Trial of Retinol and Isotretinoin In Skin Cancer Prevention: A Randomized, Double-Blind, Controlled Trial[1]

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Abstract

The objective of this study was to examine the effect of retinol and isotretinoin on the incidence of nonmelanoma skin cancer in high-risk subjects. A total of 525 participants with a history of at least four basal cell carcinomas (BCCs) and/or cutaneous squamous cell carcinomas (SCCs) were entered into a randomized, double-blind, placebo-controlled trial, performed in free-standing study clinics. Participants were randomly assigned to receive oral retinol (25,000 units), isotretinoin (5–10 mg), or placebo supplementation daily for 3 years. The time to first new occurrence of BCC or cutaneous SCC was used as the outcome measure. During the study period, 319 BCCs and 125 cutaneous SCCs were diagnosed clinically and pathologically. There were no differences between those who received retinol, isotretinoin, or the placebo, with regard to the time to first occurrence or to the total number of tumors noted. No beneficial effects were noted with regard to the prevention of nonmelanoma skin cancer with either retinol or isotretinoin.

Introduction

In a prior study, published in this month's issue of *Cancer Epidemiology, Biomarkers & Prevention*, Moon *et al.* (1) describe the use of retinol as a putative skin cancer prevention agent in patients early in the cancer promotion pathway; these individuals had multiple precancerous actinic keratoses and a history of fewer than three skin cancers. Here, we evaluate the effects of retinol and the synthetic retinoid, isotretinoin, in those with more advanced skin cancer promotional state, namely, those with a history of four or more BCCs[5] and/or SCCs.

Patients and Methods

Participants. Participants were men and women with a history of four or more pathologically confirmed BCCs or cutaneous SCCs. The most recent tumor had to have been diagnosed in the preceding year. Participants were recruited through media announcements and referrals by dermatologists. To be eligible, an individual had to be between 21 and 85 years old, ambulatory, and capable of self-care, with no diagnosis of a life-threatening condition or internal cancer within the past year and normal or near normal laboratory values in a routine screening panel of tests. They must have been planning to live continuously in Arizona for the succeeding 3 years. Individuals with a diagnosis of basal cell nevus syndrome or xeroderma pigmentosum were excluded from the study.

Study Design. Between January, 1985 and June, 1990, 719 people were entered in the study, a randomized, double-blind chemoprevention clinical trial. A total of 525 participants successfully completed the run-in period and were randomized. Study clinics were established in Tucson, Phoenix, and Yuma, AZ, and in San Diego, CA. The study was approved by the University of Arizona Human Subjects Committee. An internal Scientific Committee reviewed clinical and laboratory symptom data every 6 months; an external Data and Safety Monitoring Committee reviewed accrual and safety data approximately every 12 months. The trial remained double-blind, and the Data and Safety Committee never recommended early termination.

At the first visit to the clinic, each participant was given a detailed explanation of the elements of the protocol, and socioeconomic, dietary, and medical data were obtained. A blood specimen for baseline chemistries was obtained, and an informed consent was signed. A study dermatologist provided a detailed skin examination for all those participants who were not referred by a community dermatologist, who had provided recent written documentation of a skin examination.

To assure compliance before randomization, each person was given a 3-month supply of placebo capsules in single-blind fashion. At the end of this 3-month run-in period, if at least 75% compliance was achieved, as documented with pill counts and medication diaries, the participants were randomized to one of three daily interventions: 25,000 units of retinol, 10 mg of isotretinoin, or placebo capsules. Participants who weighed less than 145 pounds were given 5 mg per day of isotretinoin. Medication packaging, quality assurance, and labeling were provided by Hoffmann-LaRoche, Inc. (Nutley, NJ), and med-

Received 12/3/96; revised 8/5/97; accepted 8/11/97.
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[1] This study was supported, in part, by National Cancer Institute Grants CA-34256 and CA-27502. T. E. M. held the Katherine O'Connor Research Professorship, University of Texas M. D. Anderson Cancer Center, Houston, TX.
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[5] The abbreviations used are: BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

ication distribution was coordinated by the National Cancer Institute Drug Repository.

If baseline clinical chemistry values were outside the 95% normal limit, another blood sample was obtained. If repeat chemistry values were within the eligibility limits, the subject was advised to continue treatment.

Participants returned for clinic visits 1 month after random allocation and every 6 months thereafter. At each visit, adherence and possible toxicity were closely monitored. This included a detailed questionnaire and repeat blood chemistries. If skin biopsies had been taken since the last study visit, the pathology slide was obtained for review by the study pathologist (J. L. B.).

On the last study visit, all participants were given a detailed exit interview and were examined by the study dermatologist. All skin lesions suspicious for skin cancer were biopsied for review by the study pathologist.

Safety Monitoring and Laboratory Measures. Clinical signs and symptoms were monitored at every visit using an assessment form for mucocutaneous side effects, including cheilitis, conjunctivitis, xerosis (dry skin), exanthems, skin infections, alopecia, and peeling of the palms and soles. Evidence of other side effects of therapy such as myalgia, arthritis, epistaxis, and headaches was sought. Blood specimens were analyzed to monitor levels of cholesterol, triglyceride, hemoglobin, blood cell count, platelet count, and liver function (aspartate aminotransferase and alanine aminotransferase).

Outcome Measures. The time to first occurrence of SCC and time to first new BCC after randomization, pathologically confirmed by the study pathologist, were the primary outcome measures. Skin cancers that were diagnosed after study closeout or after the subject's third study follow-up year (36 months postrandomization) were not included, as specified in the protocol. A skin examination was performed by a study dermatologist or by the participant's dermatologist at least once every 6 months. Clinically suspicious skin lesions were biopsied. Skin biopsies were identified by subject self-report, review of pathology records, or a regional skin cancer registry. A pathology slide of all diagnostic biopsies was requested in all cases and independently read the study pathologist.

Statistical Analysis. Once randomized, the participant was considered eligible for analysis and follow-up, without regard to adherence. Efforts were made to keep adherence high and to return participants to assigned treatments if they had previously stopped.

The required sample size was calculated to be 498 eligible people, randomly assigned to one of three equal-sized groups (a retinol group, an isotretinoin group, and a placebo group; Ref. 2). 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 first cancer persisted for at least 3 years (3, 4).

Analyses of the primary outcome measures were based on the Cox proportional hazards model and adjusted for the *a priori* selected characteristics: sun exposure, skin type (tendency to sunburn), age, sex, number of prior skin cancers, and number of moles and freckles (5). The PHREG procedure in the SAS computer program system was used for these analyses (6). The Cox modeling approach was suitable because subject follow-up and biopsy of skin lesions were frequent, although possibly irregular, and were always less than 6 months and, commonly, every 3–4 months.

Table 1 Characteristics of participants at randomization

Characteristic	Placebo (n = 174)	Isotretinoin (n = 178)	Retinol (n = 173)
Age			
<66 yr	87 (50%)	75 (42%)	76 (44%)
>66 yr	87 (50%)	103 (58%)	97 (56%)
Sex			
Female	48 (28%)	52 (29%)	46 (27%)
Male	126 (72%)	126 (71%)	127 (73%)
Clinic			
Phoenix	62 (36%)	61 (34%)	57 (33%)
Tucson	91 (52%)	93 (52%)	89 (51%)
Yuma	5 (3%)	9 (5%)	17 (10%)
San Diego	16 ((%)	15 (8%)	10 (6%)
Prior skin cancers			
4–10	113 (65%)	116 (65%)	118 (68%)
>10	55 (32%)	49 (28%)	47 (27%)
Weekly sun exposure			
0–10 h	84 (48%)	88 (49%)	81 (47%)
>10 h	90 (52%)	90 (51%)	92 (53%)
Skin sun sensitivity[a]			
Always/usual	70 (40%)	74 (42%)	70 (40%)
Moderately	68 (39%)	72 (40%)	65 (38%)
Less often	36 (21%)	32 (18%)	38 (22%)
No. of moles/freckles			
0–7	91 (52%)	82 (46%)	88 (51%)
>7	51 (29%)	41 (23%)	36 (21%)
Unknown	32 (19%)	55 (31%)	49 (28%)
Vitamin use (all types)			
No	48 (28%)	47 (26%)	48 (28%)
Sometimes	40 (23%)	43 (24%)	45 (26%)
Yes	86 (49%)	88 (50%)	80 (46%)
Serum retinyl palmitate			
<10.0 ng/ml	61 (35%)	53 (30%)	57 (33%)
10.0–22.1 ng/ml	50 (29%)	63 (35%)	59 (34%)
>22.1 ng/ml	57 (33%)	59 (33%)	56 (32%)
Unknown	6 (3%)	3 (2%)	1 (1%)
Dietary vitamin A			
1,737–7,166 units	53 (30%)	57 (32%)	52 (30%)
7,167–10,392 units	53 (30%)	57 (32%)	51 (29%)
10,393–91,010 units	54 (31%)	49 (28%)	58 (34%)
Unknown	14 (9%)	15 (8%)	12 (7%)

[a] Frequency of sunburn.

Results

A total of 719 participants were enrolled in the trial. A total of 525 participants completed the run-in period and were randomized to either retinol, isotretinoin, or placebo treatment. Of the 194 participants (27%) who were not randomized, 71 chose to cease participation, 78 were ineligible because they failed to meet one or more of the inclusion criteria, 37 had clinical symptoms, 6 were insufficiently compliant with adherence to the protocol, and 2 were lost to follow-up.

The demographic, clinical, and other characteristics of the participants are shown in Table 1. The three intervention groups had very similar distributions of all characteristics at randomization. Men constituted 72% of the total number of enrollees. This reflected the higher incidence of skin cancer among men (7).

Calculated adherence to the intervention was very similar between the three groups and was high throughout the study. Over 95% of the participants reported taking at least 50% of the total number of capsules, and over 80% of the participants reported taking at least 75% of the total number of capsules. There were no differences in compliance between the three groups.

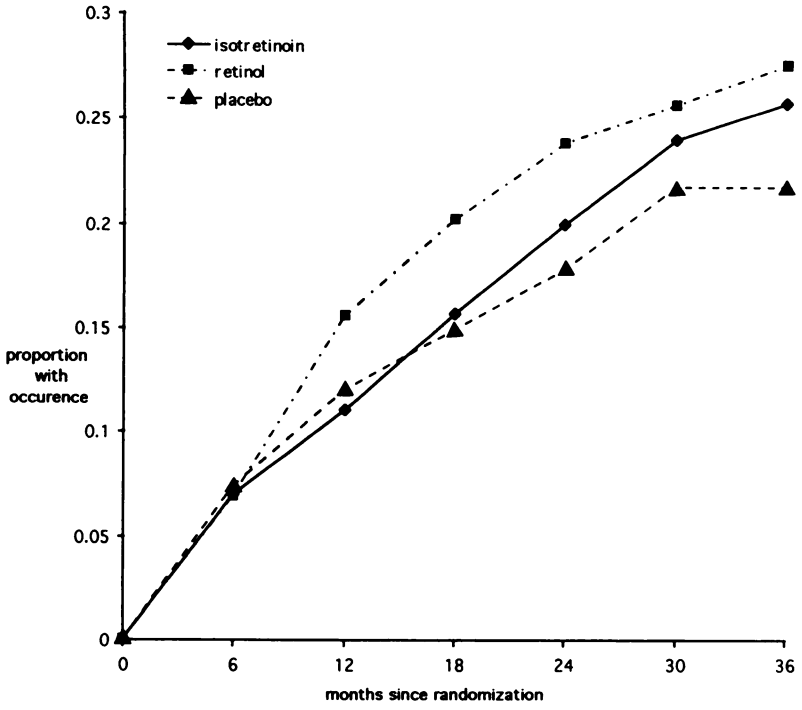

Fig. 1. Cumulative proportion of participants with a first new SCC, according to intervention assignment.

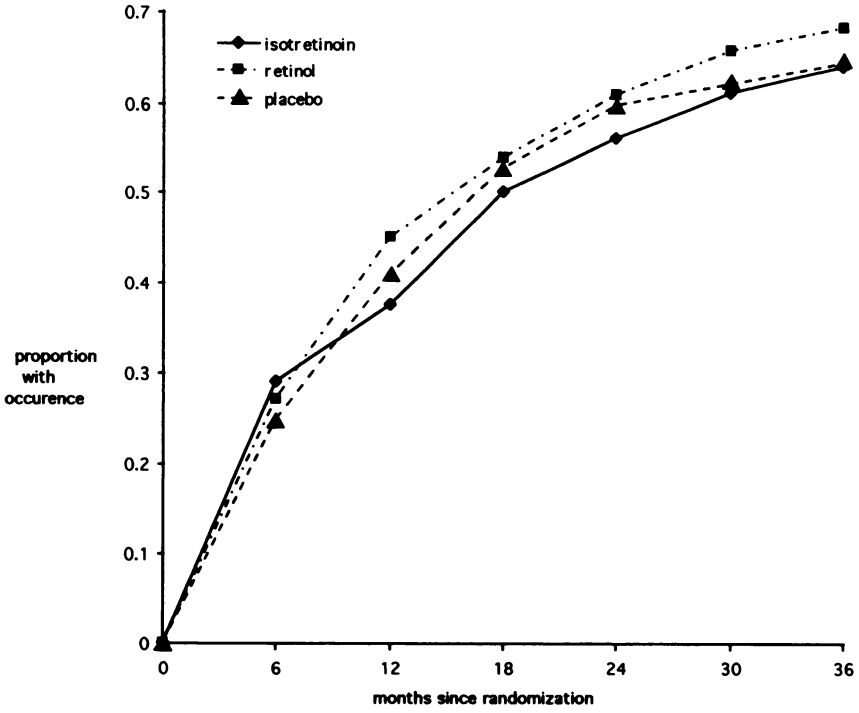

Fig. 2. Cumulative proportion of participants with a first new BCC, according to intervention assignment.

Attrition rates were high in all groups. This may have been partly due to the strong message given to each person by the interviewers with regard to potential toxicity. Many participants, including those on the placebo, may have been sensitized to consider any deviation from normal as being related to the study medication.

A total of 125 cutaneous SCCs were diagnosed clinically and confirmed pathologically during the course of the study. Retinol-treated participants accounted for 41 tumors (32.8% of the total); isotretinoin-treated participants had 40 lesions (32% of the total); and those on placebo capsules had 41 tumors (32.8% of the total). A total of 319 BCCs were diagnosed

Table 2 Numbers of patients experiencing clinical toxicity[a]

Visit no.	Mucocutaneous	Musculoskeletal	Vascular	Central nervous system	No. of subjects
Isotretinoin treatment					
1	17 (9.7%)	8 (4.6%)	9 (5.1%)	3 (1.7%)	175
3	8 (5.2%)	0	0	0	153
5	7 (6.3)	0	1 (1.5)	0	111
7	1 (1.5%)	1 (1.5%)	1 (1.5%)	0	68
9	0	0	0	0	29
11	0	0	0	0	12
Retinol treatment					
1	5 (2.9%)	3 (1.7%)	0	2 (1.2%)	173
3	6 (4.1%)	1 (0.7%)	0	1 (0.7%)	145
5	3 (2.6%)	1 (0.9%)	0	0	117
7	1 (1.4%)	0	0	0	74
9	0	0	1 (2.6%)	0	39
11	0	0	0	0	18
Placebo treatment					
1	1 (0.6%)	0	0	0	173
3	0	2 (1.3%)	1 (0.6%)	0	155
5	1 (0.8%)	2 (1.6%)	0	0	124
7	1 (1.2%)	0	0	1 (1.2%)	81
9	1 (2.2%)	0	0	0	46
11	0	1 (4.5%)	0	0	22

[a] Level 2 or greater.

clinically and pathologically during the course of the trial. Those on retinol had 106 tumors (33.2% of the total); those who were given isotretinoin developed 103 lesions (32.2% of the total); and those treated with a placebo had 110 tumors (34.4% of the total). There were no differences in the number of tumors between the three treatment groups.

Figs. 1 and 2 present follow-up for end point ascertainment (time to first skin cancer), as assessed according to intervention and follow-up periods. There were no differences between those who received the placebo *versus* those who were given either isotretinoin or retinol, with regard to time to first occurrence of either a BCC or a cutaneous SCC.

The number of participants who experienced a level 2 or greater toxic event during the study is shown in Table 2. Clinical symptoms and signs were combined into four categories. The proportion of people with these side effects was higher in the isotretinoin-treated group, but the overall degree of toxicity was modest.

Discussion

The hypothesis tested in this study was that retinol and/or isotretinoin could prevent cutaneous SCC or BCC better than could a placebo in subjects with a high risk of developing these lesions. The individuals recruited appeared to be appropriate because 125 cutaneous SCCs and 319 BCCs occurred. The participants were variably compliant with the treatments, as noted in Table 2. The three randomized groups were comparable in all respects. The primary end point for analysis was the time to the onset of the first clinically and pathologically diagnosed skin cancer. The data shows no differences in this end point between any of the groups. Thus, with the parameters used, no beneficial effects were noted with regard to skin cancer prevention. Using similar methodology, a previous study reached the same conclusion after prolonged treatment with low-dose isotretinoin in subjects with many previous skin cancers (8). The results parallel those reported after patients with multiple previous skin cancers were treated with β-carotene (9).

Other investigators have reported positive results using systemic retinoids in patients at high risk for skin cancer (10–13). The patients had more serious underlying problems, such as xeroderma pigmentosum or chronic immunosuppression, and the doses used were substantially higher, in the case of isotretinoin, compared to the present study. It would be difficult to justify these high doses for chronic use in otherwise healthy patients with multiple skin cancers, such as those who participated in the present study.

The methodology used in this trial has been detailed elsewhere (2). It was found to be quite workable, although the logistics of multiple study sites were complicated. In spite of close communication between the participants and the study coordinators, there was a high dropout rate in all groups. The long length of the trial and the concern about potential serious toxicity were both important factors in decreased participation over time. As noted in Table 2, there were relatively few instances of level 2 or greater toxicity in any of the groups. As expected, even at the low doses used, more participants in the isotretinoin group had side effects of level 2 toxicity.

We chose to treat patients at high risk for the development of BCCs and cutaneous SCCs with low-dose isotretinoin or vitamin A (retinol). We selected retinol because of the known retinoid cancer chemoprevention effects and because of its excellent safety profile at the dose chosen (25,000 units per day). Isotretinoin was chosen as the second retinoid to study for two reasons: there is data that suggests that this compound has potent chemopreventive effects; and the toxicity of isotretinoin is dose related, relatively well tolerated, and reversible upon cessation of the drug (14). Because the toxic effects are primarily cutaneous, they are easily diagnosed.

Although the agents used in low dosage in this trial were not effective in chemoprevention of skin cancer, the methodology is useful in exploring the effects of other drugs. Using the same procedures, the study by Moon *et al.* (1) describes beneficial effects in preventing cutaneous SCCs in subjects with many actinic keratoses and few, if any, skin cancers. It appears

that the chemopreventive effects of retinoids are more pronounced in the early stages of cancer promotion.

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