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The Effectiveness of Adherence Intervention in a Colon Cancer Prevention Field Trial[1]

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Background. Adherence interventions were implemented in a 1-year community-based colon cancer prevention clinical trial (n = 110) using wheat bran fiber and calcium dietary supplements. The adherence promotion strategy was guided by a theoretical model.

Methods. The adherence intervention contains both a generalized portion given to all participants and an individualized portion given to marginal (50–74% intake) and low (under 50% intake) adherers. A regression model was employed to assess the effectiveness of the interventions both at the first intervention and at subsequent times.

Results. The Health Behavior in Cancer Prevention Model-based adherence promotion intervention was associated with retention of participants, both during the run-in period and after randomization (P = 0.05); and maximization of the percentage of the 13.5-g recommended fiber supplement consumed during the trial (92.5%). The positive effects of the adherence intervention were greater with first-time nonadherers and the control group than with the experimental group. The high-fiber group had notably more biological GI effects from the increased fiber intake, more preexisting comorbidities, and lower perceived cognitive and physical health status.

Conclusions. Randomized participants had excellent adherence overall. Retention rates in the trial were better than would be expected without the adherence intervention, especially among those participants who may have been at higher risk for dropping out of the study. This suggests that a systematic, theoretically based adherence strategy should be further tested in clinical trial settings in which lower adherence is a problem.

INTRODUCTION

Colorectal cancer kills 60,500 Americans annually. An estimated 157,500 were diagnosed in 1991 (1). Since the 5-year survival rate is only 52%, cancer prevention is a high priority for the National Cancer Institute (NCI). However, effective community-based clinical trials require that a sufficient number of active partic-

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ipants remain in the trial long enough for meaningful hypothesis testing. Adherence promotion is currently recognized as an essential element of successful field trials. This article reports the results of an adherence promotion intervention in a community-based, colon cancer prevention program project.

The adherence intervention described here addresses two research questions: Was the adherence intervention related to high adherence, and was it related to retaining participants in the trial who might otherwise have withdrawn following randomization, but who had to be evaluated anyway? Adherence is a negotiated agreement between study participant and the study team. The participant is actively involved in addressing the hard issues of changing lifestyle patterns to accomplish a health-related goal (2). Primary adherence measures for this study were percentages of recommended fiber and calcium intake. Secondary adherence measures were monthly adherence calendar completion and keeping clinic visits. The goal was to maximize the consumption of fiber and calcium up to the prescribed dose. The fiber adherence is the focus of this article; however, retention in the clinical trial was equally paramount and considered a form of adherence in itself.

A model-based approach was used to assess reasons for nonadherence so that study personnel could target interventions effectively to help the marginal adherers (50–74% of the recommended dose of fiber consumed) and the poor adherers (<50%) increase protocol adherence. Quantitative data on participants' psychosocial adherence motivators as well as biological indicators were routinely collected.

It has been estimated that one in three patients fail to follow the treatment recommendations of their health care providers (3). The implications of nonadherence in treatment settings are sobering in terms of health outcomes, costs associated with treatment, and potential malpractice litigation (4). For this reason, there has been a virtual explosion of research aimed at identifying the causes and treatments of nonadherence. Most researchers agree that there is no single reason for nonadherence and, further, that no single intervention can effectively address nonadherence. Several patient factors, however, are consistently noted as being partially predictive. These include satisfaction with the client–provider relationship (5); the perceived ability or self-efficacy of the individual to perform the adherent behaviors (6); adequate knowledge of the disease and means for preventing or treating it (7); and a positive, supportive social network that can provide reinforcement to the individual for practicing the behaviors (8). Treatment variables that have been shown to influence adherence include the complexity and duration of treatment (5). In general, the simpler the regimen and/or the shorter the duration, the more likely the patient will be to adhere.

The Clinical Study

Adherence was promoted in the context of a colon cancer prevention field study. The study was a 1-year Phase IIb wheat bran fiber and calcium trial (n = 110 participants) (9). The fiber/calcium study was supported by the NCI (10). Participants in this fully crossed randomized design were randomly assigned to

either the high (13.5 g) or low (2.0 g) fiber and either the high (1500 mg) or low (200 mg) calcium group. The study site was a colon cancer prevention clinic in an Arizona retirement community. The primary objective was to measure the effects of treatment with wheat bran fiber and calcium for 9 months on a [^{3}H]thymidine-labeling index in rectal mucosa, a marker of epithelial regeneration, in individuals with resected adenomatous colon polyps. A secondary objective was to assess the effectiveness of the adherence enhancement program, as described in this article.

Sample characteristics. Participants in the study were identified through gastrointestinal endoscopy unit records, pathology reports, and physician referrals. Participants must have had a history of adenomatous colon polyp resection to be considered eligible for the trial. Other eligibility criteria based on baseline nutritional status and related health history were employed as well. In addition, participants must have had a baseline dietary fiber intake of less than 30 g/day, elemental calcium intake of less than 2 g/day, and supplemental calcium intake of less than 500 mg/day. The participants must have had good physical performance status and no history of invasive cancer within the 12 months prior to participating in the study. Laboratory blood values for creatinine and bilirubin were assessed as eligibility criteria as well. The sample (n = 110) included 64% men and 36% women ranging in age from 51 to 77 (mean = 67 years; SD = 5.1). Participants identified an average of 3.9 comorbidities (range of 1 to 9, SD = 1.9, including colon polyps), which included primarily high blood pressure (48.3%), diverticulosis (36.4%), and arthritis (34.0%), as would be expected in this age group. Participants resided in an upper socioeconomic status retirement community where the average age is 70. Relevant to adherence in this study is the finding that this community is also fairly mobile, with one-third spending at least 2 months each year, usually in the summer, away from home.

Measures of adherence. The two adherence measures for the study were the returned, unused portions of fiber and calcium supplements and the monthly calendars on which study participants recorded the amounts of the supplements that they ingested daily. Participants were provided and asked to eat one small box of wheat bran fiber cereal (approximately 1 oz) each day and consume six calcium tablets (three at a time, with a meal other than the fiber one). On their calendars participants circled the portion of the box of fiber (either 0, ¼, ½, ¾, or 1 or more) that they ate and noted how many tablets of calcium they took (ranging from zero to six).

Adherence scores were computed in two forms: percentage of dose consumed and categorical level—good ($\geq$75% of the target dose consumed), and marginal (50–74%), and poor (<50%). The cut points were based on estimated biologically active levels; i.e., 75% was the minimum needed to be considered "treated." Less than 50% represented a large deviation from the minimum dose. Adherence rates were exceptionally good. The overall mean fiber adherence was 93.3% (SD = 13.18, with a range of 0.0 to 141.6%) while the mean calcium adherence was 94.2% (SD = 10.06, ranging from 0.0 to 117.7%). Returned box counts and intake calendars revealed that some participants consumed more than the requested dose, which explains adherence rates greater than 100%. While participants were not

encouraged to eat more than one serving of cereal per day, some chose to if they did not feel fully satisfied by the prescribed one-box dose. They would thus circle a "1+" on the adherence calendar for that day's assessment.

MATERIALS AND METHODS

The Health Behavior in Cancer Prevention Model

The adherence literature in clinical treatment practice settings is extensive, yet the application of recommendations in treatment settings is not always readily transferred to the clinical research arena. Several sociobehavioral theories and models of human behavior change that have been advanced in the past several decades have been adapted with moderate degrees of success to the health care setting—most notably the Health Belief Model (11). This model originally specified that in order for an individual to take preventive action to avoid disease, he or she would need to feel personally *susceptible* to the disease and that the occurrence of the disease would have some level of *severity* attached to it. Further, there must be the belief that taking some preventive actions would be *beneficial* and that there would not be overwhelming psychological and environmental *barriers* associated with the preventive behavior. Research utilizing the Health Belief Model in its original form has been extensive yet only modesty correlated with adherence (12). Later adaptations to the model included the addition of demographic factors (age, sex, ethnicity, etc.), structural factors (knowledge, previous experiences), and sociopsychological factors (social class, peer and reference group pressure, etc.). While the Health Belief Model itself has not been as applicable in the cancer prevention setting, its usefulness as a platform for other models specific to prevention is nonetheless valuable. It also serves as the impetus for the Health Behavior in Cancer Prevention Model (HBCP) (13) used to guide the general and individualized adherence interventions described in this article.

The HBCP model also incorporates Bandura's (6) self-efficacy work, the locus of control concept (14), and Rotter's (15) health value orientation. As shown in Fig. 1, the model is staged to specify the paths or mechanisms through which adherence occurs. Specific variables in the model include the participants': (a) demographic or personal characteristics (for example, age and marital status); (b) health status (both physical and cognitive); (c) social support (family and friends who encourage healthy behavior); (d) knowledge about colon cancer; (e) perceived susceptibility to getting colon cancer; (f) perceived severity, if they actually had colon cancer; (g) perceived barriers and benefits for being in the study and eating the fiber; (h) perceived ability to do what was asked in the study (self-efficacy); (i) values about their health; (j) perception of who is responsible for self-health-maintenance (locus of control); and, (k) satisfaction with the relationship with the research clinic staff (16–19, 7, 20, 6). Both perceptions and biological data are considered in health status. The HBCP model provided a finite number of variables on which to intervene in an orderly fashion.

To measure the model variables, participants were first asked to respond to a Health Behavior Questionnaire (HBQ) (21). The HBQ contains each of the non-

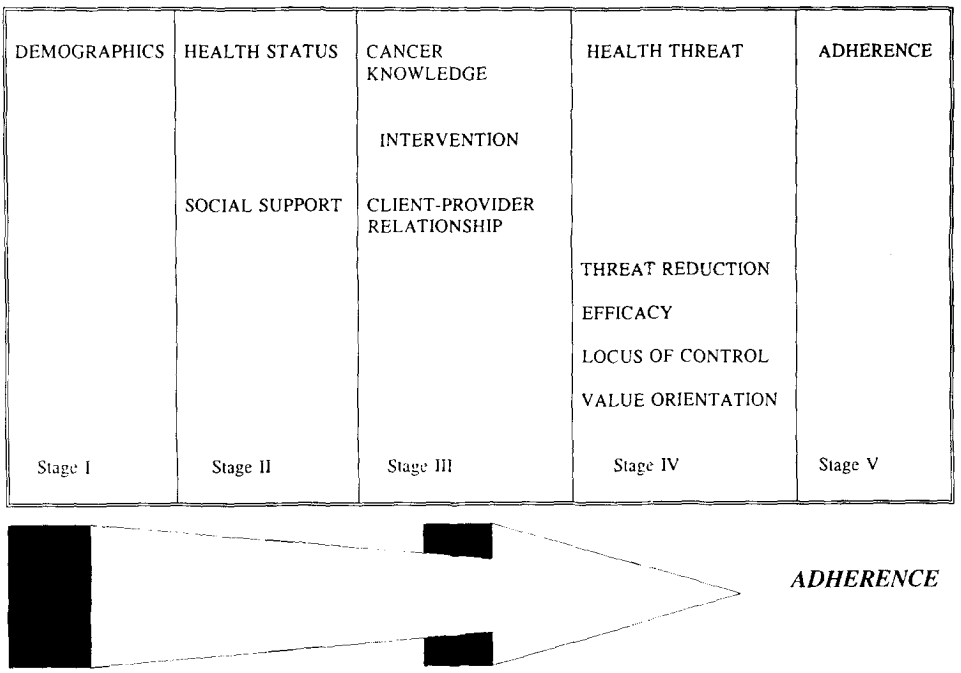

FIG. 1. Health Behavior in Cancer Prevention Model, based on (13).

demographic variables in the model. The measures are 4- to 12-item scales. The measurement properties are satisfactory (21). They include internal consistency reliability coefficients alpha or theta ranging from 0.74 to 0.88 except for Barriers (0.68) and the Chance subscale of the Wallston *et al.* (22) Health Locus of Control Scale (0.65). Principal component factors related to each scale showed satisfactory loadings (23) ranging from 0.44 to 0.90. Latent variable analysis measurement models confirmed the measurement structure (24). HBQ responses were compiled into a two-page Health Behavior Profile (HBP) that summarized each participant's model-based beliefs and attitudes relative to those of a standard population of the same type (25). The HBP was used to assess participants' baseline and subsequent levels of the model variables as well as to guide interventions when a participant became a marginal or poor adherer.

Intervention Strategies for Adherence

The planning of clinical field studies requires manageable adherence enhancement protocols that do not become more complicated over time (26). A separate Behavioral Science Core was established to coordinate adherence efforts. In addition to defining the criteria for adherence, the Behavioral Science Core developed written, standardized protocols that were used to assess, monitor, enhance, and intervene on adherence as appropriate. For example, protocols were developed to address issues such as: (a) how to keep field staff and participants blinded to the treatment group while managing and documenting side effects experienced

by the participant; and (b) how participants could adhere to medication and fiber supplement requirements while on vacation.

The standardized adherence interventions were based on the HBCP as well as on a previously completed feasibility study (27). The two-part adherence strategy included both generalized and individualized portions. The generalized part was given to all participants and included such things as appointment reminder postcards, instructions for eating the fiber and taking the calcium pills to minimize side effects, monthly adherence assessments, calendars to record fiber and calcium intake, and newsletters. Content and timing of articles in the monthly newsletter that was sent to participants were based on model predicted concerns or behaviors (28).

The individualized adherence intervention was given only if a participant became a marginal or poor adherer. Marginal adherers received a less intense intervention than poor adherers. The focus of the intervention for marginal adherers was one of guided participant-generated solutions to the identified adherence problems and minimal follow-up. In contrast, poor adherers received staff/participant-generated solutions and closer follow-up including a mailed letter and/or phone call 1 week after the intervention.

As another illustration of how the model guided the development of interventions, the intervener could assess reasons and plan interventions for poor adherence by reviewing the HBP. Once physical toxicity was ruled out, if a participant's calendar showed poor adherence for the previous month and his or her HBP indicated a high Barriers score but average scores on other variables, the intervener would initiate a discussion of possible barriers. Solutions were suggested to the participant, and once a plan was mutually negotiated, a behavioral goal-setting contract was signed.

Paramount to the project's success was the extensive personnel training. Standardized protocol training of the interveners was accomplished through workshops that included lectures, group discussions, problem-solving, and role-playing (29).

Data Analysis

The data analysis was designed to address the two research questions in the study: (a) Was the adherence intervention related to improved adherence? (b) Was the intervention effective in retaining some participants in the trial after randomization who were at high risk for complete nonadherence by keeping them eating at least some fiber even though it might not be the optimal dose?

The ideal assessment of an adherence intervention would be carried out by randomly assigning nonadherers to intervention and nonintervention groups and then comparing their subsequent adherence histories. This design is not feasible for most trials; since the goal of maintaining high adherence generally outweighs the goal of measuring adherence intervention effects; it is not permissible to form a nonintervention group. Consequently, the appropriate method of analysis must be observational and use the appropriate models for analyzing change as described in Plewis (30).

The model employed here is based on the assumption that in the absence of an

adherence intervention program, the relationship between adherence y measured at a particular time and adherence x measured one month earlier is of the usual regression form $y = b_0 + b_1x +$ error. As described in Plewis (30), this model explicitly accounts for regression to the mean. This simple linear regression model would generally be expanded to include additional factors in situations where there are intervention and nonintervention groups. Here, z would be defined as the indicator of intervention (1 for an intervention, 0 otherwise), and the model would be of the form $y = b_0 + b_1x + b_2z +$ error or

$$y = b_0 + b_1x + b_2z + b_3xz + \text{error}.$$

From the adherence standpoint, the above models need to be modified to allow for the fact that membership in the intervention group is determined by the value of x. In this case, $x < 75$ would automatically trigger an intervention ($z = 1$). It is then appropriate to define a new explanatory variable (31),

$$w = \begin{cases} (75 - x) & \text{if } x < 75 \\ 0 & \text{if } x \geq 75, \end{cases}$$

and to employ the analytic model $y = b_0 + b_1x + b_2wz +$ error. This model specifies a line with intercept b_0 and slope b_1 for values of x above 75, and a line with intercept $b_0 + 75b_2$ and slope $b_1 - b_2$ below 75. These two lines meet at the adherence boundary, $x = 75$, so that it is appropriate to judge the adherence intervention as being successful to the extent that $b_1 - b_2$ is less than b_1, that is, to the extent that b_2 is large and positive.

There was another factor that required attention: f, the indicator of an individual being in the high-fiber group (thus $f = 1$ means high fiber, $f = 0$ means low fiber). It was also necessary to distinguish between a first intervention (indicated by z_1) and all subsequent interventions (indicated by z_2). Thus, the model employed for analysis was

$$y = b_0 + b_1x + b_2wz_1 + b_3wz_2 + b_4wz_1f + b_5wz_2f + \text{error}.$$

We chose to use this model for analysis. However, in studies that have heterogeneous groups, it may be desirable to include other factors such as demographics.

RESULTS

By substituting possible values for the key variables, z_1, z_2, and f, we can interpret the slope coefficients in this model. The key variables were whether participants were on high or low fiber and whether the intervention was the first or a subsequent one. Possible values for these variables are either 0 or 1. The model interpretations are as follows: $b_1 - b_2$ is the slope of the line to the left of $x = 75$ for first intervention among all subjects, $b_1 - b_3$ is the same slope for the low-fiber group at their subsequent interventions, while $b_1 - (b_3 + b_5)$ is the same slope for the high-fiber group at subsequent interventions. Rather than reparameterizing in terms of the slopes in these three groups, the form of the regression

equation was retained in order to be able to assess the first and subsequent intervention effects and the high-fiber group effects separately.

Table 1 shows how many of the total 1,130 routine adherence assessments resulted in adherence (≥75%) or nonadherence (<75%), and how many first and subsequent interventions were done; e.g., 1,075 adherence assessments required no intervention; whereas 22 assessments prompted a first adherence intervention, 11 a second, but only 1 a fifth intervention for a total of 55 of 1,130 assessments requiring intervention.

The regression fit to the entire data set is shown in Table 2. In fitting the data, it was determined that b_4 was negligible and not statistically significant, and so the simpler model without this term was used. All of the remaining effects were significant ($P = 0.003$ to 0.05), as was the effect of the previous adherence level ($P = 0.001$).

The overall slope of the relationship between preceding and current adherence was about 0.53. Since the estimate of b_2 (0.21) was significant and positive, we conclude in response to research question 1 that there was a beneficial intervention effect associated with the first intervention for both high- and low-fiber groups. The significant and positive estimate for b_3 (0.71) indicates that in the low-fiber group, the intervention was associated with a beneficial effect, while the significant negative estimate of b_5 (-0.97) indicated that the high-fiber treatment was associated with a negative effect on adherence promotion at subsequent interventions.

These relationships are displayed in Fig. 2, which shows the regression lines for adherers [0], first-intervention nonadherers [1], subsequent-intervention nonadherers in the low-fiber group [2], and subsequent intervention in the high-fiber group [2f]. The effect associated with the first intervention was improved adherence. This effect was even more pronounced in subsequent interventions in the low-fiber group, where the slope of the fitted line actually became negative. If participants receiving subsequent interventions had been as healthy and had as few GI side effects as the consistently good adherers and the first-intervention group, the subsequent-intervention group would be expected to follow a similar,

TABLE 1
ORDINAL NUMBER OF THE ADHERENCE INTERVENTION RECEIVED BY PARTICIPANTS, BY ADHERENT OR NOT

	Adherent?	
Intervention received	Yes	No
None	1075	10
First	—	22
Second	—	11
Third	—	7
Fourth	—	4
Fifth	—	1
Total	1075	55

Note. n = 1,130 adherence assessments.

TABLE 2
REGRESSION RESULTS FOR CURRENT ADHERENCE BASED ON 1130 MEASUREMENTS

Variable		Parameter estimate	Standard error	T for HO: parameter = 0	Prob > $\|T\|$
Intercept	b_0	43.395	3.473	12.49	0.0001
x	b_1	0.534	0.036	14.68	0.0001
wz_1	b_2	0.207	0.108	1.92	0.0548
wz_2	b_3	0.711	0.322	2.20	0.0278
wz_2f	b_5	−0.967	0.322	−2.99	0.0028

Note. $R^2 = 0.2926$. Equation: $y = b_0 + b_1 x_1 + b_2 w z_1 + b_3 w z_2 + b_4 w z_1 f + b_5 w z_2 f +$ error, where y, current adherence; x, previous adherence; w, $(75 - x)$ if $x < 75$ and 0 if $x \geq 75$ and z_1, first intervention; z_2, all subsequent interventions; f, high-fiber group.

if less dramatic, curve. However, they were not as healthy and had more GI symptoms, as discussed in detail later. In subsequent interventions among the high-fiber subjects, adherence was estimated to have been worse than it would have been if one extrapolated the line above 75 to values of x below 75.

We note that of the 55 occurrences of low adherence, in 10 cases an intervention did not take place. In some instances an intervention was not possible because the participant decided to drop out of the study (usually for physiological toxicity reasons). These instances were not included in the regression analysis, since they would have contributed an artifactual elevation of the slope of the line for adherers. In other cases, the problem resolved itself (e.g., participant recovered from the flu) and an intervention was not necessary. Thus, we have a small number of cases that were used to help fit the solid line in Fig. 2 for x below 75%. See Tables 3a and 3b for a description of the reasons cited for nonadherence and dropout in all intervenable instances.

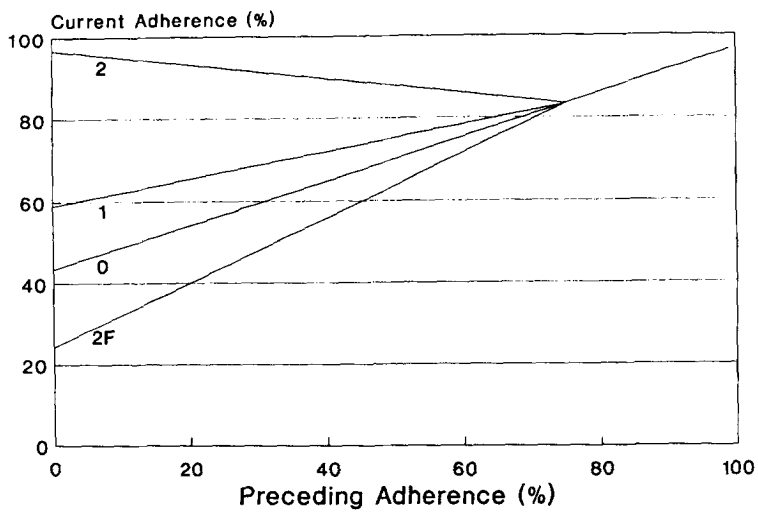

FIG. 2. 0, Adherers; 1, first intervention; 2, subsequent interventions (low fiber); 2F, subsequent interventions (high fiber).

TABLE 3a
REASONS CITED FOR NONADHERENCE

ID	Sequence of low adherence[a]	Adherence score (%)	Reasons for nonadherence	Number of Co-morbidities (and sex)	Baseline GI problems?	Bowel preps used
			High-fiber group			
21	7	60.00	Vacation	4 (m)	No	None
24	8–13	0–39.29	Ulcer pain increased with fiber intake; also doesn't like fiber cereal	5 (m)	Had ulcer at baseline	None
29	5 9	48.28 27.40	Abdominal pain Vacation	9 (f)	Daily pain, diverticulosis, colitis	Lomotil Pepto
47	6	72.41	Vacation	5 (m)	No	Pepto
52	1, 2, 3 5	54.29–65.38 64.16	Poor calendar recording Diarrhea (level 1 toxicity)	4 (f)	Continuous gas, diverticulosis	None
53	1	50.00	Vacation	7 (m)	Diverticulosis, ulcers	Metamucil
71	5, 6 7	64.00, 53.57 72.41	Diarrhea (level 1 toxicity) "Oozing" stools; doesn't eat if going out	3 (f)	No	None
77	9	71.43	Gas pains and abdominal discomfort	3 (m)	Loose stools, diverticulosis, colitis	None
89	5, 9, 10, 13	67.86, 70.37 50.00, 72.73	Severe gas	5 (m)	21 Stools/wk gas, diverticulosis	None
135	5 8 10	50.00 45.83 54.84	Vacation Gas Undergoing diagnosis of bladder cancer	1 (m)	No	None

Low-fiber group

34	3	65.63	Cannot remember when going out to eat or having visitors	5 (m)	Frequent constipation or hemorrhoids	Colace Metamucil
54	2	60.71	Bad taste to cereal	3 (f)	No	None
	3	46.67	Bad taste to cereal			
	7	66.67	Vacation, upset due to death of friend			
59	1[b]	71.43	Started fiber late	3 (m)	Frequent constipation or hemorrhoids	None
68	2	71.43	Skipped fiber	2 (m)	No	None
91	7	67.86	Bout with diverticulosis, root canal	4 (m)	Diverticulosis, freq constipation or hemorrhoids	Metamucil
96	2	43.59	Diarrhea, hemorrhoids	4 (f)	Frequent constipation or hemorrhoids	Metamucil
	4	60.71	Diarrhea			
98	5	71.43	Eating out	7 (m)	Ulcer, frequent constipation or hemorrhoids	None
109	6, 9	67.86, 71.43,	Constipation	2 (f)	14 Stools/wk	None
	12, 13	73.08, 68.97	Constipation			
	11	71.05	Constipation, traveling			
112	2	53.57	Elevated blood sugar, pt. blamed cereal	3 (m)	Diabetes	None

[a] Sequence number in which assessment of adherence was done. All but the first two were 1 month apart.
[b] Did not receive individualized adherence intervention.

TABLE 3b
REASONS CITED FOR DROPOUTS

ID	Month off study	Sequence of low adherence[a]	Adherence score (%)	Reasons for nonadherence	Number of Co-morbidities (and sex)	Baseline GI problems?	Bowel preps used
				High-fiber group			
32	4	None		Dropout–dislike new cereal	4 (m)	Frequent constipation or hemorrhoids	None
78	5[b]	5	46.43	Dropout–dislike new cereal	4 (f)	None	None
95	6	None		Dropout–due to constipation	3 (f)	None	Metamucil
100	6	2	53.57	Lots of gas	4 (f)	Diverticulesis, frequent constipation, or hemorrhoids	Metamucil
		4[b]	64.29	Flu, urinary tract infection			
		5[b]	15.63	Dropout-cannot tolerate cereal			
114	7	5	28.57	Diarrhea and loose stools	2 (m)	None	None
		6	25.00	Diarrhea			
		7[b]	21.43	Dropout—constant diarrhea			
124	10	8	71.43	Abdominal inflammation and discomfort. Dropped—due to failure to keep appointment or to return calls from staff	4 (m)	Frequent constipation or hemorrhoids, ulcer	None
142	6	None		Dropped—husband's insistence	4 (f)	None	None
				Low-fiber group			
25	49	2	64.29	Loose stools, G.I. discomfort (run-in), Dropout—change in fiber, inc. bm's, GI discomfort, difficulty giving enemas, and change in nursing staff	4 (f)	Continuous gas, weekly pain, diverticulosis, frequent constipation or hemorrhoids	Other laxatives daily
94	9	None		Dropout—Could not cope with taking fiber anymore	2 (f)	None	None

[a] Sequence number in which assessment of adherence was done. All but the first two were 1 month apart.

The first research question addresses high adherence levels for those who stayed in the trial. The two-part intervention had general and individualized aspects. The generalized intervention was associated with success in terms of the high proportion (68%) of consistently good adherers and high average overall adherence. The individualized portion is also associated with improved adherence, especially for first interventions and the low-fiber group. Qualitative review of the nursing notes showed that reasons for initial marginal or poor adherence were similar except for blatant cereal intolerance that consistently indicated poor adherence. Although the interveners used the HBP to identify out-of-range HBQ variables to target for intervention, the link between the HBQ variables and adherence outcome remains unclear because the progress notes do not consistently identify the specific out-of-range HBQ variable(s) that were covered in each intervention.

The second research question was also answered in the affirmative; i.e., many participants who were at high risk for going off the trial were retained on study. Those on high-fiber doses had more gastrointestinal side effects and thus had a harder time adhering. The adherence intervention was associated with understandably less effect for them on subsequent interventions. However, the key finding is that most still remained in the trial even though they had subsequent marginal and poor adherence.

Nonadherers were mostly similar to adherers but differed in key ways. The groups did not differ by age, gender, or objective health status. Specifically, although men were more likely than women to be nonadherers (see Tables 3a and 3b), two-thirds of the total study sample was male, thus making the nonadherer group similar to the rest of the study group. Nonadherers' number of comorbidities at baseline (mean = 4.2, SD = 1.7) was not significantly different from that of the rest of the study population (mean = 3.8, SD = 1.9). However, more nonadherers entered the study with lower perceived health status, diverticulosis, and constipation, and more were on the high-fiber intervention with concomitant gastrointestinal complaints. Specifically, those who received at least one adherence intervention differed from those who maintained good adherence levels in that the nonadherers perceived their health status to be lower than the consistently good adherers ($P < 0.05$). Ninety percent of those nonadherers who completed the study entered with low perceived health status that did not resolve during the study, versus 56% of the consistently good adherers. This suggests that while objectively the group is not documentably different in terms of their overall disease status, the group of nonadherers *perceived* their cognitive and physical health status to be lower overall. This highlights the need to design interventions targeted toward attitudinal health status variables.

Two specific types of gastrointestinal baseline comorbidities were associated with low adherence in this trial, as shown in Table 3a. Although not statistically significant, diverticulosis, which was reported in 36.4% of the total study population, was more prevalent in the nonadhering high-fiber treatment group (35%) than in the low-fiber group (20%). Similarly, there were more baseline constipation problems among low-fiber nonadherers (60%) than among the high-fiber group (17%). While randomization to a treatment group was not in any way

affected by assessment of baseline comorbidities, this finding is noteworthy and would help explain some of the variance in adherence related to toxicity barriers.

Understandably, the incidence of gastrointestinal complaints seemed to be related to the higher fiber dose, which tends to present more biological side effects. The high-fiber intervention was associated with more participants who had instances of low adherence. Of these, most were retained in the trial to completion. There were similar numbers of low adherers in both the low- and high-fiber groups who completed the study, even though there were more intervenable dropouts in the high-fiber group (64% vs 50%) (Table 3b). Most of the dropouts in the high-fiber group were due to gastrointestinal difficulties (e.g., chronic diarrhea) or unrelated problems (e.g., surgery, death of a relative) and not for psychosocial reasons. Since they were receiving the experimental treatment intervention which had a higher drop-out rate, it was important to try to retain these participants in the trial. Therefore, participants may have been instructed to eat decreased amounts of fiber each day or eat small portions of it throughout the day in order to counteract some of the toxicity problems. These instructions may have recurred for several months. When this failed, as it did in some instances, 8 of 110 participants decided to drop out. As would be expected, constipation was reported as a problem in the low-fiber treatment group. The exception was one individual who reportedly had diarrhea but who also entered the study taking Metamucil on a daily basis, which could have contributed to the problem.

Of note is the impact of vacations on adherence. Since the study population is composed of mostly retired individuals of middle to upper socioeconomic status, many of the participants in this study took vacations during the summer months, which sometimes affected their adherence. In those instances, every attempt was made to make eating the fiber as easy as possible. Fiber was mailed to the participants if they were going to be away for longer than 1 month, and they were sent monthly contact sheets asking them to mail back their calendars in order to assess their adherence while on vacation. This worked remarkably well, but there were a few instances in which vacationing interrupted routines enough to cause adherence to suffer.

DISCUSSION

The results showed that both research questions were answered positively. The generalized and individualized adherence intervention strategy is clearly associated with high adherence levels throughout the 12-month trial (particularly for consistently good adherers and persons receiving their first individualized intervention). The overall 92.5% average fiber intake adherence rate over 12 months compares favorably to the DeCosse *et al.* (32) levels ranging from 38.9 to 66.8% (depending on the treatment condition) after 48 months on trial. The participants in their study were familial polyposis patients with colectomies. The National Heart, Lung, and Blood Institute report (33) on the status of adherence in a broad spectrum of situations gives similarly lower average trial adherence rates as well.

Several participants at high risk for withdrawing from the trial were retained in the project, given the adherence intervention. The participants requiring more than one intervention differed in important ways from those who were able to

maintain good adherence levels: more were in the high-fiber treatment group and therefore had more barriers to overcome than the low-fiber group; more had diverticulosis or constipation; and they averaged lower entering and sustained perception of their overall cognitive and physical health status. The current findings support the Ho *et al.* (27) findings that the intervention is associated with higher overall adherence plus a notable impact on more of the population at risk.

Those participants who required more than one adherence intervention gave essentially the same reasons for low adherence as others who returned to good adherence after one intervention. However, the 19 who required one or more individualized adherence interventions, but who remained in the trial, increased the power of the study markedly, because all randomized participants must be evaluated whether or not they keep eating fiber. Since this study was naturalistic in nature, it is not possible to discern exactly how many participants were saved from withdrawing. However, 35 of the 110 participants became marginal or poor adherers at some point in the study.[3] They are considered at risk for withdrawing and were potentially saved to consume at least some fiber rather than dropping out of the study. Those who stayed in the trial (86%) received at least some fiber. However, if those who had not adhered had left, only 69% would have received the treatment. Assuming the adherence intervention contributed to their retention in the trial, a maximum of 86% of the 110 randomized people actually received the treatment instead of withdrawing versus the 69% who would have been treated if the nonadherers had left the study.

Important implications of this adherence strategy for clinical trials include retention of participants on trial and vital sustained intake of the cancer prevention agent during the trial for the vast majority of evaluable participants. The strategy needs to be tested with predominantly low-adhering populations as well. Implications for clinical practice suggest the potential impact of an organized approach to adherence enhancement in routine clinical practice to sustain cancer prevention strategies in the population.

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[3] Twelve of those 35 nonadherers were not intervenable because their nonadherence was related to illness or other circumstances unrelated to the study.

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