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Design and Recruitment for Retinoid Skin Cancer Prevention (SKICAP) Trials[1]

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Abstract

The retinoid skin cancer prevention (SKICAP) trials are a set of double-blind, randomized, placebo-controlled clinical trials. The SKICAP-actinic keratoses (AK) trial tests the hypothesis that daily supplementation of retinol (25,000 IU) for 5 years reduces the incidence of skin cancers in high-risk individuals, those with a history of greater than ten clinically or pathologically diagnosed AK and, at most, one prior pathologically confirmed cutaneous squamous cell carcinoma (SCC) or basal cell carcinoma (BCC). The SKICAP-SCC/BCC (S/B) trial tests the hypothesis that daily supplementation of retinol (25,000 IU) or 13-*cis*-retinoic acid (5 or 10 mg) for 3 years reduces skin cancer incidence in very high-risk individuals, those with a history of at least four pathologically confirmed SCCs or BCCs. Between 1984 and 1988, 2800 participants were enrolled at two clinics on the SKICAP-AK trial; and between 1985 and 1990, a total of 719 participants were enrolled at four clinics on the SKICAP-S/B trial. The initial recruitment strategy was referral by dermatologists, but low accrual necessitated the use of other strategies to achieve enrollment goals, which included involving additional clinics and using paid trial-specific advertisements in print and electronic media. Thirteen % of the SKICAP-AK participants and 36% of the SKICAP-S/B participants were enrolled through dermatologist referral, whereas paid advertisements resulted in enrollment of 87% of SKICAP-AK and 43% of SKICAP-S/B participants. A population-based skin cancer registry was used to identify and enroll the remaining 21% of the SKICAP-S/B participants. This communication describes the design of the trials, the strategies, results, and costs of recruitment, and baseline participant characteristics.

Introduction

The incidence rates of SCC[5] and BCC have continued to increase (1, 2).[6] Non-melanoma skin cancers (SCC and BCC) are the most common types of cancer in the United States, and their occurrence results in a substantial increase in the risk of additional skin cancers, morbidity rates, and treatment costs (3–8). Residents of Arizona experience a three to seven times greater incidence of nonmelanoma skin cancers than the general population of the United States.[6]

A history of AK has been accepted generally by dermatologists as a marker for identifying individuals at increased risk of skin cancer. In many cases, AK progress to nonmelanoma skin cancer and are, thus, potential premalignant lesions (5, 7, 9). A history of nonmelanoma skin cancer has been used to identify individuals at very high risk of subsequent skin cancer (4).

AK, SCC, and BCC have distinctive clinical and pathological characteristics, which makes their diagnoses routine for dermatologists. The relatively common diagnoses of these cutaneous lesions and the fact that they serve as markers of increased risk of subsequent skin cancer establishes nonmelanoma skin cancer as a model for cancer prevention research.

Retinoids have been the leading agents suggested to have cancer prevention effects in humans (10, 11). Although epidemiological studies have not produced consistent results on the association of vitamin A and the risk of cancer, clinical studies of the treatment of skin cancer, AK, and other proliferative lesions have produced encouraging results (12–18). In addition, retinol and its related compounds, retinoids, have been found to be active in the prevention of cancer occurring in several organs in animal studies, including epithelial sites such as the skin (19–24).

To evaluate the effect of retinoids in the prevention of nonmelanoma skin cancer, we designed and are completing two randomized chemoprevention clinical trials. This article describes the design, results, and cost of the trials; the recruitment strategies used to enroll participants; and the baseline characteristics of enrolled participants.

Materials and Methods

The retinoid skin cancer prevention (SKICAP) trials are two separate double-blind placebo-controlled, randomized chemoprevention clinical trials. The SKICAP-AK trial enrolled subjects from June 1984 through November 1988 to test the

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[5] The abbreviations used are: SCC, squamous cell carcinoma; BCC, basal cell carcinoma; AK, actinic keratoses; S/B, SCC/BCC; DSMC, Data and Safety Monitoring Committee; RA, retinoic acid; PSA, public service announcement.
[6] T. Moon, personal data.

hypothesis that retinol supplementation (25,000 IU/day for 5 years) reduces the incidence of skin cancer in high-risk individuals with a history of at least 10 AK. The SKICAP-S/B trial enrolled subjects from January 1985 through June 1990 to test the hypothesis that retinoid supplementation (25,000 IU/day or 10 mg/day 13-*cis*-RA for 3 years) reduces skin cancer incidence in very high-risk individuals with a history of at least four prior SCCs or BCCs. Both trials estimated the incidence of adverse effects associated with the study retinoids. The SKICAP trials were carried out at clinics in Phoenix and Tucson, AZ. Clinics were also established in Yuma, AZ, and San Diego, CA, for the SKICAP-S/B trial. At least one study dermatologist was assigned to each clinic to perform skin examinations.

Organization. The co-principal investigators who coordinated the trials had responsibility for the study protocol and all aspects of the trials. The Tucson Coordinating Center provided specially trained clinic coordinators to ensure uniform protocol conduct and a trained staff at each clinic to conduct subject recruitment, interviews, follow-ups, and extensive interface with subjects, investigators, and community dermatologists. The medical director (N. L.) provided inservice training and supervised selected skin examinations performed by all SKICAP clinic personnel to ensure standardized examination procedures.

Committees for the trials included: (*a*) the Scientific Committee of intramural faculty, which periodically reviewed the conduct and all scientific and medical aspects of the trials; (*b*) the Data Coordinating Committee, which provided data management and analyses of trial data; (*c*) the Pharmacology Committee, which independently analyzed subjects' blood specimens for retinoids and other serum nutrients without knowledge of the intervention assignment; and (*d*) the external DSMC, which independently reviewed trial data for beneficial and adverse affects. The Data Coordinating Committee prepared semiannual reports for the National Cancer Institute on the conduct and safety aspects of the trials, without specifying intervention assignment. Confidential progress reports were also prepared for the DSMC who were at liberty to unblind the trials as they saw fit. The DSMC developed guidelines for possible recommendation for early termination of the trials, according to a policy that required that extreme differences exist between intervention groups early in the conduct of the trials and that smaller differences exist as the trials progressed (25). The trials remained blinded, and the DSMC did not recommend early termination.

Subject Eligibility. The SKICAP trials eligibility criteria were: free-living women and men between 21 and 84 years of age; anticipated, 5-year minimal continual residence within travel distance of a SKICAP clinic; willingness to return for semiannual follow-up clinical visits; willingness to limit supplementation of nonstudy vitamin A to no more than 10,000 IU/day; ambulatory condition, capable of self-care and without diagnosis of life-threatening diseases; no diagnosis or treatment of cancer within 1 year of enrollment (other than SCC or BCC); clinical laboratory values within the 95% limit of normal for total cholesterol; liver function, serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT), WBC count, hemoglobin level, and platelet count; and no history of xeroderma pigmentosum or basal cell nevus syndrome.

Additional eligibility criteria were required for the SKICAP-AK trial, which included a history of >10 AK diagnosed clinically or pathologically, the most recent of which had to have been diagnosed within the preceding year; and a pathologically confirmed record of, at most, one prior SCC or BCC. Additional criteria for the SKICAP-S/B trial included a history of at least four pathologically confirmed SCC or BCC, the most recent of which had to have been diagnosed in the preceding year; a triglyceride level below the 95% upper limit of normal; and, for women, no childbearing potential and not breast feeding.

Subject Recruitment. Recruitment strategies for both trials included dermatologist referrals, PSAs, and self referrals resulting from paid media advertisements. Additionally, SKICAP-S/B participants living in southeast Arizona were identified through a skin cancer registry. The population-based southeast Arizona registry, including the three-county medical referral region for Tucson, was used from January 1990 throughout the remaining 15 months of recruitment. The practice logs of the Yuma and San Diego clinics included all patients seen by a single dermatological practice in each community.

PSAs were used constantly throughout the recruitment period for both trials and included press releases, newspaper articles featuring interviews with staff, radio announcements, and occasional TV announcements during newscasts. Posters and flyers describing the trials were distributed at various public places, including dermatologists' offices.

Letters were mailed to all dermatologists in the Phoenix and Tucson areas inviting them to refer their eligible patients for screening and enrollment.

The letters were often mailed monthly. Dermatologists were given a stipend of $75 for each of their patients who was successfully enrolled and randomly allocated to a trial intervention. Payment was based on the participants' self-report and the concurrence of the dermatologist. The purpose of the stipend was to reimburse the dermatologists for their efforts in reviewing patient records to ensure eligibility and for encouraging their patients to participate in the SKICAP trials.

Participant self-referral resulting from paid newspaper, radio and TV advertisements began in October 1985 and continued throughout the recruitment periods. Volunteers were screened for eligibility using a standardized procedure. They were asked how they had heard of the trials, and if they had a regular dermatologist and were scheduled for an enrollment visit. The participant self-report was the primary criterion for classifying him/her as a self-referral or a referral by a dermatologist. Paid advertisements were initially prepared by a professional agency, with consultation from an academic communications professional. The analysis of recruitment costs was based on simple descriptive statistics related to the number of paid advertisements, the funds expended for each type of media, and the number of self-referrals separately tabulated for each trial from October 1985 through the end of the recruitment periods.

Enrollment and Run-In (First) Visit. At the participants' first visit to a SKICAP clinic, they reviewed the study design and eligibility criteria and signed the informed consent. Information regarding the participant's socio-demographic status, sun exposure history, skin reaction to sun exposure, medical history, supplemental vitamin intake, smoking, and other health habits was recorded. Participants enrolled during the first 2 years of the SKICAP trials were informed that a 3-year study duration was planned. Those who enrolled after year 2 and those who continued on the study were informed of a 5-year study duration. Study dermatologists provided and documented skin examinations for all participants (if not already documented on SKICAP forms by their own dermatologist) and

completed the pathology checklist listing the date of all prior skin biopsies. All participants were asked to complete a self-administered food frequency questionnaire (26), which quantified the intake of both micro-and macro-nutrients. Participants provided a 33-ml fasting blood specimen for determination of the required clinical laboratory values. Participants also provided an additional 10-ml blood specimen for determination of preintervention retinyl palmitate plus retinol for SKICAP-AK participants and 13-*cis*-RA for SKICAP-S/B participants. Participants were informed that they would be contacted throughout the duration of the trials and monitored for skin cancer regardless of whether they continued to take their capsules.

SKICAP-AK participants were further informed that they would be randomly assigned to receive either daily capsules containing 25,000 IU retinol or placebo capsules. They then began a single-blind, 3-month placebo run-in period to evaluate their ability and willingness to adhere with the study protocol. They were given a bottle containing 100 placebo capsules and instructed to take one capsule each day but no more than one capsule per day. Participants were given a reusable seven-compartment capsule container to help with their intervention adherence and shown how to insert one capsule in each compartment weekly. Monthly medication calendars were also provided with instructions on recording the time of day capsules were taken and any questions the participant had on that day.

SKICAP-S/B participants were advised that they would be randomly assigned to one of three daily interventions: 25,000 IU retinol, 10 mg 13-*cis*-RA, or placebo. Participants with smaller body weight (<145 pounds) were assigned 5 mg/day; they similarly began a 3-month placebo run-in period and were given two bottles, one containing 100 retinol placebo capsules and a second containing 100 or 200 13-*cis*-RA placebo capsules, and were instructed to take no more than one or two capsules each day (depending on body weight). They were also instructed about the conduct of the protocol and given the same adherence aids.

Medication packaging, quality assurance, and labeling were provided by Hoffman-La Roche, Inc. (Nutley, NJ), and medication distribution was coordinated by the National Cancer Institute Drug Repository.

At the conclusion of the initial visit, the participants had their next appointment scheduled and received a reminder card before leaving the clinic. One month after the first visit, participants were contacted (initially by phone and as the trials progressed by mail) to motivate and monitor their adherence to the run-in schedule. Participants indicating that they had missed at least one capsule during the 7 days before this contact were mailed a SKICAP reminder bookmark. Those missing at least three capsules in the 7 days before this contact also received a telephone call to motivate adherence and were mailed a form outlining tips to help them remember when to take capsules. One month before the second visit, participants were mailed a postcard reminding them of the date and time of their upcoming SKICAP appointment.

Random Allocation (Second) Visit. When participants returned after the end of their run-in period, their remaining capsules were counted to determine the percentage of capsules not returned, and they had a personal interview. The interview confirmed eligibility, evaluated clinical symptoms and adherence, and invited questions the subject might have regarding the study protocol. Participants satisfying all eligibility criteria, achieving at least 75% capsule-count adherence, and willing to continue the study were considered eligible for the randomized portion of the clinical trial. Unknown to the participants, they were then randomly assigned and given a 6-month supply of capsules containing either the retinoid or the placebo, given further motivation and aids for adherence, informed to call the study clinic should they have questions between study visits, and scheduled for a follow-up visit.

Clinical laboratory values were reviewed, discussed with the participants, and shared with their physician. Values outside the 95% of normal limits required a repeat blood sampling. If the repeat clinical chemistry values were within the eligibility limits, participants were randomly assigned and given a supply of the assigned capsules. Clinical signs and symptoms questionnaires were repeated to provide the baseline (at the end of the run-in period but pre-randomization) assessment used to evaluate safety and adverse events.

A random permuted block design was used (size 4 for SKICAP-AK and size 6 for SKICAP-S/B). Intervention assignment was stratified according to the participants' self-reported sun exposure (<10 *versus* ≥10 per week) and anticipated skin reaction after 30 minutes of sun exposure (always or usually burns *versus* burns moderately, rarely, or never).

Follow-up Visits, Monitoring, and Motivating Adherence. Participants returned for study clinic visits 1 month after random allocation and then every 6 months thereafter. Clinical signs and symptoms questionnaires were completed during the interviews, adherence was evaluated by calculating the percentage of capsules not returned, medication calendars were collected, participants were motivated to adhere to medication schedules, participants' questions were discussed, and 6-month supplies of capsules were distributed.

If capsules were not returned during the visit, participants were asked to return the capsules to the clinic within the next week. Self-reports of adherence were used for participants not returning capsules within 1 week of their clinic visit. Annual blood specimens with random analyses of retinyl palmitate was another measure of adherence. Serum retinyl palmitate levels were only used to obtain group adherence assessment and were not used during follow-up visits.

Participants were contacted by telephone or postcard between visits so the clinic staff could assess symptoms, motivate and monitor adherence, and remind them about appointments. In addition, adherence was reinforced between visits by use of adherence aids (bookmarks or reminder tips), cards mailed for special occasions, and certificates awarded for appreciation. The participants' vital status were assessed yearly and during study close out (27).

Safety Monitoring. An assessment questionnaire was used to monitor clinical symptoms of alopecia, chelitis, conjunctivitis, dry skin, dysuria, epistaxis, exanthems, fatigue, headaches, menstrual changes, nausea/vomiting, peeling palms or soles, skin infections, and stiffness. Information on clinical symptoms was collected at each follow-up visit. Clinical laboratory analyses of blood specimens were performed to monitor levels of serum total cholesterol, liver function (SGOT and SGPT), WBC count, hemoglobin, platelet count, and triglyceride (SKICAP-S/B only). Clinical laboratory information was provided from a 33-ml blood specimen collected at the first and third visits (1 month after random allocation) and then every year for SKICAP-AK participants and every 6 months for SKICAP-S/B participants. Blood specimens were measured by a standard automated multitest analysis at different laboratories of a commercial pathology service. Normal ranges were based on the specific clinical laboratory. Values outside 95% of the normal limits required a repeat blood sampling. Safety monitoring procedures were based on reported skin, hepatic, nervous sys-

tem, and gastrointestinal symptoms associated with retinoids (28–36). Study interviewers referred possible adverse events and abnormal laboratory values to the coprincipal investigator (N. L.), who blindly assessed whether the condition was likely related to study intervention.

Clinical Pharmacology. Participants in both trials provided an additional 10-ml blood specimen for analysis of retinoids. Specimens were obtained from all SKICAP participants at enrollment, at 1 month after randomization and annually thereafter (only SKICAP-AK participants with even-numbered identification provided annual specimens). Sera were analyzed by HPLC at the Arizona Cancer Center Clinical Pharmacology Laboratory for retinyl palmitate and retinol for SKICAP-AK participants and for 13-*cis*-RA and retinyl palmitate for SKICAP-S/B participants (37, 38). All analyses were blinded, and results were not available to clinic staff. Quality assurance of retinoid analysis was provided as part of the National Institute of Standards and Technology procedures (39).

Trial End Points. The first occurrence and total number of SCCs and BCCs pathologically diagnosed after participants were randomized were the primary end points. All skin biopsies performed after random allocation were identified by participant self-report at study follow-up visits, by review of pathology records of dermatologists, pathology laboratories, and the southeast Arizona skin cancer registry. Diagnostic pathology slides were requested for all biopsies and centrally reviewed by the trial dermatopathologist (J. B.).

Participants were examined for skin lesions by a study dermatologist or their own dermatologist at least once each year. Skin lesions suspicious for skin cancer were referred for biopsy and possible treatment to the participant's dermatologist. Participants unable to return for a follow-up visit were examined and had a blood specimen collected by a nonstudy dermatologist, and written documentation was provided. Participants referred for biopsy were followed by study staff to ensure that a biopsy was performed and that the diagnosis was obtained.

Termination and close-out procedures for both trials included scheduling all randomized participants for an exit interview and full-body skin examination conducted by a study dermatologist. All skin lesions suspicious for skin cancer were recorded, and the participants were referred for biopsy and treatment. Participants with suspicious lesions were also followed by the study staff to ensure that biopsies were performed, diagnoses were obtained, and diagnostic pathology slides were reviewed by the study dermatopathologist.

Questionnaires on clinical signs and symptoms were completed during the exit interview. Vital statuses were assessed for every randomized participant who could not be contacted or scheduled for an exit interview.

Participants going off medication during the 3-month placebo run in were taken off of the study and were not followed. Participants randomized to intervention were considered eligible for follow-up and analysis of end points without regard to adherence. Efforts were made to keep adherence high and to return participants to the medication if they stopped.

Statistical Considerations. The investigators determined the required sample size for the SKICAP-AK trial to be 2236 randomized participants (with equal assignment to retinol or placebo). To achieve the randomization goal, 2900 individuals were anticipated to be enrolled. The sample size calculations were based on a number of assumptions, including: (*a*) an average annual incidence of a first new skin cancer (SCC or BCC) in the placebo group of 3.5% and an annual incidence of a first new SCC of 2.0%; (*b*) a 25% reduction in first new skin cancer incidence throughout a 5-year intervention follow-up and a 35% reduction in first new SCC incidence in the retinol group; (*c*) a 30% incidence of participants ceasing to take the capsules during the 5-year intervention; (*d*) a 5% incidence of participants assigned to take a placebo would start to take retinol on their own; (*e*) a 10% incidence of participants failing to have a skin exam recorded during the study because they died or there were other reasons; and (*f*) a 23% incidence of participants not being randomized. These assumptions were based on previous skin cancer studies (4–8, 40). Sample size calculations were based on a power of at least 80% and a 5% two-sided significance level assuming that an exponential time to new skin cancer persisted for at least 5 years (41, 42).

Retinol efficacy will be evaluated related to the null hypothesis that there is no difference between intervention groups in the time to first new skin cancer (BCC or SCC) and the time to first new SCC after randomization. Primary analyses will follow the "intention to treat principle." Analyses of the hypotheses will be based on the log rank statistic (43) and adjusted for sun exposure per week and skin type (tendency to sunburn). The log rank statistic will be adjusted for confounding factors by using the Cox proportional hazards model (43). The usual Cox modeling approach will be suitable because participant follow-up and detection of suspicious skin lesions (by study, private dermatologists, or self-identification) was frequent, although possibly irregular, always <12 months, and commonly every 4–6 months.

Another null hypothesis to be evaluated will be that there is no difference between intervention groups in the total number of new skin cancers or total number of new SCCs per participant over the 5-year follow-up. One approach for the analysis of this hypothesis will be based on a Poisson regression model (44), as proposed for the analysis of other skin cancer chemoprevention trials (45, 46).

Other outcomes and regression models will be analyzed. These include whether: (*a*) baseline blood levels of retinol or retinyl palmitate modifies the effect of retinol; (*b*) there is a delay in the retinol effect by 1 or more years; and (*c*) there is an indication of a dose-response effect.

Interim analyses were carried out approximately every 2 years for a total of 6 years, with a conservative stopping rule that depended on the difference in first new skin cancer, a critical value of $z \geq 3.0$ for all interim tests, and $P = 0.05$ for the final analysis (25).

The required sample size for the SKICAP-S/B trial was calculated to be 498 randomized participants (166 assigned to each of the three intervention groups) and 712 enrolled individuals. The assumptions used included: (*a*) a 30% average annual incidence of a first new skin cancer (SCC or BCC) in the placebo group; (*b*) a 23% reduction in first new skin cancer incidence throughout a 3-year intervention; (*c*) a 35% incidence of participants ceasing to take their capsules during the 3 years of follow-up; (*d*) that no participants assigned to placebo would start taking retinol or 13-*cis*-RA; (*e*) a 10% incidence of participants failing to have a skin examination because they were lost to follow-up or dead; and (*f*) a 30% incidence of participants enrolled would not be randomized. These assumptions were also based on results of previous studies and other skin cancer prevention trials (4–8, 40). Sample size calculations were based on a power of 90%, a 5% two-sided significance level, and the assumption that an exponential time to new skin cancer persisted for at least 3 years (41, 42).

Retinoid efficacy will be evaluated for the same null hypotheses and the use of the adjusted log rank statistic as

Table 1 Annual enrollment and random allocation, according to study and clinical center

Year	SKICAP-AK				SKICAP-S/B							
	Tucson		Phoenix		Tucson		Phoenix		Yuma		San Diego	
	Enrolled	Randomized	Enrolled	Randomized	Enrolled	Randomized	Enrolled	Randomized	Enrolled	Randomized	Enrolled	Randomized
1984	213											
1985	521	485	233	125	107	81	7	6				
1986	468	459	421	337	37	30	11	3	14	8		
1987	451	349	340	306	60	36	101	49	8	7	9	
1988	116	152	37	81	27	33	73	62	15	8	37	26
1989		3			131	65	49	49	5	8	14	13
1990					8	28	4	11			2	2
Total	1769	1448	1031	849	370	273	245	180	42	31	62	41

Table 2 Enrollment[a] and costs, according to recruitment strategies used at Phoenix and Tucson clinics

	SKICAP-AK		SKICAP-S/B		
	Physicians	Media	Physicians	Media	Registry[b]
Enrolled (%)	279 (13)	1790 (87)	187 (36)	222 (43)	111 (21)
Costs	$17,175	$84,363	$10,200	$69,826	$2,726
Enrollment costs/subject	NA[c]	$47.13	NA	$314.53	$24.56
Randomization costs/subject	$75.00	$57.48	$75.00	$431.02	$36.35

[a] Enrollment and costs were tabulated between October 1985 through October 1988 for the SKICAP-AK study and between October 1985 through April 1990 for the SKICAP-S/B study. Before October 1985, 731 participants were enrolled in SKICAP-AK and 95 were enrolled in SKICAP-S/B.
[b] Use of a population based skin cancer registry to identify eligible individuals was only available for the Tucson clinic between November 1988 through April 1990.
[c] A stipend was paid to referring dermatologist only for a participant that was enrolled and randomized. NA, not available.

described for the SKICAP-AK trial. Other outcomes and regression models similar to those proposed for the SKICAP-AK trial will also be analyzed.

Results

A total of 2800 participants were enrolled in the SKICAP-AK trial (Table 1). The Tucson clinic enrolled 1769 participants (63%), and the Phoenix clinic, which began enrollment in June 1985, enrolled 1031 participants (37%). Enrollment was completed within a time period only 10% longer than projected, and 97% of the enrollment goal was achieved. A total of 2297 participants were randomized to retinol or to placebo intervention groups; 503 (18%) participants were not randomized. These participants were not randomized either by their own decision (201 participants) or because they were ineligible at the second visit (140 participants), had clinical symptoms (65 consistent with retinol clinical symptoms and 60 not consistent with retinol), were lost to follow-up (13 participants), had <75% capsule-count adherence (22 participants), or died during run in (2 participants). The distribution of participants by reasons for not being randomized were similar for the two clinics.

Recruitment for the SKICAP-AK trial was initially planned to be based on the referral of patients from Tucson dermatologists and PSAs. The PSAs incurred minimal costs (approximately $500, which consisted of minimal staff time) and yielded minimal self-referrals (<25) to either of the SKICAP trials. When monthly enrollment numbers were not consistently achieved, the Phoenix clinic was established with referrals from a portion of the Phoenix area dermatologists. Beginning in May 1985, additional recruitment strategies were considered. An academic communications consultant provided information on alternate strategies, and a plan was developed to implement and evaluate the cost of paid study advertisements in print and electronic media.

In October 1985, a paid SKICAP advertisement campaign was initiated to encourage individuals to determine their willingness to participate in the SKICAP-AK trial. From October 1985 through October 1988, newspaper, radio, and television advertisements were prepared, and space or time was purchased. The major metropolitan daily newspapers and regional weekly or monthly newspapers in both the Tucson and Phoenix areas were used and evaluated.

These recruitment strategies yielded over 11,000 inquiries at the Tucson and Phoenix clinics about participating in the SKICAP-AK trial. Referrals from dermatologists totalled 279, with 238 coming from Tucson dermatologists (Table 2). The remaining inquiries were from individuals responding to the paid SKICAP-AK advertisements. Paid advertisements in the Phoenix area yielded about the same number of inquiries as was generated in Tucson, although Phoenix has about 2.5 times more people than Tucson. Paid advertisements in the daily metropolitan newspapers resulted in the highest response, over 10,000 (89%) inquiries, whereas television advertisements resulted in 1,034 inquiries, radio in 34 inquiries, and other less frequently distributed newspapers or advertisement media in 236 inquiries. Table 2 also shows that $101,538 was used for the dermatologists' referral stipends and paid media advertisements during the use of multiple recruitment strategies. The $75 referral stipend paid to dermatologists for each participant enrolled and randomized accounted for $17,175 of the total costs. The other $84,363 paid for media advertisements, which

Table 3 Characteristics of participants at enrollment and randomization, according to study

Characteristic	SKICAP-AK		SKICAP-S/B	
	2800 Enrolled (%)	2297 Randomized (%)	719 Enrolled (%)	525 Randomized (%)
Age (yrs)				
<40	154 (06)	116 (05)	15 (02)	12 (02)
40–49	264 (09)	223 (10)	35 (05)	28 (05)
50–59	644 (23)	533 (23)	94 (13)	80 (15)
60–69	1,144 (41)	949 (41)	291 (40)	215 (41)
≥70	594 (21)	476 (21)	284 (39)	190 (36)
Gender				
Female	833 (30)	679 (30)	188 (26)	146 (28)
Male	1,967 (70)	1,618 (70)	531 (74)	379 (72)
Education				
<High school graduate	192 (07)	152 (07)	67 (09)	47 (09)
High school graduate	497 (18)	389 (17)	138 (19)	101 (19)
Some advanced education	980 (35)	788 (34)	253 (35)	191 (37)
College graduate	543 (19)	467 (20)	151 (21)	107 (20)
Graduate school	587 (21)	501 (22)	110 (15)	79 (15)
Unknown	1	0	0	0
Marital status				
Single, never married	105 (03)	87 (04)	24 (03)	16 (03)
Divorced/separated	252 (09)	195 (09)	49 (07)	30 (06)
Widowed	213 (08)	171 (07)	59 (08)	50 (10)
Married, living with spouse	2,229 (80)	1,844 (80)	587 (82)	429 (82)
Unknown	1	0	0	0
Vitamin use				
No	766 (27)	621 (27)	206 (29)	143 (27)
Occasional	792 (28)	653 (28)	164 (23)	128 (24)
Yes	1,241 (44)	1,023 (45)	349 (48)	254 (48)
Unknown	1	0	0	0
Cigarette use				
Never smoked	1,092 (39)	921 (40)	233 (32)	181 (34)
Former smoker	1,341 (48)	1,098 (48)	386 (54)	272 (52)
Current smoker	358 (13)	278 (12)	98 (14)	72 (14)
Unknown	9	0	2	0
Skin type				
Always or usually burns	1,213 (43)	1,007 (44)	289 (40)	214 (41)
Burns moderately	1,045 (37)	871 (38)	283 (39)	205 (39)
Rarely or never burns	538 (19)	417 (18)	147 (20)	106 (20)
Unknown	4	2	0	0
Sun exposure per week				
0–5 h	510 (18)	407 (18)	162 (23)	122 (23)
6–10 h	660 (24)	538 (23)	191 (27)	131 (25)
11–20 h	798 (28)	667 (29)	214 (29)	163 (31)
>21 h	831 (30)	685 (30)	152 (21)	109 (21)
Unknown	1	0	0	0
Moles and freckles				
0–7	1,092 (39)	1,091 (47)	266 (37)	261 (50)
>8	627 (22)	627 (27)	130 (18)	128 (24)
Unknown	1,081 (39)	579 (25)	323 (45)	136 (26)
Previous skin cancers				
0	2,254 (81)	1,852 (81)	65 (09)	2
1	406 (14)	330 (14)	11 (02)	2
2–3	127 (04)	104 (04)	100 (14)	23 (04)
4–6	10	8	221 (31)	187 (36)
7–9	3	3	130 (18)	126 (24)
10+	0	0	192 (27)	185 (35)
Skin protection used	1,827 (65)	1,614 (70)	549 (74)	419 (80)
Clinical center				
Tucson	1,769 (63)	1,448 (63)	370 (52)	273 (52)
Phoenix	1,031 (37)	849 (37)	245 (34)	180 (34)
Yuma			42 (05)	31 (06)
San Diego			62 (09)	41 (08)

Table 3 Continued

Characteristic	SKICAP-AK		SKICAP-S/B	
	2800 Enrolled (%)	2297 Randomized (%)	719 Enrolled (%)	525 Randomized (%)
Serum retinyl[a] palmitate (ng/ml)				
Low	928 (33)	797 (35)	219 (30)	171 (33)
Middle	834 (30)	691 (30)	232 (32)	173 (33)
High	893 (31)	728 (32)	249 (35)	171 (33)
Unknown	145 (05)	81 (04)	19 (03)	10 (01)
Dietary vitamin A (IU)[b]				
Low	719 (26)	692 (30)	171 (24)	162 (31)
Middle	715 (26)	693 (30)	167 (23)	161 (31)
High	719 (26)	691 (30)	171 (24)	161 (31)
Unknown	647 (23)	221 (10)	210 (29)	41 (08)

[a] Tertile values were computed separately according to study. For SKICAP-AK study, the ranges were 0–6.0, 6.1–20.0, and 20.1–637.8; for SKICAP-S/B study, the ranges were 0–9.9, 10.0–22.1, and 22.2–240.6.
[b] Tertile values by study: for SKICAP-AK the ranges were 1,194–6,979, 6,980–10,627, and 10,628–41,404; for SKICAP-S/B the ranges were 1,737–7,166, 7,167–10,392, and 10,393–91,010.

resulted in 1,790 (87%) enrollees of which 1,468 were randomized, yielding a cost of $57.48/enrolled and randomized participant.

A total of 719 participants were enrolled on the SKICAP-S/B trial (Table 1). The Tucson clinic enrolled 370 (51%) participants, the Phoenix clinic enrolled 245 (34%), the Yuma Clinic enrolled 42 (6%), and the San Diego Clinic enrolled 62 (9%). Recruitment was conducted at the Tucson clinic for the entire 5.5-year enrollment period. Recruitment began at the Phoenix Clinic in June 1985 and lasted for 5 years. Recruitment began at the Yuma clinic in May 1986 and lasted for 4 years. Recruitment began at the San Diego clinic in November 1987 and lasted for 3.5 years. Recruitment achieved 101% of the enrollment goal. The duration of enrollment was 1.8 times longer than initially planned.

A total of 525 participants completed the run-in period and were randomly assigned to retinol, 13-*cis*-RA, or placebo; 194 SKICAP-S/B participants (27%) were not randomized. These participants were not randomized either by their own decision (71 participants) or because they were ineligible at the second visit (78 participants), had clinical symptoms (23 were consistent with retinol or 13-*cis*-RA symptoms observed previously and the remaining 14 were not), had a <75% capsule count adherence (6 participants), or were lost to follow-up (2 participants). The distribution of participants' reasons for not being randomized was similar for the clinics. A total of 525 participants completed the SKICAP-S/B run-in period and were randomly allocated to retinol, 13-*cis*-RA, or placebo.

The same basic paid SKICAP advertisement campaign used in Tucson and Phoenix was also used for the SKICAP-S/B trial. Study-specific advertisements were developed and space or time was purchased. The SKICAP-S/B recruitment strategies yielded 1482 inquiries at the Tucson and Phoenix clinics from October 1985 through April 1990. Referrals from dermatologists totaled 187 individuals, with 170 living in the Tucson area. A total of 1295 inquiries were self-referrals resulting in 222 enrollments, of which 162 were randomized. Paid advertisements in Phoenix yielded approximately twice the number of inquiries per advertisement as in Tucson. Radio and television were not used in Phoenix, partly because of the higher cost in this area plus the modest success observed in Tucson.

Table 2 shows that $82,752 was expended on recruitment for the SKICAP-S/B trial during the Phoenix and Tucson clinic use of multiple recruitment strategies. The $75 referral stipend for dermatologists accounted for $10,200 for the two clinics. Media advertisement costs totaled $69,826 and resulted in 162 individuals being randomized, yielding a cost of $431.02/participant enrolled and randomized.

Table 2 also shows that 111 individuals were identified from the southeast Arizona skin cancer registry. Staff time and study resources required to contact the individuals and screen them initially by phone yielded 75 participants that were randomized for a cost of $36.35/participant.

Table 3 shows the distribution of key participant characteristics at enrollment and at randomization. For each trial, there was a marked similarity in the distribution of characteristics at the time of enrollment and at randomization. Reported use of sunscreens was the only exception; participants randomized had a slightly higher frequency of sunscreen use compared with all individuals enrolled.

SKICAP-S/B and SKICAP-AK participants had similar characteristics, except that the SKICAP-S/B participants were slightly older (67 *versus* 63 years), had fewer median hours (11 *versus* 13 h) of reported sun exposure/week, and lower cigarette use (34 *versus* 40% never smoked). SKICAP-S/B and SKICAP-AK participants had similar gender distribution (70–72% male), education (72–76% had at least some post-high school education), marital status (80–82% were married and living with their spouse), reported vitamin consumption (72–73% reported at least occasional use of supplemental vitamins), serum retinyl palmitate levels, and dietary vitamin A intake.

Discussion

The SKICAP trials were among the earliest cancer chemoprevention trials supported by the National Cancer Institute. When the trials were designed and enrollment begun, there were no clear guidelines on the best methods to: (*a*) select an effective dose of a chemopreventive agent and what should be the minimal intervention duration; (*b*) define and monitor adverse retinoid events, especially with the moderate retinoid doses selected; and (*c*) motivate and monitor adherence.

Recruitment for both SKICAP trials was initially planned to be based on patient referral by dermatologists and PSAs. When this proved insufficient to achieve monthly recruitment goals, additional recruitment strategies were undertaken. Dermatologist referral was effective in enrolling 13% of SKICAP-AK participants and 36% of SKICAP-S/B participants

during the Phoenix and Tucson clinic use of multiple recruitment strategies. The $75 stipend for each patient referral was considered an important incentive by most dermatologists. The greater proportion of participants referred to the SKICAP-S/B trial appeared to reflect the available pool of eligible participants and greater morbidity of skin cancer compared with AK. The long recruitment period, very long study intervention duration, and large patient volume of their clinical practice were mentioned by many dermatologists as disincentives for continued high-participant referral.

Use of paid media advertisements was highly successful in enrolling 87% of SKICAP-AK participants and 43% of SKICAP-S/B participants. The majority of individuals enrolled with only AK or one prior skin cancer did not see a dermatologist regularly, thus, contradicting the *a priori* view of dermatologists and contradicting the assumption used in initially planning SKICAP-AK recruitment. Our observation that 43% of SKICAP-S/B participants self-reported media as the primary reason they enrolled, although all had seen a dermatologist regularly, was informative. This may reflect the extent of the physician-patient relationship. Also, the spouses of many participants accompanied them to at least the first study visit, which may reflect a role of the spouse in recruiting participants.

The very large self-referral (87%) of participants on the SKICAP-AK trial using paid advertisements appears not to have been reported previously for disease prevention trials. Possible explanations for the success of paid advertisements include the format and content of the advertisements (using lay language and black background with white type), the placement of the advertisements in the community/home section of the print media, and the underrecognized ability of free-living individuals to self-refer for a long-duration cancer prevention trial, SKICAP-AK. Placement of paid advertisements in the major daily metropolitan newspapers yielded the greatest number of self-referrals. The cost per participant randomized on the SKICAP-AK was approximately 75% the cost for referral by a dermatologist. Clearly, the SKICAP trials enrollment required recruitment strategies in addition to referral by dermatologists.

Recruitment for the SKICAP-S/B trial required a third strategy to complete enrollment. The availability of a southeast Arizona population-based skin cancer registry was a unique resource. Use of the registry was not only the most cost-effective strategy for enrolling on the SKICAP-S/B trial but was essential to complete enrollment.

As designed, the SKICAP trials will provide a clear test of the effect of retinoids on the prevention of human skin cancer. The number of participants enrolled in both SKICAP trials is sufficient to detect a reduction in the number of newly diagnosed SCCs and the combined number of BCCs plus SCCs. The planned intervention duration for the SKICAP-AK trial will detect a reduction of at least 35% in SCC risk and 25% in combined BCC plus SCC risk. The SKICAP-S/B intervention duration will detect a reduction of at least 23% in the combined BCC plus SCC risk. The duration of the retinoid intervention, the sample size, and the participants' adherence will influence the final size of the risk that can be evaluated.

Other studies of retinoids begun or reported during the conduct of the SKICAP trials have indicated that retinoids are effective, primarily for treating epithelial cancers (16–18, 47). Skin is the largest epithelial organ. The published results of the clinical trials to prevent skin cancer evaluating β-carotene (29) and 13-*cis*-RA (48) illustrate that those agents were not effective at the doses used and with the subjects enrolled. The level of risk of future skin cancer, as measured by the subjects' history of proliferative skin lesions (only AK, a few BCC or SCC, or many BCC and SCC), may be important markers of effectiveness for retinoids and carotenoids. The effect of retinoids on the prevention of skin cancer as evaluated by the SKICAP trials will be reported in later communications.

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Appendix:

Southwest Skin Cancer Prevention Study Group
Clinical Centers—Dermatologists
- Tucson Clinic, AZ
  - Norman Levin, M.D.
  - Libby Edwards, M.D.
- Phoenix Clinic, AZ
  - Fillmore K. Bagatell, M.D.
  - Jerold L. Powers, M.D.
  - Kenneth W. Koldys, M.D.
- Yuma Clinic, AZ
  - Robert Anderton, M.D.
- San Diego Clinic, CA
  - Kenneth Gross, M.D.

Scientific Committee
- Thomas E. Moon, Ph.D., Principal Investigator
- Norman Levine, M.D., Co-Principal Investigator
- David Alberts, M.D., Clinical Pharmacologist
- Frank Meyskens, M.D. (through 1990), Medical Oncology
- Michael Schreiber, M.D., Community Dermatologist
- David Earnest, M.D., Adverse Events
- Robert Door, Ph.D., Pharmacy Director
- Cheryl Ritenbaugh, Ph.D., Dietary Intake

Data Coordinating Center
- Thomas E. Moon, Ph.D., Chairman and Biostatistician
- Norman Levine, M.D., Medical Director
- Brenda Cartmel, Ph.D., SKICAP Coordinator
- Jerry Bangert, M.D., Dermatopathologist
- Steve Rodney, Data Base Coordinator
- Gloria Alvillar, Clinic Coordinator
- Lynn Ferro, Clinic Coordinator
- Susan Shomo, Clinic Coordinator
- Patti King, Clinic Coordinator
- Emily Cardoza, Clinic Coordinator
- Janet Foote, Clinic Coordinator

Pharmacology Committee
- David Alberts, M.D.
- Yei-Mei Peng, Ph.D.
- M. J. Xu, M.D.

Data and Safety Monitoring Committee (External)
- Charles H. Hennekens, M.D., Harvard University School of Medicine
- David W. Nierenberg, M.D., Dartmouth Medical School
- Ross L. Prentice, Ph.D., Fred Hutchinson Cancer Research Center

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