A Randomized Controlled Trial to Assess Sunscreen Application and Beta Carotene Supplementation in the Prevention of Solar Keratoses

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Background: Solar keratoses (SKs) are among the strongest determinants of skin cancer, but little is known about the success of measures to control these common skin tumors.

Objective: To determine whether daily sunscreen application and/or beta carotene supplementation retards the rate of occurrence of SKs in adults in the medium term.

Design: Randomized controlled trial conducted between February 1992 and August 1996.

Setting: General community of the subtropical township of Nambour, Australia (latitude, 26° south).

Participants: A total of 1621 adults aged 25 to 74 years.

Interventions: Participants were randomized to daily use of sunscreen (application of a high-protection sunscreen to their head, neck, arms, and hands every morning) or application of sunscreen at their usual discretionary rate. They were also randomly assigned to take either one 30-mg tablet of beta carotene or one placebo tablet each day.

Main Outcome Measure: Change in the prevalent number of SKs in the intervention group relative to change in the control group.

Results: The ratio of SK counts in 1994 relative to 1992 was lower in people randomized to daily sunscreen use (1.20; 95% confidence interval, 1.04-1.39) than in those randomized to discretionary sunscreen use (1.57; 95% confidence interval, 1.35-1.84). This 24% reduction is equivalent to the prevention of an average of 1 additional SK per person over that time. A reduction in the rate of change of SK prevalence was also seen in the sunscreen intervention group relative to the discretionary sunscreen group between 1994 and 1996, but it was not significant. No effect on the rate of change of prevalent SK counts was seen among those taking beta carotene supplements relative to those taking placebo tablets.

Conclusions: Daily application of sunscreen retarded the rate of SK acquisition among adults in a subtropical environment, while a beta carotene supplementation of 30 mg/d had no influence on the occurrence of SKs.

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patients 40 years or older who had a history of skin cancer. Dietary control measures have also been considered. In a single randomized controlled trial, Black et al showed that cumulative SK count was significantly decreased among 38 patients randomized to a low-fat diet compared with patients keeping a normal diet. Beta carotene supplementation has been observed to reduce the number of skin tumors (including benign papillomas) in mice.

Since the effectiveness of sunscreen application in preventing SKs in the general community is unknown and because of the possible effectiveness of dietary supplements, we addressed these questions in a community-based intervention study. In the Nambour Trial, a random sample of residents in a subtropical township were followed up over 4½ years at regular intervals. In this framework, we assessed whether the auxiliary measures of regularly applying sunscreen to the skin or taking daily beta carotene supplements could prevent the development of SKs in the community.

METHODS

PATIENTS

This randomized controlled trial to evaluate the prevention of SKs was conducted in conjunction with a trial to evaluate the effectiveness of daily sunscreen application and beta carotene supplementation in preventing BCCs and SCCs. Full details of the conduct and outcome of the skin cancer prevention trial have been reported previously. In 1986, 3000 participants aged between 20 and 69 years were randomly selected from the residents of Nambour, a township in southeast Queensland, Australia (latitude, 26° south), and invited to take part in a skin cancer screening survey. To be eligible for the intervention study, the 2095 participants of the 1986 study were required to also take part in the baseline survey of 1992 and give written consent to remain in the randomized trial until 1996. Complete skin examinations were carried out in February 1992, August 1994, and August 1996 by dermatologists involved in the study survey but unaware of treatment allocation. Only trial participants who had all 3 skin examinations were included in this study.

Participants were randomly assigned to 1 of 4 treatment groups: (1) daily use of a broad-spectrum sunscreen with a sun protection factor of 16, plus one 30-mg tablet of beta carotene; (2) daily use of the same sunscreen, plus one placebo tablet; (3) one daily 30-mg tablet of beta carotene only; and (4) one daily placebo tablet only. Those not randomized to daily sunscreen application were asked to continue applying sunscreen at their own discretion. The use of a placebo sunscreen was not considered ethical in this highly exposed population. Daily use of sunscreen entailed the application of sunscreen to all exposed sites on the head (face, and scalp if exposed), neck, arms, and hands every morning. The study sunscreen was a standard cream rated as water resistant with a sun protection factor of 16. Compliance with the requested sunscreen application regimen was assessed in 2 ways. First, the measured weights of all returned sunscreen bottles were recorded every 3 months. Second, participants completed questionnaires in the third and fifth years of the trial, in which they reported their average frequency of sunscreen use in a normal week and their use of other sun protection strategies, among other things.

The beta carotene and placebo tablets were identical in appearance and taste. Participants were advised to take them with meals. The dosage of 30 mg/d was determined to be the lowest dose of beta carotene that would be biologically effective without causing widespread skin discoloration among participants. The number of pills remaining in medication calendar packs was counted every 3 months to assess compliance.

Detailed questionnaires about skin color and reaction to sunlight, sun exposure patterns, skin cancer history, and personal habits such as smoking were completed at the time of the 1992 survey and were updated at the 1996 survey.

During each of the 3 skin examinations (in 1992, 1994, and 1996), dermatologists recorded counts of SKs on 14 separate body sites. An SK was defined as a discrete, irregularly scaly (keratotic) lesion with or without pigmentation. Counts were recorded as the number of defined SKs observed on each site, except where this number exceeded 50 or on sites where more than 50% of the skin surface area was confluent with keratoses. On these sites, SK counts were said to be indeterminate.

To examine SK development more intensively, similar data collection methods were applied to a random subsample of 100 participants. Participants were surveyed every 6 months, for a total of 18 months starting from 1992. A more detailed regimen was used for counting and mapping SKs present on their heads, necks, arms, and hands.

STATISTICAL METHODS

Site-specific SK counts were combined to calculate the number of prevalent SKs on the total body at each skin examination. In addition, the SK counts on the sites to which sunscreen was applied according to the treatment protocol (head, neck, arms, and hands) were summed to calculate the total SK number on “sunscreen application sites.” We examined 4 distinct outcomes, based on changes in these 2 summary SK counts from baseline (February 1992) to the intermediate survey (August 1994), and from the 1994 survey to the final August 1996 survey.

These 4 outcomes were modeled against the intervention variables, using a general linear model that allowed for repeated measures. The analysis also included the following potential confounding factors recorded in 1992: sex; age (dichotomized as “younger than 50 years” or “50 years or older”); eye color (blue/gray, green/hazel, brown); hair color (blond, light brown, red, dark brown/black); skin reaction to acute sun exposure (burn only, burn then tan, tan only); smoking status (never, ever, current); previous history of actinic (sun-induced) skin cancer; and potential occupational sun exposure over a lifetime (mainly outdoors, both indoors and outdoors, mainly indoors).

We used a negative binomial distribution to model SK counts in each instance. It is known that such a distribution is particularly appropriate for modeling counts of events that tend to cluster within susceptible individuals, resulting in a proportion of zero counts much higher than would be expected under the Poisson model. The fitted negative binomial distribution showed good agreement with the observed distribution, both visually and formally (goodness-of-fit test; P = .68).

The models were all fitted using the GENMOD procedure in the SAS statistical software, version 8.0 (SAS Institute, Cary, NC). Estimation and evaluation of significance of the intervention effectiveness was achieved by specification of a year × intervention interaction term in the model. The use of a log-link function for the negative binomial model indicates the changes over time, and the intervention effectiveness is measured as relative, rather than absolute, effects. For example, for the 1992-1994 period, for each of the 2 protocols of sunscreen application (daily and discretionary) we obtained an estimated ratio of SK counts in 1994 relative to 1992. The magnitude of this ratio in the “daily sunscreen” group, relative to the
"discretionary sunscreen" group (provided by the interaction term and hereafter called the relative ratio [RR] for the intervention) provides a single measurement of the effect of sunscreen use on the rate of change in the number of prevalent SKs. All estimates were adjusted for both the confounders listed above and the other arm of the intervention. These methods were also applied to the data arising from the substudy, which included observations at 6-month intervals.

RESULTS

Of 1647 eligible residents of Nambour who participated in the baseline skin cancer survey in 1992, 1621 gave signed consent to participate also in the trial and were randomly allocated to 1 of the 4 treatment groups (Figure). Of these, 1195 (74% of the original trial participants) remained part of both subsequent skin surveys in 1994 and 1996. As shown previously, allocation to treatment was unrelated to participants’ baseline characteristics relevant to risk of skin cancer, including age, sex, skin type, sun exposure, and history of skin cancer; and there was no significant difference in SK counts between the treatment groups at allocation. A further 79 individuals were excluded because they had indeterminate SK counts recorded at any of the sites, but they did not differ from those included regarding treatment group assignment or risk factors for skin cancer. These exclusions and loss to follow-up did not result in alteration of the distribution of risk factors in the population over the course of the trial.

Among the 1116 (69% of 1621) individuals included in the analysis, 598 (54%) had no SKs in 1992, 558 (50%) had no SKs in 1994, and 525 (47%) had none in 1996; the mean number of SKs on the whole body was 3.7 in 1992, 4.3 in 1994, and 4.9 in 1996; and on the prescribed sunscreen application sites the corresponding means were 3.5 in 1992, 4.0 in 1994, and 4.5 in 1996. Thus, on average, each adult in the study gained 1 new SK over the 4½-year intervention period.

For the February 1992 to August 1994 period, the estimated increase of SKs on the whole body among those applying sunscreen daily was 20%, while it was 57% in the control group (Table 1). Thus, the ratio of the increase in the number of prevalent SKs in the daily sunscreen application group, compared with that in the discretionary application group, was 76%. For sunscreen application sites, the comparable ratio was 78%. These estimates, adjusted for the potential confounding factors listed above, were statistically significant at the .05 level. For the August 1994 to August 1996 interval, however, the observed effect of the intervention was diminished. The increase in total body SKs for those receiving daily sunscreen application was 95% of the increase observed in the control group, and a similar result was found for the sunscreen application sites.

A beta carotene supplementation of 30 mg/d showed no significant effect on SK counts in either period (Table 2). In the 1992-1994 period the percentage of the increase in prevalent SK counts was almost identical in each group. In the 1994-1996 period, individuals who received beta carotene supplements had a higher increase than individuals who received placebo tablets (20% vs 7%), but this difference was not significant. Results were similar for SK counts on sunscreen application sites.

There was some modification of the effect of the sunscreen intervention in the first period due to age, tanning ability, and past history of skin cancer. The RR for the intervention in individuals younger than 50 years was
59% (95% confidence interval [CI], 43%-80%), compared with 92% (95% CI, 72%-117%) in those older than 50 years. People who tanned after sun exposure benefited more from sunscreen application (RR, 70%; 95% CI, 56%-91%) than those who burned (RR, 111%; 95% CI, 74%-165%), and a greater effect was seen among people without a history of skin cancer (RR, 68%; 95% CI 52%-89%) than those with a history (RR, 96%; 95% CI, 70%-131%). No consistent differences were seen in the effect of daily sunscreen among current smokers, ex-smokers, and individuals who never smoked (data not shown). For the beta carotene intervention between 1992 and 1994, and for both interventions over the second period, no notable effect modification was observed.

The smaller sample of participants who had SK counts at 6-month intervals showed results similar to those of the whole study population. In each 6-month interval, sunscreen had a protective effect, although at varying magnitudes; however, estimates were less precise because of the smaller sample size. For the first 6 months of 1992, the ratio of SK increase in the sunscreen treatment group compared with that in the control group was 83% (95% CI, 52%-132%), rising to 96% (95% CI, 61%-153%) in the latter half of that year, and dropping again to 74% (95% CI, 55%-99%) over the first 6 months of 1993. Comparing counts recorded in 1992 and at the end of the 18-month study resulted in an RR of 56% (95% CI, 34%-93%).

Our study found that the number of prevalent SKs increased over the course of the trial in all groups, consistent with the rapid accumulation of SKs in adults of this age living in a subtropical environment. Despite this, requesting a random half of participants to apply sunscreen daily resulted in a decrease in their average rate of SK acquisition, especially in the first 2 1/2 years of the trial. The increase in SK counts between February 1992 and August 1994 in the intervention group at large was approximately 24% lower than that experienced by the control group, and SK acquisition was almost 44% less in the more intensively monitored subgroup. This is tantamount to the prevention of an average of 1 additional SK per person over that time.

Our results in the short-to-medium term are consistent with those of the 2 previous intervention studies, which showed that sunscreen application slowed the development of SKs.7,8 Naylor et al9 found a reduction in SK acquisition rates among 37 dermatologic patients of approximately 30% per year, and Thompson et al7 reported an actual decrease in mean SK counts over one summer among sunscreen users in 431 people with pre-existing SKs. The greater magnitude of the protective effect in the previous trials7,8 may partly reflect the fact that Naylor and colleagues tracked only incident (rather than the
beta carotene supplementation of 30 mg/d offers little protection against the development of sun-induced skin tumors in humans. It is clear from our results that a daily application of sunscreen can play a strong role in minimizing SK acquisition rates in the general community. Prevention of SKs will greatly reduce the costs associated with their treatment, and is also a marker of the effectiveness of sunscreens for the prevention of skin cancer. Regular sunscreen use should thus continue to be advocated as an important sun protection strategy, including among those who would be considered at relatively low risk of actinic skin tumors, such as the young or those with skin that tans easily.

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REFERENCES


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