date, the PCPT and the Breast Cancer Prevention Trial (BCPT) conducted by the National Surgical Adjuvant Breast and Bowel Project *(29,30)*, required enrollment of large numbers of healthy individuals at increased risk of cancer of the prostate (PCPT) or breast (BCPT). In both trials, initial concerns that the oncologists who enroll and treat most of the patients for cooperative group trials would have difficulty recruiting study subjects from a healthy population proved to be unfounded. In fact, the PCPT stimulated creative partnerships between SWOG institutions and organizations such as the Department of Veterans Affairs clinics and urology practices, enabling the achievement of the target sample size. The success of this effort provides evidence that behavioral research studies that require populations other than cancer patients are possible within an oncology cooperative group.

Emphasis on Quality Control

The SWOG has established a system for data analysis and collection that includes careful attention to quality control. Behavioral research conducted within the SWOG can build on expertise in study design and implementation, including development of forms, tracking and reminder systems, and training modules.

Organizational Infrastructure

Cooperative groups provide an opportunity for behavioral scientists to develop protocols with multidisciplinary input from oncologists (from disciplines of medical oncology, radiation oncology, gynecologic oncology, surgical oncology, and pathology), nurses, basic scientists, epidemiologists, statisticians, and patient advocates. Most behavioral research in the SWOG has been generated by three committees: 1) the Behavioral and Health Outcomes Subcommittee of the Cancer Control Research Committee, 2) the Committee on Women and Special Populations, and 3) the Nurse Oncologist Committee. These committees, in conjunction with the 13 committees that focus on specific cancer sites, allow cross-fertilization of ideas in a "think-tank" environment that provides immediate interdisciplinary feedback and efficient development of ideas. Thus, the cooperative group offers considerable potential for developing translational research to integrate behavioral and biologic parameters.

In addition, the SWOG holds national meetings twice a year that are attended by a substantial proportion of the membership. These meetings provide a forum to publicize studies, to answer questions, to obtain feedback from investigators across the country about how a protocol is proceeding, and to conduct specialized training sessions. The structure of the SWOG, like that of many other cooperative groups, also includes certified data managers and clinical research associates in all member organizations. These individuals have considerable experience in recruitment and accrual, data collection and entry, and medical records abstraction, providing a cadre of research staff who is available for behavioral as well as clinical research.

Challenges

Quality-Control Mechanisms Geared Toward Clinical Outcomes

In many clinical sites, the quality-control mechanisms that are used routinely in the day-to-day conduct of treatment trials are not always appropriate or sufficient for a behavioral intervention or measure. For example, although QOL questionnaires are becoming more routine as a data-collection mechanism, the newness of this approach requires additional attention to ensuring that questionnaire data are collected in a timely fashion. In addition, statisticians with expertise in analytic techniques specific to behavioral research are rarely found in the cooperative-group setting. To address these challenges, behavioral scientists in the SWOG have undertaken a number of training activities, including educating the Statistical Center staff who monitor data quality about how to answer questions from investigators, nurses, and clinical research associates at SWOG institutions and determine when data forms need improvement.

Institutional staff also need ongoing training about outcome assessment in general and in the specific context of research issues that may not surface in therapeutic research. For example, unlike chart data documenting treatment information, QOL data need to be collected according to schedule because they cannot be retrieved at a later date. Ensuring that QOL data are collected as specified required new strategies for tracking data, monitoring institutions, and reminding data managers in advance when QOL data-collection points were approaching. The SWOG has ensured that quality-control procedures are specified precisely in the protocol and institutionalized at the statistical center. These procedures are necessary to communicate that data forms for behavioral science research are regarded as being just as important as those for treatment clinical trials.

In the SWOG, we are fortunate to have access to statisticians who are interested in learning more about the statistical issues presented by QOL and other behavioral research. For example, even state-of-the-art quality-control procedures cannot prevent the missing data problems that are associated with advanced-stage disease. Methodologic research is needed to develop appropriate analytic techniques for datasets with severe missing data problems *(31,32)*. Such research issues are of great theoretical interest to statisticians.

Behavioral Science Not the Major Focus Within Cooperative Groups

Behavioral and social scientists are a distinct minority in oncology cooperative groups. There have been occasions within the SWOG institutions when behavioral scientists have enthusiastically supported behavioral interventions, but these interventions either failed to proceed to full protocol development or were opened as protocols but failed to accrue their target sample size. Such failures can occur when clinicians in the disease committees do not endorse the interventions proposed by the behavioral scientists. The clinicians may feel that the ideas demand heavy resources, involve skills not present among institutional staff, are not feasible in the context of treatment delivery, or do not pose what seem to be interesting or useful questions.

Such experiences reveal the need for behavioral scientists to work closely with physicians to understand current and innovative therapies in a given disease, as well as the constraints posed by particular treatments on potential behavioral interventions. The importance of interdisciplinary or transdisciplinary *(33)* collaboration at an early stage of the study design cannot be overemphasized. In addition, behavioral scientists have expended substantial effort at educating the SWOG membership about the distinct contributions of their field and their potential applications in cancer clinical trial research. There are ample opportunities at the semiannual SWOG meetings to present workshops and to participate in educational sessions.

Competing Priorities of Institutional Staff

The settings in which SWOG members typically work pose limitations on the kinds of behavioral research that can be carried out. SWOG clinics are busy, and their staff primarily treat patients and only secondarily conduct research. In addition, although research staff are experienced at conducting treatment clinical trials, they may have little or no experience in conducting behavioral research and may lack the specialized personnel to conduct behavioral interventions. In addition, behavioral research requires stringent quality-control procedures *(12,30,34,35)* that come at a high cost, particularly in terms of staff time *(35)*. In the context of competing priorities, institutions may decide not to activate or promote behavioral studies.

Behavioral scientists in the SWOG have begun to understand how to integrate behavioral research in SWOG institutions and address competing priorities by recognizing that getting any study, particularly a behavioral study, up and running in a cooperative group takes much longer than implementing a study in a single institution. For example, addressing the different concerns of Institutional Review Boards (IRBs) around the country, as study coordinators are called on to do, requires considerable time and patience. However, now that some initial behavioral studies have made it through the IRB process, the approval process for future trials should be less cumbersome. In addition, extra resources (e.g., outside funding) may be required for training, recruitment of additional personnel, or centralized conduct of an intervention or data collection. For example, external funding was obtained for the behavioral intervention trial for women with breast cancer recurrence to support the telephone activities of the peer counselors at a central location, because individuals with these skills were unlikely to be available at individual institutions. For behavioral research to be sustained in cooperative groups, therefore, additional targeted funding—through federal grants, pharmaceutical company support, or other means—for infrastructure development and maintenance is necessary, as is support for methodologic research and pilot studies. Based on the authors' experiences in the SWOG over the past decade, the methodologic strengths of conducting behavioral research in the cooperative group setting and the unique contributions such studies can make are likely to be viewed positively in the review process.

Conclusions

Over the past decade, the SWOG has supported, initiated, and completed pioneering efforts in behavioral research related to QOL assessment and the full scope of cancer prevention and control. The first behavioral intervention—a telephone counseling program for recurrent breast cancer patients—is currently ongoing, while an intervention to increase BSE directed at

healthy women was successfully completed. Behavioral scientists and clinicians as well have learned valuable lessons about how to work in a cooperative group over this period that provide a foundation for future behavioral research in the context of cancer. The multidisciplinary behavioral projects in progress at the SWOG have received peer-reviewed national funding, reflecting the high level of scientific rigor that can be maintained in the group setting. However, the availability of funding is an ever-present constraint on the development of behavioral research.

The recommendations of an NCI Working Group on Behavioral Research in Cancer Prevention and Control were published recently *(1,36,37)*, and a new strategy for cancer control research from NCI's Division of Cancer Control and Population Sciences (DCCPS) has been outlined *(38)*. These recommendations all explicitly identify social and behavioral sciences as the basic science for cancer control research. DCCPS has recently initiated a number of targeted research opportunities in cancer control research that could be appropriately based in cooperative groups (e.g., PA-CA-99-163, "Exploratory Grants for Behavioral Research in Cancer Control"; RFA-CA-99-014, "Basic Biobehavioral Research on Cancer-related Behaviors"). Moreover, a January 2000 workshop cosponsored by DCCPS and the NCI Division of Cancer Prevention focused on expanding the participation of behavioral scientists within the CCOP.

All of these recent developments, as well as the changing health care system, offer exciting opportunities for cancer prevention and control research *(37,38)*. Partnerships among behavioral scientists, cooperative groups, and the NCI have the potential to provide benefits to all and, ultimately, to reduce the burden of cancer for both the individual and the larger community *(39)*.

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NOTES

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