

Short Communication

Predictors of Inactivation and Reasons for Participant Inactivation during a Skin Cancer Chemoprevention Study¹

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Abstract

Maintaining good compliance is a major challenge in long-term cancer chemoprevention trials. Minimizing the number of inactive participants during a trial is an important factor in maximizing compliance. Identifying reasons for and predictors of inactivation is the first step in being able to reduce participant inactivation. In this skin cancer chemoprevention trial, the 2,297 participants were randomized to receive 25,000 IU of retinol daily or a placebo. Median follow-up time was 3.8 years. The reason for inactivation was determined for each participant who stopped taking the study capsules. Six hundred and seventy-seven (29.7%) participants became inactive during the 5-year study. There was no significant difference between the number of participants inactivating by treatment group or sex. The most common reasons for inactivation were illness of subject, spouse, or a close relative (18.6%) and experience of a clinical symptom consistent with vitamin A ingestion (17.1%). Participants in the vitamin A group (10.1%) more frequently cited symptoms coded as “not consistent with vitamin A” as the reason for inactivation compared with those in the placebo group [5.4% ($P < 0.05$)]. The inactivation rate was highest in the first month of the trial and declined thereafter. A low education level (hazard ratio, 1.59) and unmarried status (hazard ratio, 1.29) were the only significant predictors of inactivation. These findings may be useful in developing targeted strategies to decrease inactivation and thereby increase compliance in future chemoprevention trials. However, these findings need to be confirmed because published research in this area is very limited.

Introduction

One of the major goals in a chemoprevention trial is maintaining good compliance with the study regimen throughout the trial. Once participant accrual has been achieved, the power of a trial is dependent on participant compliance with the study

regimen. In large part, good compliance is achieved by keeping participants active in the study because by definition, once a participant becomes inactive, their compliance becomes zero. The term “inactive” has been used instead of the traditional word “dropout” because dropout infers that a participant had no further involvement in a study, whereas those who become inactive continue to be followed periodically for ascertainment of the study end point. Minimizing the number of participants who become inactive is of great importance to researchers in this area.

Chemoprevention trials are generally of long duration and require large numbers of participants; any benefit is not measurable by the individual. All of these factors are likely to reduce compliance with the study regimen. When large numbers of participants are involved in a trial, it is very expensive and difficult to give the individualized attention to each participant that might enhance compliance. Data from treatment trials show that when a participant does not perceive that the intervention is beneficial to them, they are less likely to remain active (1).

Few published reports have evaluated the reasons for inactivation or predictors of inactivation in prevention trials. In the CARET³ Phase II pilot studies, significant predictors of inactivation for the asbestos-exposed participants were being nonwhite, having a history of high blood pressure, having higher baseline levels of negative mental health (*i.e.*, anxiety, depression, and fatigue), and reporting of specific symptoms during the placebo run-in period (2). In the smoker participants, the reporting of symptoms during the placebo run-in period was the only significant predictor of inactivation (2). Participants in these trials were at high risk for lung cancer but otherwise healthy. The most common reasons for inactivation in both pilot studies were general health issues and reported monitored symptoms that were seen as specific to the CARET vitamins. In a study of the outcomes of a placebo run-in period in a head and neck cancer chemoprevention trial, the authors reported that 35 of 391 former cancer patients were not randomized after a placebo run-in period (3), mainly due to loss of interest in participation ($n = 20$). A Karnofsky score of 100 and at least a high school education were significant predictors of randomization after the placebo run-in phase. Lower compliance in treatment regimens has been found to be associated with low educational levels, complexity of the regimen, and frequency of side effects and symptoms (4, 5). Some studies have found lower compliance associated with increasing age, but this is not a consistent finding (4).

Reasons for inactivation are of importance to researchers for at least two reasons. Firstly, an imbalance in inactivation rates between treatment arms for a specific reason may indicate that the intervention is having detrimental effects. Generally,

Received 1/17/00; revised 6/14/00; accepted 6/26/00.

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¹ Supported by National Cancer Institute Grants CA-34256, CA-27502, and CA-23074.

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³ The abbreviations used are: CARET, Carotene and Retinol Efficacy Trial; HR, hazard ratio; CI, confidence interval.

anticipated adverse effects would be detected by routine monitoring. However, subtler detrimental effects, such as a change in some aspect of quality of life, may only be detected through the monitoring of inactivation rates and reasons for inactivation. Secondly, monitoring of the reasons for inactivation may afford the opportunity to address some of the reasons while the trial is ongoing. Identifying predictors of inactivation could allow a group of participants to be targeted to receive enhanced support to maintain their active status and thus decrease the ultimate inactivation rate.

Describing predictors of inactivation may also be useful for future studies. With such knowledge, researchers could, if appropriate, exclude individuals at greater risk of becoming inactive or preferably offer greater support to them once enrolled in a trial. In this study, the reasons for participants becoming inactive while enrolled in a large skin cancer chemoprevention study are described. Characteristics of participants who became inactive are also discussed.

Materials and Methods

Trial Design. A total of 2,297 participants who had at least 10 clinically diagnosed actinic keratoses were randomized to receive either 25,000 IU of vitamin A (retinol) daily or a placebo. If eligible, participants were randomized to the trial after a 3-month placebo run-in period. Eligibility criteria included a 75% or greater compliance rate during the run-in period as measured by capsule count. The study, conducted at the University of Arizona Cancer Center, was approved by the University of Arizona Human Subjects Committee, and informed written consent was obtained from all participants. The details of the trial design and results have been described elsewhere (6–8).

Demographic information and other baseline information were collected by use of a self-administered questionnaire at the enrollment visit. Participants were seen 1 month after their randomization visit and semiannually thereafter. At each visit, participants were asked specifically if they had experienced specific symptoms and/or health problems (8). When a participant reported a symptom or sign classified as possibly related to vitamin A ingestion, the interviewer categorized the severity using standardized definitions. A set protocol was used to determine whether dose reduction or cessation of the capsules was necessary (8) to assess the association between the symptom and the intervention.

Blood parameters were assessed at enrollment (3 months before randomization), at 1 month after randomization, and annually thereafter. Dose modification, following a set protocol, was used if any of the prespecified safety criteria were met (8).

A participant was defined as inactive if he/she discontinued the study capsules permanently. Accommodation was made where possible to maintain a participant's active status; when necessary, a participant could permanently reduce their dose or temporarily discontinue their study capsules and still remain active. For example, a participant who reported a symptom deemed "not associated with vitamin A," such as stomach pains, could stop and start the capsules to see if their symptom was associated with taking the capsules without becoming inactive. However, if the participant decided to stop taking the capsules, the participant was inactivated.

When a participant became inactive, the reason for his/her inactivation was categorized by the interviewer into one of four categories: (a) participant had a symptom consistent with vitamin A; (b) participant had a symptom that was not consistent

Table 1 Reasons for subjects becoming inactive

Reason	Vitamin A N (%)	Placebo N (%)	P
Abnormal blood parameter	29 (8.4)	35 (10.6)	0.33
Clinical symptom	60 (17.3)	56 (16.9)	0.88
Both clinical symptom and abnormal blood parameter	1 (0.3)	3 (0.9)	0.29
Symptoms not consistent with vitamin A	35 (10.1)	18 (5.4)	0.02
Illness of subject, spouse, or close relative	60 (17.3)	66 (19.9)	0.38
Participant moved out of the locality of the study center	18 (5.2)	17 (5.1)	0.99
Too busy or lost interest	30 (8.6)	17 (5.1)	0.07
Lost to follow-up	17 (5.9)	15 (4.5)	0.81
Fulfilled commitment to study	18 (5.9)	26 (7.6)	0.16
Fear of possible side effects from intervention	10 (2.9)	12 (3.6)	0.59
Other	68 (19.6)	66 (19.9)	0.93
Total	346	331	

with vitamin A; (c) participant not willing to continue; or (d) participant lost to follow-up. A symptom consistent with vitamin A toxicity was defined as being one of the 14 clinical symptoms or one of the specified laboratory assessments that were being monitored during the trial. The interviewer recorded a narrative describing the reason for inactivation at the time of inactivation. Only one reason for inactivation was coded for each participant. When more than one reason was given for inactivation, the interviewer asked further questions to determine which of the multiple reasons was the foremost reason for the participant's inactivation. The exception to this was when a participant stated that a symptom consistent with vitamin A was one of the reasons for their inactivation; in this case, "symptom consistent with vitamin A" was the reason coded. At the end of the study, the reasons for inactivation were reviewed by one of the authors (B. C.) and further categorized as shown in Table 1.

Statistical Analysis. The χ^2 test was used to analyze the reason for inactivation as reported by participants at the time of discontinuation of the capsules, and Cox proportional hazards analysis was used to analyze baseline predictors of inactivation. Fifteen of the 2297 randomized participants were determined to be ineligible for the study after being randomized. These participants were asked to stop taking the capsules when they were determined ineligible and are not included in the analysis. Active participants who died were censored at date of death. All other active participants were censored at their last contact date. The date of last contact was used as the date of inactivation for participants who were classified as lost to follow-up ($n = 32$). The analysis investigating predictors of inactivation was conducted both including and excluding participants who were directed by the study staff to stop taking the study capsules due to symptoms associated with vitamin A.

Results

A total of 677 (29.7%) participants became inactive during the study (30.1% in the vitamin A group and 29.2% in the placebo group). There was no difference in the proportion of participants who became inactive by treatment group.

The reasons for inactivation by treatment arm are shown in Table 1. Examples of illnesses of the subject, spouse, or a close relative are cancer, stroke, and fractures. Symptoms coded as not consistent with vitamin A, such as dizziness, stomach pains, and diarrhea, were cited as the reason for inactivation more frequently by participants in the vitamin A group (10.1%) than

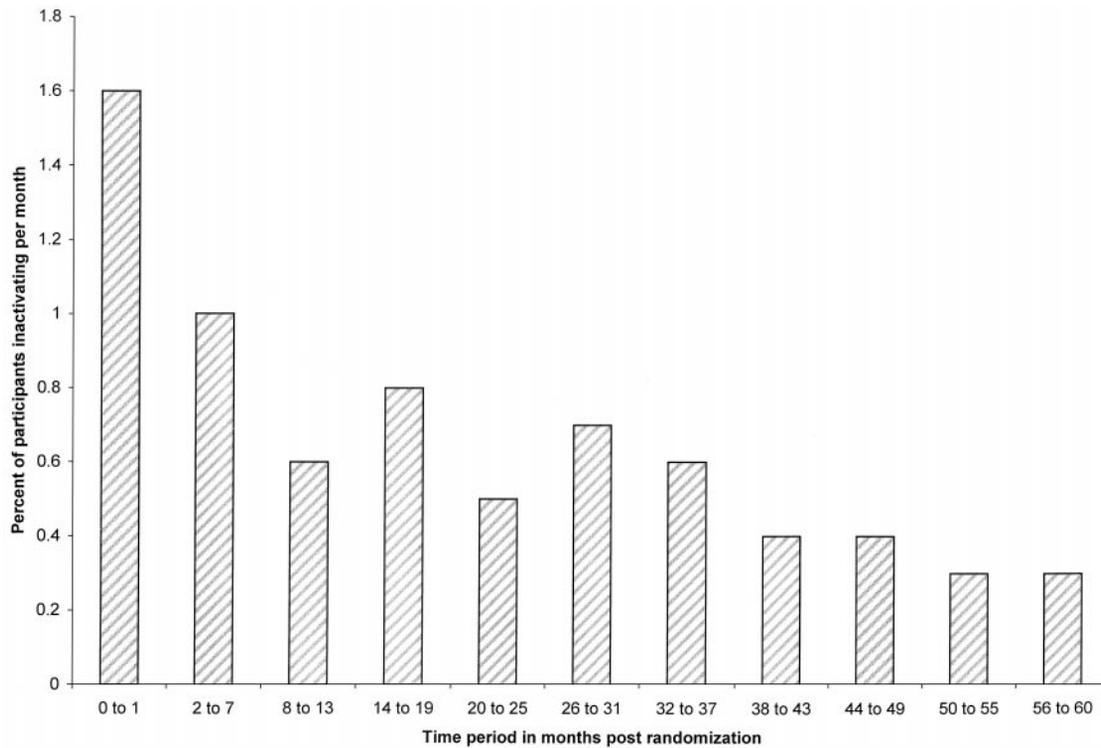


Fig. 1. The percentage of participants inactivating over the course of the study.

by those in the placebo group [5.4% ($P < 0.05$)]. Within this category, 12 participants (10 of whom were receiving vitamin A) described symptoms related to the gastrointestinal tract such as diarrhea and stomach pain.

There were no significant differences in the reasons given for inactivation between women and men. The number of participants becoming inactive over time is shown in Fig. 1. Note that in this table, the first period presented is only 1 month, as compared with 6 months for the other periods. These periods represent the length of time between visits. The monthly rates are expressed as a percentage of those who were active at the beginning of the period. The monthly inactivation rate was as follows: month 1, 1.6%; months 2–7, 1.0%; months 8–13, 0.6%; months 14–19, 0.8%; months 20–25, 0.5%; months 26–31, 0.7%; months 32–37, 0.6%; months 38–43, 0.4%; months 44–49, 0.4%; months 50–55, 0.3%; and months 56–60, 0.3%. The median time to inactivation was 18 months. The reasons for inactivation for the group who became inactive in the first 18 months of the trial were somewhat different from the reasons of those who became inactive after at least 18 months. All participants who became inactive because they felt they had fulfilled their commitment to the study did so after 18 months on study. In the first 18 months of the study, participants were more likely to become inactive because of a clinical symptom ($P < 0.05$), a symptom not associated with vitamin A ($P < 0.001$), or relocation away from the study center ($P < 0.05$). They were less likely to become inactive because of an abnormal blood parameter ($P < 0.001$) or loss to follow-up ($P < 0.05$).

Of the 64 participants whose reason for going off medication was due to having an abnormal blood value, 60 (94%) were required to discontinue their medication as per the study protocol. Similarly, 55 of the 116 (47%) participants whose

reason for going off medication was due to having a clinical symptom that might be related to vitamin A were required to discontinue the capsules.

Predictors of Inactivation. The demographic and personal characteristics of the study population are reported elsewhere (6, 7), except for a history of high blood pressure reported by 31.8% of participants and a prior health condition (namely, angina, heart disease, stroke, or diabetes) reported by 17.2% of participants. In the univariate analysis, participants who became inactive were more likely not to have graduated from high school (5.7% versus 8.9%; $P < 0.05$) and more likely to be unmarried (17.9% versus 23.9%; $P < 0.05$). No other characteristics were significantly different between those who became inactive and those who did not. Results from the multivariate model (Table 2) show that participants who did not graduate from high school had a significantly greater hazard of inactivating during the study compared with those who were college graduates (HR, 1.6; 95% CI, 1.2–2.2). High school graduates or those with some college education or vocational school training did not differ significantly from those who completed their college education.

The hazard of inactivation for those who were not married was 29% higher (HR, 1.29; 95% CI, 1.1–1.6) than that for participants who were married. Age at randomization was not related to the likelihood of inactivating. Current smokers at enrollment had an increased hazard of becoming inactive compared with those who never smoked (HR, 1.27; 95% CI, 0.99–1.61) that almost achieved statistical significance ($P = 0.06$), and former smokers compared with those who never smoked also had a somewhat increased risk of becoming inactive (HR, 1.16; 95% CI, 0.98–1.37). No differences in predictors of inactivation were seen when those participants who were re-

Table 2 Predictors of inactivity during a skin cancer chemoprevention trial

Predictors	Parameter estimate	Significance (P)	HR	95% CI
Gender	0.11	0.23	1.11	0.93–1.33
Treatment group	−0.002	0.56	1.00	0.99–1.00
Marital status	0.25	0.008	1.29	1.07–1.55
Age ^a	−0.003	0.51	1.00	0.99–1.01
Education				
College graduate or postgraduate	1.00			
Some college or vocational school	0.12	0.17	1.13	0.95–1.35
High school graduate	0.01	0.92	1.01	0.81–1.27
Some high school or less	0.46	0.002	1.59	1.19–2.12
Employment ^b	−0.04	0.71	0.96	0.79–1.17
Clinic	−0.15	0.07	0.86	0.73–1.01
Smoking status				
Never	1.00			
Former	0.15	0.09	1.16	0.98–1.37
Current	0.24	0.06	1.27	0.99–1.61
Vitamin user	0.005	0.96	1.00	0.84–1.19
Sunscreen user	−0.05	0.55	0.95	0.80–1.12
Prior health condition	0.02	0.84	1.02	0.83–1.26
High blood pressure	0.11	0.18	1.12	0.95–1.32

^a Entered as a continuous variable in the multivariate model.

^b Entered as employed *versus* not employed in the model.

quired to discontinue the study because of an abnormal blood index or clinical symptom were excluded from the analysis.

Discussion

The finding that there were no differences in the proportion of participants becoming inactive between the two treatment groups supports the finding that there were no overt side effects of long-term ingestion of 25,000 IU of vitamin A (8). However, these study results should be viewed in the light that they are based on a secondary analysis of the trial data; this analysis was not the major objective of the trial.

The two predictors of inactivation identified in this study, being unmarried and having less than a high school education, have been reported to be associated with lack of compliance in treatment trials (4), and low educational level has been associated with less likelihood of being randomized after a placebo run-in period in a head and neck cancer chemoprevention trial (3). However, in the two pilot CARET studies, neither of these demographic variables was associated with inactivation (2).

Inactivation early in the study (the highest rate in our study was in the first month of the study) has a much greater effect on the power than inactivation later in the study (9). A longer or more rigorous run-in period to prevent randomization of participants who are not fully committed to the study may reduce the number of participants inactivating early in the trial. However, this may affect the generalizability of results if subjects eliminated during the run-in differ on factors related to the primary outcome variables (10). It is unclear whether providing

more support during the early stages of a study would help decrease inactivation rates.

Because “illness of the participant, spouse, or relative” and “symptom not related to vitamin A” were commonly given as reasons for inactivation, future studies should explore methods in which the burdens of the trial could be minimized to retain such participants, such as reducing visit requirements, or participants could be reactivated, where possible.

Recovery of dropouts has been used successfully in at least one treatment trial (11), in which 70% of dropouts reestablished medication-taking behavior after a 6-month period. Reactivation was routinely offered to inactive participants in CARET; however, no report on the outcome of the program is available.

Our results add to the few detailed published studies of predictors of compliance in chemoprevention trials. There remains a need for additional studies to be published in this area so that a determination can be made as to whether there are any consistent factors that predict compliance. It is possible that the source populations differ so greatly that consistent predictors will not be identified. However, if consistent predictors are identified, methods can be developed and tested in future chemoprevention trials to increase compliance, tailoring interventions to participants whose profiles identify them as the most likely to become inactive.

Acknowledgments

We are indebted to Hoffman-LaRoche for providing the intervention capsules.

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Cancer Epidemiol Biomarkers Prev 2000;9:999-1002.

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