*Short Communication*

# Prolonged Prevention of Squamous Cell Carcinoma of the Skin by Regular Sunscreen Use

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## Abstract

**Half of all cancers in the United States are skin cancers. We have previously shown in a 4.5-year randomized controlled trial in an Australian community that squamous cell carcinomas (SCC) but not basal cell carcinomas (BCC) can be prevented by regular sunscreen application to the head, neck, hands, and forearms. Since cessation of the trial, we have followed participants for a further 8 years to evaluate possible latency of preventive effect on BCCs and SCCs. After prolonged follow-up, BCC tumor rates tended to decrease but not significantly in people formerly randomized to daily sunscreen use compared with those not applying sunscreen daily. By contrast, corresponding SCC tumor rates were significantly decreased by almost 40% during the entire follow-up period (rate ratio, 0.62; 95% confidence interval, 0.38-0.99). Regular application of sunscreen has prolonged preventive effects on SCC but with no clear benefit in reducing BCC.** (Cancer Epidemiol Biomarkers Prev 2006;15(12):2546–8)

## Introduction

Around half of all cancer in the United States is skin cancer (1). In Western populations worldwide, the burden of skin cancer is similar and very costly (2). Yet, skin cancers are largely preventable (3). We previously reported reduction of squamous cell carcinomas (SCC) of the skin and of their precursors, actinic keratoses, in people who applied sunscreen regularly in a 4.5-year randomized trial in the subtropical Australian community of Nambour (4, 5). There was no decrease in the incidence of basal cell carcinomas (BCC; ref. 5), although among people with multiple BCCs, the appearance of subsequent BCCs was delayed by the daily sunscreen intervention compared with non-daily application by the control group (6). On this basis, we postulated that BCCs may have a protracted pathogenesis. We therefore evaluated a possible latency of effect of sunscreen intervention on BCC and SCC among trial participants in the period after the trial had ceased.

## Patients and Methods

**Study Population.** In the Nambour Trial, 1,621 residents of the Nambour township were randomized either to application of a broad-spectrum Sun Protection Factor 16 sunscreen to head, neck, arms, and hands every morning (intervention group) or to use of sunscreen at their usual, discretionary frequency, including no use (controls; ref. 5).

**Data Collection.** Participants received full skin examinations by dermatologists unaware of treatment allocation at the start (1992), midway (1994), and at the finish (1996) of the trial, and any clinically diagnosed skin cancers were histologically confirmed. Skin cancers diagnosed between surveys were ascertained by regular questionnaires and by physicians' notifications with medical record verification. After the trial ended in 1996, all participants, including those who withdrew from active follow-up, consented to have subsequently diagnosed skin cancers notified to the investigators by regional pathology laboratories in Queensland. In addition, active participants completed 6-monthly questionnaires with information about any new skin cancers treated, as well as the amount of time spent outdoors on weekdays and weekends, and sunscreen use. In 2000, participants were offered a further full skin examination by a dermatologically trained physician, with histologic confirmation of suspected skin cancers.

Although 14 participants had moved outside the state of Queensland, they continued to complete questionnaires, thus enabling pathology reports of skin cancers to be obtained. We checked the likely magnitude of loss to follow-up among participants by estimating the proportion who had moved outside Queensland without notifying us of their address (and thus would be excluded from the skin cancer monitoring system). By verifying current residential addresses of a random sample of 50 passive participants through online telephone directories (of ''listed'' telephone numbers only) and the Australian Electoral Roll, we showed Queensland addresses for 90%.

Ethical approval was obtained from institutional ethics committees.

**Statistical Analysis.** Intention-to-treat analysis was carried out separately for all histologically confirmed BCCs and SCCs occurring on the head, neck, arms, and hands between 1993 and 2004 (cancers diagnosed in the first year of intervention were excluded; ref. 5). Treatment effect on cancer incidence rates was assessed using Poisson and negative binomial regression applied to persons affected and tumor counts, respectively. Treatment effectiveness was assessed overall in

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**Table 1. Distribution of sunscreen allocation by participation status**

| Participation status follow-up study | Total | Trial treatment group | | *P** |
|---|---|---|---|---|
| | | Daily sunscreen | Discretionary sunscreen | |
| Active participant residing in Queensland | 861 | 417 (48%) | 444 (52%) | 0.36 |
| Active participant outside Queensland | 14 | 5 (36%) | 9 (64%) | 0.29 |
| Passive participant | 609 | 322 (53%) | 287 (47%) | 0.16 |
| Died | 137 | 68 (50%) | 69 (50%) | 0.93 |
| Verification of a random sample of 50 passive participants | | | | |
| Moved interstate or untraceable | 5 | 3 (60%) | 2 (40%) | 0.39 |
| Known to reside in Queensland | 45 | 18 (40%) | 27 (60%) | |

*$\chi^2$ test.

trial and follow-up periods combined (1993-2004) and separately in the total follow-up period (September 1996 to December 2004) and late follow-up period (January 2001 to December 2004).

## Results

Of 1,621 residents enrolled in the trial, 137 died during the follow-up period, leaving 1,484 (92%) followed to the end of 2004. Of these, 875 (59%) were still actively completing follow-up questionnaires in 2004, whereas 609 (41%) were being monitored for skin cancer through pathology records only (hereafter termed ''passive participants''). The distribution of randomized sunscreen allocation among the passive participants and the minority of untraceable participants outside Queensland reflected the random assignment at baseline (Table 1). As well, propensity to sunburn, proportion of outdoor workers, proportion with severe elastosis, or a positive skin cancer history did not vary between follow-up groups (Table 2). Although fair skin was slightly more common in active (57%) compared with passive participants (52%, $P = 0.03$), there was again no difference in treatment allocation ($P = 0.26$) by skin color (data not shown).

With regard to BCC incidence rates, there were no significant effects of sunscreen use seen after an 8-year follow-up, although the late follow-up period showed a nonsignificant 25% decrease in BCC tumor incidence in the former sunscreen treatment group (rate ratio, 0.75; 95% confidence interval, 0.49-1.14; Table 3). In contrast, SCC incidence rates, both in terms of persons newly affected and numbers of tumors, were significantly reduced in the former sunscreen treatment group irrespective of study period. After 8 years of trial follow-up, tumor-incidence of SCC was 38% lower (rate ratio, 0.62; 95% confidence interval, 0.38-0.99), and SCC incidence (persons affected) was 35% lower (rate ratio, 0.65; 95% confidence interval, 0.43-0.98) in the former sunscreen treatment group (Table 3).

During the follow-up period, the amount of time spent outdoors on weekdays and weekend days was not different between the two trial treatment groups (data not shown).

## Discussion

Despite allowing for a prolonged lead-time, there was no clear preventive effect of regular sunscreen use on BCC. There was a tendency towards a decreased incidence of BCC tumors in the sunscreen treatment group some 5 years after cessation of the sunscreen intervention. This is consistent with the reduced rate of occurrence of multiple BCCs seen in the sunscreen intervention group during the trial period (6), although we cannot exclude chance causing this apparent decrease after a prolonged latent period. By contrast, SCC continued to be highly amenable to prevention by using regular sunscreen, such that the number of persons with SCC and the number of SCC tumors was reduced in the long term by regular sunscreen use, up to 8 years after cessation of the intervention. Although most of the prolonged effectiveness can be attributed to the former allocated daily sunscreen application during the trial, the prolongation was undoubtedly enhanced by a more frequent use of sunscreen, which persisted in the intervention group more than in the control group in the follow-up period (25% versus 18%; $P = 0.004$; ref. 7).

We have previously shown that there were no differences in UV exposure or time spent outdoors between the trial groups (8). The number of sunburns during the trial in participants in the daily sunscreen group was marginally lower than those in participants in the discretionary sunscreen group ($P = 0.05$), but >80% of the participants did not get sunburned at all during the trial (8). Moreover, the amount of time spent outdoors during the follow-up period was not different between the two sunscreen treatment groups; thus, our data do not support the notion that the observed effects of sunscreen on SCC are due to a change in sun exposure behavior during or after the trial.

Our data also show that differential loss to follow-up is highly unlikely to explain the observed results. We have shown that at least 90% of passive participants are likely to reside in Queensland and therefore have their skin cancers captured by our monitoring system. That is, we estimate that <5% of the total study population would have been lost to follow-up. Moreover, there was no differential loss among those who moved from Queensland nor among those with a high skin cancer risk.

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**Table 2. Baseline characteristics by participation status**

| Participation status follow-up study | Baseline characteristics | | | | |
|---|---|---|---|---|---|
| | Skin reaction to strong sun: always burn | Skin color: fair | Occupation: always outdoors | Elastosis of the face: severe | Had skin cancer before the trial |
| Active ($n = 875$) | 177 (20%) | 502 (57%) | 148 (17%) | 237 (27%) | 199 (23%) |
| Passive ($n = 609$) | 130 (21%) | 314 (52%) | 122 (20%) | 188 (31%) | 157 (26%) |
| *P** | 0.60 | 0.03 | 0.13 | 0.11 | 0.18 |

*$\chi^2$ test.

**Table 3. Incidence of histologically confirmed basal cell and squamous cell carcinomas on the head, neck, arms, and hands, by sunscreen treatment group**

| Outcome and follow-up period | BCC | | | SCC | | |
|---|---|---|---|---|---|---|
| | Daily sunscreen, incidence† (no.) | No daily sunscreen, incidence† (no.) | Rate ratio* (95% confidence interval) | Daily sunscreen, incidence† (no.) | No daily sunscreen, incidence† (no.) | Rate ratio* (95% confidence interval) |
| Persons affected | | | | | | |
| Trial + total follow-up period (1993–2004) | 1,296 (121) | 1,270 (119) | 1.02 (0.78-1.35) | 546 (51) | 811 (76) | 0.65 (0.45-0.94) |
| Total follow-up period (1996–2004) | 1,516 (97) | 1,494 (96) | 1.02 (0.75-1.37) | 625 (40) | 934 (60) | 0.65 (0.43-0.98) |
| Late follow-up (2001–2004) | 1,820 (55) | 2,085 (63) | 0.86 (0.59-1.26) | 695 (21) | 1,390 (42) | 0.49 (0.28-0.83) |
| Total number of tumors | | | | | | |
| Trial + total follow-up period (1993–2004) | 2,474 (231) | 2,840 (266) | 0.87 (0.64-1.20) | 868 (81) | 1,516 (142) | 0.59 (0.38-0.90) |
| Total follow-up period (1996–2004) | 2,422 (155) | 2,770 (178) | 0.89 (0.64-1.25) | 953 (61) | 1,587 (102) | 0.62 (0.38-0.99) |
| Late follow-up (2001–2004) | 2,548 (77) | 3,408 (103) | 0.75 (0.49-1.14) | 960 (29) | 1,952 (59) | 0.49 (0.27-0.87) |

*Rate ratios are given relative to the ''no daily sunscreen'' reference group, with 95% confidence intervals.
†Incidence per 100,000 person-years at risk.

Although some concern has been raised that regular use of high-protection sunscreens may compromise vitamin D synthesis in the skin (9), others have shown that individuals who avoid sun exposure (10) and use sunscreen (11) can maintain normal levels of vitamin D. It has also been suggested that persons who use high-protection sunscreens may increase the duration of their sun exposure (12), but neither our data nor results of a recent randomized trial support this (13).

We conclude that regular use of sunscreen can have prolonged benefits in preventing SCCs of the skin. There is no clear benefit of regular sunscreen application in reducing BCC tumors, even in the long term.

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