PREDICTORS OF PARTICIPANT RETENTION IN TWO CHEMOPREVENTION FEASIBILITY TRIALS

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ABSTRACT

Retention of participants for intervention and follow-up activities is critical in cancer chemoprevention trials. Little has been published about retention patterns and predictors of retention in prevention studies. The Carotene and Retinol Efficacy Trial (CARET) provides an opportunity to study retention of volunteer participants in a large, long-term clinical trial. Two pilot studies were conducted in different populations to test the feasibility of critical strategies for the long-term study. Thirteen percent of the asbestos-exposed workers and 18% of the smokers became inactive during the pilot study. Of those remaining active, all but 2% of asbestos-exposed workers pilot study participants and 5% of smokers pilot study participants chose to participate in the full-scale efficacy trial. Five baseline predictors of inactivity for the asbestos-exposed participants emerged: being non-White, being a current smoker, having a history of high blood pressure at baseline, reporting two or more increases in symptoms during the placebo run-in, and having higher baseline levels of negative mental health measures (i.e. anxiety, depression, and fatigue). The only significant predictor of inactivity for smoker pilot participants was reporting symptoms during the placebo run-in. The most frequently reported reasons for becoming inactive during the pilot studies were general health issues and problems and symptoms that were seen as specific to the CARET vitamins. These findings suggest areas that could be tested to optimize retention in clinical trials.

(**Ann Behav Med** 1999, *21*(3):210–215)

INTRODUCTION

Retention of participants for intervention and follow-up activities is critical in cancer chemoprevention trials. Use of the intention to treat principle (1) means that, once randomized, a participant's follow-up data must be included in endpoint analyses, regardless of the participant's adherence with the study protocol. Therefore, the power of the study is enhanced if adherence to the intervention and follow-up activities is maximized. Conversely, any participant who does not adhere to the protocol will reduce the power of the study and may affect the study's ability to detect differences in the main disease outcomes.

Several characteristics of these large-scale prevention trials make retention of participants difficult. For example, the length of follow-up is usually several years; the study population is usually healthy, even if at higher than average risk for a specific cancer; clinical care is generally not provided; and the direct potential benefit to any single individual is small. Several thousand participants are usually required to test the preventive regimen's efficacy, with lack of frequent personal attention and contact increasing difficulties in retention. In addition, interventions with poor adherence are not useful in clinical practice. In order to enhance retention, there is a need for a better understanding of factors affecting retention and reasons for ending involvement.

Little has been published about retention patterns and predictors of retention in prevention studies. From the research on adherence to treatment regimens, we know that variables which act to reduce participation include complexity of the regimen, frequency of side effects and symptoms, increasing age, low educational and income levels among participants, and poor health (2,3). We must determine whether these findings apply to retaining participants in prevention trials, where attending follow-up visits is a key feature.

The Carotene and Retinol Efficacy Trial (CARET) provides an opportunity to study retention of volunteer participants in a large, long-term clinical trial. CARET is a randomized, double-masked lung cancer prevention trial conducted at six study centers across the U.S., with a coordinating center at the Fred Hutchinson Cancer Research Center, supported by the National Cancer Institute (4). CARET tested the efficacy and safety of the combination of 30 mg beta-carotene and 25,000 international units (IU) Vitamin A daily in preventing lung cancer in two high-risk populations: men and women who are current or former heavy smokers, and men with a substantial occupational history of exposure to asbestos, plus a history of cigarette smoking. The main outcome results have been reported (5,6). Briefly, there was no reduction in lung cancer rates for participants taking the active substance relative to these in the comparison arm. In fact, there was a slight increase in lung cancers among participants in the active substance

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arm of the study. Prior to the beginning of the efficacy trial, two smaller scale pilot studies were conducted to determine the feasibility and safety of the regimen in the two high-risk populations (7,8). This article reports the retention rates of participants in the CARET pilot studies, the predictors of retention, and the participant-stated reasons for refusing to continue active participation during the pilots or during the transition of participants from the pilot to the full-scale efficacy trial.

METHODS

The CARET Pilot Trials

The design of the CARET Phase II pilot studies has been previously published (6). To summarize here, the two studies assessed recruitment, safety and potential side effects of the intervention agents, and participant adherence to the intervention. The first trial in cigarette smokers was a 2 × 2 factorial trial of 30 mg beta-carotene versus placebo and 25,000 IU retinol daily versus placebo (7). Participants for the smoker trial were recruited from a mailing to local health insurance company subscribers, beginning in June 1985 and ending in December 1987. Letters were mailed to subscribers inviting participation, together with an eligibility questionnaire measuring simple health and demographic questions. Subscribers who mailed back the questionnaire and were eligible received a telephone call. These potential participants were screened for eligibility by telephone and invited to an initial clinic visit, at which eligibility was confirmed and baseline data were collected. Eligibility requirements included age (50–69 years), a smoking history of at least 20 pack-years, and either current smokers or former smokers who had stopped within 6 years of randomization into the study. Six years was selected as a cutoff to maximize participant risk from tobacco exposure. Eligible participants were entered into a 2-month placebo run-in period where they needed to maintain at least an 80% adherence to the study pills to remain eligible to be randomized. Symptoms were collected before and after the recruitment period. Eligible and interested participants were randomized to one of the four study arms and provided with the appropriate study pills. Approximately 3.7% of initial contacts yielded randomized participants, due to both eligibility requirements and lack of interest. Follow-up contacts were conducted every 2 months, alternately in person and by telephone, at which time health status, subjective (i.e. self-report) and objective (i.e. nurse-monitored) symptoms and signs, and adherence to taking the study pills were assessed. If participants showed signs or reported symptoms associated with potential pill toxicity, they were removed from the trial. Toxicity was defined as scoring a 4 or 5 in monitored signs and symptoms. The average length of time on the CARET pilot study was 10 months, approximately the planned length of time for the pilot studies.

The second pilot study recruited asbestos-exposed workers from groups of men known to have occupational exposure to asbestos (8). Recruitment sources included workers compensation programs, legal offices, pulmonary physicians, and major workplace and union groups in the areas known to have received significant asbestos exposure. The recruitment period for the Asbestos-Exposed Workers Pilot ran from June 1985 through July 1988. Eligibility criteria included age 45–74, asbestos exposure beginning at least 15 years prior to entry into the study, and either a positive chest x-ray for changes consistent with asbestos-related fibrosis of the parenchyma or the pleura or 5 years exposure in one or more of eight specified high-risk trades. Participants were randomized to 15 mg beta-carotene plus 25,000 IU retinol or placebo. Screening and follow-up procedures were similar to the procedures described for the Smokers Pilot. Baseline chest x-rays and biennial spirometry exams were offered in the Asbestos-Exposed Workers Pilot as an inducement and to obtain relevant risk factor data. All current smokers in both pilots were offered stop smoking assistance.

Transition to the Efficacy Study

Based on the success of the pilot studies in recruiting and retaining participants from the two risk groups and lack of detectable toxicity, a full-scale efficacy trial was designed and implemented beginning in July 1988 and eventually including 18,314 participants (4). The intervention for the efficacy trial was 30 mg beta-carotene plus 25,000 IU retinyl palmitate versus placebo. All of the living pilot study participants were asked to participate in the efficacy study. For those agreeing, this transition occurred at the pilot participant's regularly scheduled annual visit between July 1, 1988, and June 30, 1989, and consisted of a discussion of the new procedures and nature of the long-term efficacy trial, with a new informed consent.

Assessments

The following key variables were measured during the screening and follow-up visits, as indicated previously.

Demographics: Race and age of participants were all assessed using common single-item measures with response categories (gender, race) or blanks (age). Race was coded as White (code = 0) or non-White (code = 1), and age was treated as a continuous variable.

Smoking Status: Participants were asked whether or not they currently smoked cigarettes and coded as current smoker (code = 0) or current nonsmoker (code = 1).

Karnofsky Index: The Karnofsky Performance Status Scale is an 11-point clinician rated system that provides information on the extent of disability due to disease (9,10). Each participant scored from 0 (*dead*) through 5 (*requires considerable assistance and frequent medical care*) to 10 (*normal; no complaints*). At screening, potential participants with Karnofsky scores of 6 or below were ineligible.

Medication: All participants were asked the type, frequency, and duration of any prescription medication that they currently took. For this paper, participants were coded as taking prescription medication (code = 1) or not (code = 0).

Cancer Familial History: Participants reported all family members with any cancer history. Here we coded family history in a first-degree relative as positive (code = 1) or none (code = 0).

High Blood Pressure: Participants responded yes (code = 1) or no (code = 0) to a list of health problems as having ever occurred in their lives. We selected blood pressure from the list as a general indication of health status.

Multivitamin User: During the medication history, we collected data on use of over-the-counter substances. The variable for this analysis represents current multivitamin use (code = 1) or no use (code = 0).

Symptoms: Before and after the run-in period and at every trial visit, trained nursing staff rated each participant on a series of symptoms and signs. Each was rated on a scale of 1 to 5, where 1 was normal, and 5 was expression of severe symptom or sign. The

monitored signs and symptoms included skin redness, skin dryness, skin yellowing, chapped lips, bone pain, nose bleeds, hair loss, appetite change, weight change, headaches, nausea or vomiting, change in bowel movements, anxiety, depression, and fatigue. These data were gathered and scored using a mixture of observational ratings and queries to the participant. The symptom variable used for analyses was the reported increases from pre to post run-in period in two or more symptoms (code = 1), or none or only one symptom (code = 0). Scores for three of the signs were averaged to form a baseline mental health scale: anxiety, depression, and fatigue.

Analyses

We classified participants as inactive, for reasons other than death, when they were unable or unwilling to participate in the necessary CARET follow-up visits to collect data, check for symptoms, or adhere to the intervention regimen. At the time that the participant indicated that she or he no longer wished to participate actively in CARET, a trained interviewer asked the participant to state all the reasons for becoming inactive and coded the responses into a standardized list of reasons; no limit was placed on the number of reasons recorded. We used the word "inactive," rather than the more traditional word "dropout" because we followed participants using a reduced contact schedule even though they no longer participated in active intervention procedures.

Participants who inactivated on or before July 1, 1988 were classified as having become inactive during the pilot study; participants inactivating after July 1, 1988 were considered to have inactivated during the transition to the full-scale efficacy trial. For most participants, the date of inactivation was defined as the day the study center was notified that the participant no longer wished to take study vitamins; the participant may have actually stopped taking the capsules at an earlier date. Eighteen of the 1,845 participants were lost to follow-up during the pilot study, after intensive effort was made during the transition period to account for all randomized participants. Thus, for the 18 participants, the inactivation date was defined as either the last contact with the study center prior to notification of inactivation or the last day they took study vitamins, whichever was most recent.

To examine the predictors of inactivity during the pilot studies, we calculated maximum likelihood estimates using Cox Proportional Hazards Regression Models and tested hypotheses about the regression parameters with likelihood ratio statistics. Cox regression differs from logistic regression by including the time that the event occurred. In the present analyses, the event is inactivation, and the time scale used is days from randomization to inactivation. The inactivation date for participants who remained active throughout the pilot study was July 1, 1988, the last day before transition visits started. Cox regression model estimates are based on comparisons of those who inactivate (have the event) at each (event) time to those who remain active beyond that time. Parameters in the Cox model estimate the log relative risk of the inactivation rates associated with a unit change in a continuous covariate, such as age. In the simple case of dichotomous covariates (e.g. race = 1 or 0), the parameters estimate log relative risk for those with the covariate compared with those without the covariate.

Standard logistic regression was used to assess predictors during the transition period, as a Cox regression analysis utilizing time of event information is less appropriate due to the brief time window in which these inactivations occur. Due to the small number of asbestos-exposed participant inactivations during the transition period (n = 16), only one logistic regression model was fit for the transition period, combining data from the two exposure populations. In both models, all variables were entered simultaneously for a multivariate comparison.

RESULTS

Description of Participants

A total of 1,845 participants were randomized in the pilot studies: 816 (44%) participants in the Asbestos-Exposed Workers Pilot study and 1,029 (56%) in the Smokers Pilot study. Table 1 presents the demographic variables considered in the regression analyses and their coding. Twenty-seven asbestos-exposed participants were excluded from the analyses due to missing demographic data; of these 27 participants, 4 inactivated during the pilot study (none inactivated during the transition to the full-scale trial). An additional 4 asbestos-exposed participants, who were enrolled in the pilot study but not randomized until the transition period, were excluded from the analysis of pilot study inactivations due to having no postrandomization follow-up prior to the transition. Among the heavy smokers, 59 participants were omitted from the analyses for the same reasons as the asbestos participants; 10 and 5 inactivated during the pilot and transition periods, respectively. There where no patterns of difference between the study arms for missing data.

Participants became inactive both during the pilot studies and during the transition to the efficacy trial. Thirteen percent of the Asbestos-Exposed Workers Pilot study participants and 18% of the Smokers Pilot study participants became inactive during the pilot study. Of those remaining active throughout the pilot, all but 2% of the Asbestos-Exposed Workers Pilot participants and 5% of the Smokers Pilot study participants chose to participate in the efficacy trial.

Tables 2 and 3 present the baseline predictors of becoming inactive during the CARET pilot studies, up to but not including the transition. As seen in data presented in Table 2, five baseline predictors of inactivity for the asbestos-exposed participants reach or approach significance: being non-White, smoking status, having a history of high blood pressure at baseline, reporting two or more increases in symptoms during the placebo run-in, and having higher baseline levels of negative mental health measures (i.e. anxiety, depression, and fatigue). Other variables, including age and familial cancer history, were not significant predictors.

Table 3 presents a similar analysis for the smokers pilot participants. The only significant predictor of inactivity for smokers pilot participants was reporting symptoms during the placebo run-in. There were hints of similar influence of high blood pressure, which was predictive in the asbestos population, and of the Karnofsky scores. Note that the direction of the blood pressure effect is in the opposite direction here: high blood pressure is associated with inactivation for the asbestos population and retention for smokers.

In Table 4, we present results of a logistic regression model predicting inactivation during the transition from pilot study to efficacy study. Only 54 participants became inactive; meanwhile, 2 previously inactive participants took advantage of the invitation to reactivate at this juncture. We combined participants from the two pilot studies because there were no significant patterns of differences between the two pilot studies and because of the small sample sizes in the asbestos study (n = 19 in the asbestos study failed to make the transition). When the analyses were conducted separately for each study, no consistent patterns of difference were

TABLE 1
Baseline Demographic and Health-Related Information of Participants

Variable (Model Coding)	Asbestos-Exposed Workers N	Asbestos-Exposed Workers %	Heavy Smokers N	Heavy Smokers %
Gender				
Male (0)	789	100	510	52.6
Female (1)	0	0	460	47.4
Race				
Non-Caucasian (0)	52	6.6	30	3.1
Caucasian (1)	737	93.4	940	96.9
Smoker Status				
Never/Former (0)	617	78.2	306	31.5
Current (1)	172	21.8	664	68.5
Karnofsky (Continuous)				
5	1	0.1	0	0
6	22	2.8	8	0.8
7	81	10.3	28	2.9
8	216	27.4	92	9.5
9	126	16.0	188	19.4
10	343	43.5	654	67.4
Medication				
No (0)	331	42.0	309	31.9
Yes (1)	458	58.0	661	68.1
Familial Cancer History				
No (0)	338	42.8	326	33.6
Yes (1)	451	57.2	644	66.4
High Blood Pressure				
No (0)	528	66.9	686	70.7
Yes (1)	261	33.1	284	29.3
Multivitamin User				
No (0)	542	68.7	546	56.3
Yes (1)	247	31.3	424	43.7
Run-In Symptoms (Reports increases in two or more symptoms)				
No (0)	684	86.7	871	89.8
Yes (1)	105	13.3	99	10.2
Age (Continuous years)				
45–49	157	19.9	0	0
50–54	132	16.7	195	20.1
55–59	150	19.0	312	32.2
60–64	156	19.8	319	32.9
65–69	115	14.6	144	14.8
70–74	79	10.0	0	0
Mental Health (Continuous) (Sum of anxiety, depression, and fatigue measures)				
3–5	420	53.2	512	52.8
6–8	296	37.5	405	41.8
9–11	62	7.9	48	4.9
12–15	11	1.4	5	0.5

found. Two variables significantly predicted the choice not to make the transition to the full-scale efficacy study: smoking status (with current smokers less likely to make the transition) and number of months on the study (with those on the study for the shortest time less likely to make the transition). In addition, experiencing run-in symptoms was of borderline significance in predicting inactivity during the transition to the full-scale study, in that those experiencing run-in symptoms were less likely to inactivate during the transition.

Table 5 (left side) shows the reasons stated for becoming inactive during the pilot studies for asbestos-exposed workers and smokers pilot participants. The "Personal Reasons" category included family and work priorities, such as demands on time, illness, and death. "Miscellaneous" was a mixture of items, including fulfillment of obligations, spouse becoming inactive, and refusal to give a reason. The most frequently reported reasons for

TABLE 2
Predictors of Inactivity During the Pilot Study—Asbestos-Exposed Participants*

Predictors (Coding)	Parameter Estimate	Significance	Risk Ratio	95% Confidence Limits
Race	−0.64	0.07	0.53	0.28–1.00
Smoking Status	0.39	0.10	1.47	0.94–2.31
Karnofsky	0.10	0.29	1.10	0.92–1.32
Medication	0.05	0.82	1.06	0.66–1.69
Cancer History	−0.03	0.87	0.97	0.65–1.45
High Blood Pressure	0.53	0.01	1.70	1.12–2.60
Multivitamin Use	0.28	0.18	1.33	0.88–2.00
Run-In Symptoms	0.46	0.08	1.58	0.96–2.59
Age	0.02	0.27	1.02	0.99–1.04
Mental Health Score	0.11	0.03	1.12	1.01–1.24

* $N = 789$; 99 became inactive.

TABLE 3
Predictors of Inactivity During the Pilot Study—Smoker Participants*

Predictors (Coding)	Parameter Estimate	Significance	Risk Ratio	95% Confidence Limits
Gender	0.17	0.29	1.19	0.86–1.63
Race	0.01	0.98	1.01	0.44–2.48
Smoking Status	−0.14	0.39	0.87	0.64–1.19
Karnofsky	−0.15	0.12	0.86	0.72–1.04
Medication	−0.05	0.79	1.05	0.74–1.48
Cancer History	−0.13	0.41	0.88	0.64–1.20
High Blood Pressure	−0.28	0.11	0.75	0.53–1.08
Multivitamin Use	−0.10	0.49	0.90	0.67–1.22
Run-In Symptoms	0.52	0.02	1.69	1.11–2.56
Age	−0.02	0.15	0.98	0.94–1.01
Mental Health Score	0.06	0.23	1.06	0.96–1.16

* $N = 970$; 180 became inactive.

TABLE 4
Predictors of Inactivity During the Transition to the Efficacy Study—Both Pilot Studies*

Predictors (Coding)	Parameter Estimate	Significance	Risk Ratio	95% Confidence Limits
Population	0.43	0.30	1.54	.68–3.49
Gender	0.34	0.33	1.41	0.70–2.85
Race	0.78	0.39	2.18	0.29–16.27
Smoking Status	0.80	0.02	2.22	1.13–4.36
Karnofsky	−0.19	0.23	0.83	0.62–1.12
Medication	0.04	0.91	1.04	0.54–1.99
Cancer History	−0.16	0.58	0.85	0.48–1.52
High Blood Pressure	−0.11	0.73	0.89	0.47–1.71
Multivitamin Use	−0.02	0.94	0.98	0.55–1.73
Run-In Symptoms	−0.75	0.17	0.47	0.14–1.56
Age	−0.03	0.27	0.97	0.92–1.02
Mental Health Score	0.09	0.24	1.10	0.94–1.28
Months on Study	−0.04	0.04	0.96	0.93–1.00

* $N = 825$; 54 became inactive.

TABLE 5
Reasons for Becoming Inactive During the Pilot and Transition to the Full-Scale Trial*

	Pilot Study		Transition to Full-Scale Trial	
	Asbestos-Exposed Participants (Percent who report as reason)	Smoker Participants (Percent who report as reason)	Asbestos-Exposed Participants (Percent who report as reason)	Smoker Participants (Percent who report as reason)
Monitored Symptoms	18	29	19	16
Liver Disease	1	1	0	0
Cancer	11	6	13	9
Heart Attack/Disease	2	4	0	7
General Health Issues	42	53	31	49
Personal Reasons	6	12	0	19
Location and Transportation	11	14	25	28
Study Procedures	3	9	13	12
Wants to Take Beta-Carotene or Vitamin A	2	0	0	5
Primary Medical Doctor Advised Not to Participate	7	8	13	2
Miscellaneous	5	6	0	12
Loss of Interest	8	4	0	0
Too Busy	5	8	6	0
Too Many Medications	3	3	0	7
Other	15	12	19	28
Total Number Becoming Inactive	103	190	16	43
Number of Deaths While Active	15	14	6	2

* Participants can give more than one reason.

becoming inactive during the pilot studies were general health issues, monitored symptoms seen by study staff as specific to the CARET vitamins, and practical problems with study center location and transportation to the study center.

The reasons given for declining to make the transition to the efficacy trial are listed in the right-hand column of Table 5. As can be seen in this table, the most common reasons for not making the transition to the full-scale study are the same as those given during the pilot studies: monitored symptoms, other health issues, and location and transportation, although location and transportation were mentioned more frequently during the transition by both asbestos and smoker participants.

DISCUSSION

Retention of participants in both pilot studies was high, as was the number of participants agreeing to make the transition to the full-scale efficacy study. The rates far exceeded those predicted in the CARET design (4). This was true even though the pilot protocols required participants to stop taking pills if they had severe monitored symptoms. One of the goals of the pilot studies was to identify how best to monitor symptoms in the larger trial to insure the safety of participants taking a long-term prevention agent. We found no difference in monitored symptom rates between active and placebo arms in the pilot studies (7,8) and designed the full-scale protocol accordingly.

The only predictor of inactivation common to both the smoker participants and the asbestos-exposed participants was reporting of symptoms during the 2-month placebo run-in period. Participants reporting symptoms during the run-in were doing so in the absence of an active substance. These participants readily attributed the sensations they felt during the run-in to the pills, and perhaps they did so during the study as well. They might have been more likely to drop out due to concern about the sensations and possible future health problems attributed to the study pills. Having high blood pressure at baseline predicted retention in smokers and predicted inactivation in asbestos-exposed subjects. One possible explanation is that in the sicker group (asbestos subjects), being labeled as even sicker was a reason to become inactive, while in smokers, living with the "sicker" label was more motivating. Other predictors of inactivation—non-White race, higher levels of negative mental health at baseline—were limited to the asbestos-exposed population. Demographics of the asbestos-exposed population differ from the smoker population in many ways; notably, the population was all male and predominantly blue-collar workers and more symptomatic and less well than the smoker population. The unique nature of the asbestos participants may make them vulnerable to more anxiety, depression, and fatigue.

Predictors of not transitioning to the efficacy study were different from predictors of inactivation during the pilot studies. Measures of ill health at baseline such as a history of high blood pressure, cancer history, medication, and Karnofsky score did not appear as predictors of transition to the efficacy study. It was assumed initially that these individuals who were quite ill would be unable to participate in CARET because of the intensive visit and data collection requirements. Even with a truncated distribution of Karnofsky scores at baseline (7–10), Karnofsky score predicted retention during the pilot. Perhaps the effects of baseline Karnofsky score only affected participation in the immediate future. By the time of transition, the baseline health status was too distal to effect the decision to continue.

These findings suggest additional methods for optimizing retention in clinical trials; although, these methods should be rigorously evaluated for improvement in retention. For example, our results indicate that, prior to randomization, it may be beneficial to screen participants who report symptoms during the run-in period for their willingness or ability to participate in the study. The study protocol could anticipate ways to accommodate participants who experience illness during the study, based on the self-reported reasons for inactivation. This may include less frequent visits to a study center, substitution of visits with a

telephone contact on a temporary or permanent basis, or allowing a participant to discontinue the intervention on a temporary basis and to later restart. When designing a study, investigators must recognize that participants will enter studies at differing ages and may not fulfill the commitments they made at the beginning of the study. Accommodations in the protocol similar to those for ill health may improve retention of such participants.

These findings have relevance for research and program development in real-world clinical settings, although the data must be first replicated in these settings. The requirements of a research project—pill taking, attending visits, reporting symptoms, etc.—are similar to those found in a clinical setting, where participants take medication, come to clinic, and monitor side effects. Therefore, future research could apply these findings to a clinical setting. Early symptoms, even if not due to the treatment regimen, may be predictors of poor treatment adherence. Development of comorbidity may interfere with any treatment plan. Special supports and reminders for adherence to a treatment plan may need to be developed for patients who become more symptomatic during the course of a chronic illness. Labeling individuals as "sick" or "at risk," as in the asbestos group, may cause different vulnerabilities to later adherence problems, while healthy individuals may respond to the same treatment with better adherence. This line of research deserves careful attention.

The results of the pilot studies indicated that the intensive recruitment, screening, and follow-up procedures necessary to conduct the full efficacy trial, CARET, were feasible. The results of the efficacy trial, recently published (5,6), confirmed that, in such large-scale prevention trials, it is feasible to maintain a cohort of motivated participants for enough years to test prevention-related hypotheses and obtain significant answers.

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