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Reduced Melanoma After Regular Sunscreen Use: Randomized Trial Follow-Up

Adèle C. Green, Gail M. Williams, Valerie Logan, and Geoffrey M. Strutton

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From the Queensland Institute of Medical Research; University of Queensland; and Princess Alexandra Hospital, Brisbane, Australia.

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Corresponding author: Adèle Green, Queensland Institute of Medical Research, PO Royal Brisbane Hospital, Queensland 4029, Australia; e-mail: adele.green@qimr.edu.au.

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ABSTRACT

Purpose
Regular sunscreen use prevents cutaneous squamous cell carcinoma long term, but the effect on melanoma is highly controversial. We evaluated whether long-term application of sunscreen decreases risk of cutaneous melanoma.

Participants and Methods
In 1992, 1,621 randomly selected residents of Nambour, a township in Queensland, Australia, age 25 to 75 years, were randomly assigned to daily or discretionary sunscreen application to head and arms in combination with 30 mg beta carotene or placebo supplements until 1996. Participants were observed until 2006 with questionnaires and/or through pathology laboratories and the cancer registry to ascertain primary melanoma occurrence.

Results
Ten years after trial cessation, 11 new primary melanomas had been identified in the daily sunscreen group, and 22 had been identified in the discretionary group, which represented a reduction of the observed rate in those randomly assigned to daily sunscreen use (hazard ratio [HR], 0.50; 95% CI, 0.24 to 1.02; $P = .051$). The reduction in invasive melanomas was substantial (n = 3 in active *v* 11 in control group; HR, 0.27; 95% CI, 0.08 to 0.97) compared with that for preinvasive melanomas (HR, 0.73; 95% CI, 0.29 to 1.81).

Conclusion
Melanoma may be preventable by regular sunscreen use in adults.

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INTRODUCTION

The need for more effective prevention of melanoma is recognized around the world as climbing incidence and high mortality in white populations persist.[1-3] In the United States, approximately 68,700 new melanoma occurrences and more than 8,600 deaths were expected to occur in 2009.[4] Exposure to solar ultraviolet (UV) radiation is the only established modifiable cause of melanoma.[5,6]

Despite the known etiologic role of sun exposure, the question regarding sunscreen use to prevent melanoma remains open[7] and controversial.[8] Although case-control and cohort studies of sunscreen use and melanoma risk abound, their findings have been uninformative.[9-11] Nonrandomized studies of the melanoma-sunscreen association are unable to distinguish the main determinants of sunscreen use from those of melanoma, because they are the same—namely, susceptibility to sunburn, high occupational or recreational sun exposure, and family history.[11] The only relevant evidence comes from a randomized trial of sunscreen application in Canadian children conducted from 1993 to 1996 that showed a small reduction in new melanocytic nevi,[12] the strongest predictors of melanoma, in children allocated to a sunscreen arm, especially if the children had freckles.

Here, we present new evidence from the follow-up of a community-based, pragmatic trial of sunscreen to prevent skin cancer in Queensland, Australia.[13] By primarily aiming to evaluate prevention of basal cell carcinoma (BCC) and squamous cell carcinomas (SCC) of the skin and their precursors,[13,14] we have shown prolonged prevention of SCC by the sunscreen intervention.[15] Now, this trial and its 10-year aftermath have given us the unique opportunity to examine melanoma as a secondary trial end point by using unconfounded evidence of the long-term effectiveness of sunscreen in reducing melanoma incidence. The hypothesis was that regular sunscreen use by white adults prevents the occurrence of primary cutaneous melanoma,[11,16] with a possible latent effect of up to 10 years.

METHODS

Study Design

In 1992, 1,621 residents of the Queensland township of Nambour who were ascertained in 1986 at ages 20 to 69 years for a skin cancer prevalence survey were enlisted in the Nambour Skin Cancer Prevention Trial. Original survey participants had been randomly sampled from the Nambour electoral roll (enrollment is compulsory by law),[14] and those who participated in the trial were representative of the original sample.[17] Trial participants were randomly assigned individually by using a computer-generated, randomized list (without stratification or blocking). The 812 participants randomly assigned to sunscreen intervention were given a free, unlimited supply of broad-spectrum sunscreen containing 8% (by weight) 2-ethyl hexyl-*p*-methoxycinnamate and 2% (by weight) 4-*tert*-butyl-4′ methoxy-4-dibenzoylmethane and with a sun protection factor (SPF) of 16. They were asked to apply it to head, neck, arms, and hands every morning (and reapplication was advised after heavy sweating, bathing, or long sun exposure). The 809 participants randomly assigned to the comparison group continued using sunscreen of any SPF at their usual, discretionary frequency, which included no use.[13] Allocation of a placebo sunscreen to the control group was unethical, given the subtropical location. According to a 2 × 2 factorial design, 820 participants (n = 404 and n = 416 in daily and discretionary sunscreen groups, respectively) were also independently randomly assigned to 30 mg beta carotene, and 801 participants (n = 408 and n = 393 in daily and discretionary sunscreen groups, respectively) were randomly assigned to placebo supplements, because beta carotene potentially could counteract the oxidative damage to DNA involved in solar UV carcinogenesis.[13]

Compliance with sunscreen treatment was assessed by measured weights of returned sunscreen bottles and by questionnaires asking average frequency of use in a normal week. Intake of supplements was assessed by remaining tablet counts.[13] Dermatologists unaware of treatment allocations conducted skin examinations of participants at baseline (March 1992), including assessment of number of nevi on the back; midway (1994); and at trial end (August 1996). Participants diagnosed with suspected melanomas were referred to their physicians for immediate management. All skin cancers, including melanomas diagnosed between surveys, were ascertained quarterly with histologic confirmation of any reported. Information about risk factors for skin cancers, such as skin color, outdoor behavior, and sunburn history, was obtained at baseline, and information on sun exposure and protection was updated throughout the trial. Ethical approval was obtained from institutional ethics committees, and study participants gave their written informed consent.

Follow-Up

After the scheduled trial completion in 1996, 1,339 participants (82%, including 14 participants who moved outside Queensland) agreed to take part in the follow-up study actively (Fig 1); they completed biannual or annual questionnaires about all new skin cancers, including melanomas. In addition,

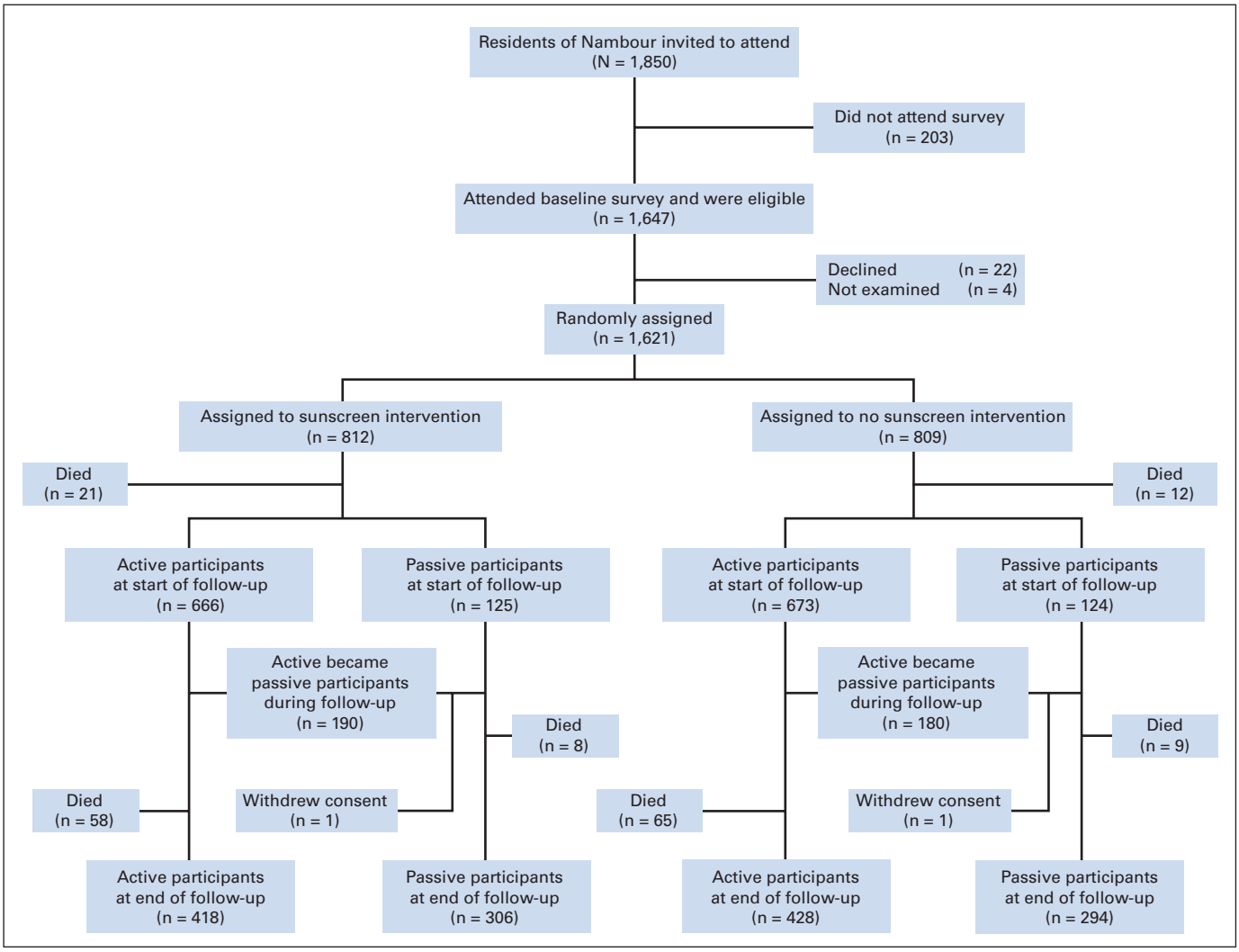

Fig 1. Nambour Skin Cancer Prevention Trial follow-up profile.

they reported average time outdoors on weekdays and weekends in the previous 6 or 12 months and average sunscreen use (although no sunscreen was supplied after 1996). Participants who withdrew from active trial participation or active follow-up were asked to continue with ongoing passive monitoring of skin cancers through their medical records.[14] Investigators thus obtained notification of all melanomas diagnosed by regional pathology laboratories in active and passive participants. Finally, we cross-checked for any melanomas diagnosed between 1992 and 2006 through a search of the Queensland Cancer Registry (because melanoma registration is compulsory, is a particularly high priority, and is considered virtually complete); however, no new melanomas were uncovered in the Cancer Registry checks that had not already been ascertained.

Review of each diagnosed melanoma was undertaken by two expert dermatopathologists who were unaware of sunscreen allocation, and reviews were based on available pathology slides. The histologic diagnosis of melanomas of any type, both in situ and invasive, was based on a constellation of features developed during several decades.[18] Melanoma in situ, lentigo maligna type, was diagnosed by using defined criteria.[19] Invasion was defined and classified according to Clark's level of invasion: Level 1 (in situ); Level 2, tumor in the papillary dermis; Level 3, tumor filling the papillary dermis and extending to the papillary dermis/reticular dermis interface; Level 4, tumor in reticular dermis; and Level 5, tumor in fat.[20] Classification by histologic type was not undertaken, although no melanoma types were excluded.

Statistical Analysis

When we formally assessed the long-term trial results for BCC and SCC to the end of 2004, one of us (G.W.) also carried out a preliminary intention-to-treat analysis on the basis of accumulated but unreviewed melanoma reports for all body sites. The decision then was made to evaluate melanoma occurrence classified according to invasiveness up to December 2006, because 15 years of follow-up (calendar time) was deemed sufficient to detect an effect of sunscreen, if present. On the basis of the observed rate of melanoma in the control group to 2004, the power was estimated to be 66%, and 50%, for detecting hazard ratios of 0.3 and 0.4, respectively, with a two-sided α of .05. As for the other skin cancer end points,[13] melanomas diagnosed in the first year of intervention were excluded a priori, because their development was unlikely to have been affected by the introduced sunscreen treatment. Cox proportional hazards regression, with the sunscreen and beta carotene interventions as two main effects, was used to examine treatment effects in relation to primary melanoma occurrence with incorporation of lead time. Individual effects of sunscreen and beta carotene were tested by using likelihood ratio tests. Subgroup analyses were performed to assess consistency of effect according to age, sex, phenotype, sun exposure, and history of skin cancer by using Cox regression and by incorporating a subgroup interaction term to detect heterogeneity of effects.

During trial follow-up, mean hours each day spent outdoors on weekdays and on weekends were calculated, and sun protection habits were assessed from questionnaire responses. Sun exposure and protection durations were compared across the two sunscreen treatment groups by using a two-sample *t* test. All reported *P* values were two sided.

Table 1. Demographic and Clinical Characteristics of Participants at Baseline in 1992 According to Sunscreen Allocation

Characteristic	Intervention*				
	Sunscreen (n = 812)		No Sunscreen (n = 809)		
	No.	%	No.	%	*P*†
Sex					
Male	356	44	354	44	
Female	456	56	455	56	.97
Age, years					
> 50	446	55	442	55	
50-59	166	20	164	20	
≥ 60	200	25	203	25	.98
Skin color					
Fair	453	56	442	55	
Medium	299	37	315	39	
Olive/brown	59	7	51	6	.57
Skin reaction to acute sun					
Burn, never tan	171	21	169	21	
Burn, then tan	552	68	547	68	
Only tan	88	11	92	11	.94
Previous occupations					
Mainly outdoors	165	20	138	17	
Indoors and outdoors	283	35	318	39	
Mainly indoors	363	45	352	44	.10
No. of sunburns					
None	97	12	88	11	
Once	131	16	144	18	
2-5	362	45	354	44	
> 5	220	27	222	27	.77
Nevi on back					
None	134	17	127	16	
1-10	537	68	526	67	
≥ 11	123	15	135	17	.66
Previous history skin cancer					
Yes	207	25	211	26	
No	605	75	598	74	.79
Clinical elastosis of neck					
Nil	188	23	167	21	
+	368	45	394	49	
++	255	31	244	30	.31
Beta carotene allocation					
Active	404	50	416	51	
Placebo	408	50	393	49	0.50

*For some characteristics, the summed total is less than the number of patients per intervention because of missing values.
†Likelihood ratio statistic for any variation.

RESULTS

Balance was achieved with respect to established risk factors for skin cancer and melanoma among the Nambour trial participants randomly assigned to sunscreen or control in 1992 (Table 1). Compliance with sunscreen treatment, assessed by average of reported frequencies of application, measured weights of returned sunscreen bottles, and diaries, was approximately 75%,[13] and 25% of the intervention group applied sunscreen to trunk and/or lower limbs as well as to the intervention sites.[21] The majority of participants in the control group either did not apply sunscreen (38%) or applied it once or twice a week at most (35%), and 8% applied it to nonintervention sites.[21] Compliance was approximately 70% for beta carotene and placebo supplementation.[13]

By the end of 2006, 846 people (52%) were actively completing questionnaires, 600 (37%) were passive participants, and 173 (11%) had died (n = 87, sunscreen group; n = 86, controls; n = 71, beta carotene group; n = 102, placebo controls), including one person who died as a result of melanoma diagnosed in 1978. One person from each sunscreen treatment group had withdrawn their permission for passive follow-up, in 2002 and 2001, respectively, and data for both were censored accordingly. There was no significant difference in mode of follow-up in relation to sunscreen allocation: duration of active follow-up was 14.3 person-years (95% CI, 14.1 to 14.4 person-years) versus 14.2 person-years (95% CI, 14.0 to 14.3 person-years), and

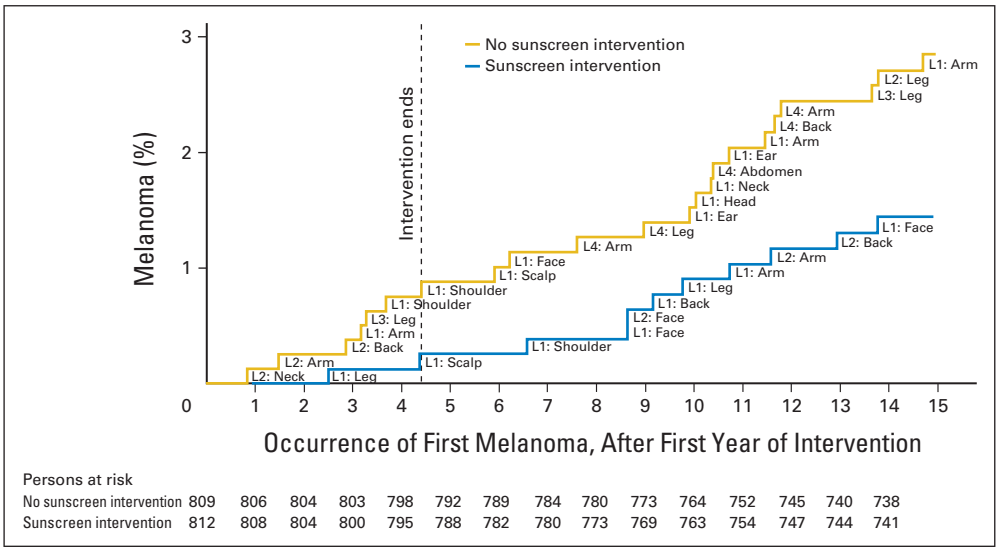

Fig 2. Occurrence of first primary melanoma by level of invasion and anatomic site in the two sunscreen treatment groups.

active response rates were 94.2% and 94.3% in each group, respectively. On the basis of reports of active participants, 25% of those randomly assigned to daily sunscreen continued to use sunscreen on a regular basis after the trial[22] compared with 18% of the nonintervention group ($P = .004$).[15] By 2001, less than 3% of either supplement group took beta carotene supplements.

In the almost 15 years from commencement of the trial in March 1992 until the end of follow-up in December 2006, 36 of the 1,621 trial participants developed first primary melanomas (n = 22, in situ; n = 14, invasive; none metastatic), and one person in each trial arm developed two primary melanomas. Three people (n = 1, intervention group; n = 2, control) who had melanomas diagnosed in 1992 were excluded a priori. In the remainder of the trial from 1993 to 1996, two participants in the daily sunscreen group and seven in the discretionary group were diagnosed with melanoma (Fig 2). From trial cessation until the end of 2006, nine more participants allocated to daily sunscreen and 15 allocated to discretionary use were diagnosed with incident melanomas (Fig 2). In all, 11 trial participants in the sunscreen intervention and 22 in the control group (Table 2) were newly diagnosed with primary melanoma between 1993 and 2006. Risk of melanoma overall was reduced in those randomly assigned to daily sunscreen compared with discretionary use (hazard ratio [HR], 0.50; 95% CI, 0.24 to 1.02; $P = .051$), although the result was of borderline statistical significance. Invasive melanoma was reduced by 73% in the daily sunscreen group (HR, 0.27; 95% CI, 0.08 to 0.97; $P = .045$; Table 2); average thickness was 0.53 mm in the sunscreen group and 1.2 mm in controls ($P = .08$) on the basis of the original pathology reports (except for one level 2 melanoma in the control group for which thickness measurement was unavailable). There were no significant differences between intervention and control arms with respect to either in situ melanomas (8 *v* 11, respectively; HR, 0.73; 95% CI, 0.29 to 1.81) or melanomas on prescribed application sites (HR, 0.46; 95% CI, 0.17 to 1.20). When a multivariate proportional hazards regression was carried out that included sex, skin type, numbers of nevi, previous history of skin cancer, and sun exposure along with the two treatment categories, the overall effect estimate for sunscreen varied little (HR, 0.49; 95% CI, 0.24 to 1.02). Regarding outcome according to beta carotene randomization, 16 and 17 melanomas occurred in those taking active and placebo supplements, respectively (HR, 0.89; 95% CI, 0.45 to 1.76).

Table 2. First Primary Melanomas During 1993-2006 According to Randomized Sunscreen Intervention During 1992-1996 and Risk of Melanoma

Melanoma by Level	No. of Participants Affected		Analysis		
	Sunscreen (n = 812)	No Sunscreen (n = 809)	Hazard Ratio	95% CI	*P**
All	11	22	0.50	0.24 to 1.02	.051
I: in situ	8	11	0.73	0.29 to 1.81	.493
Invasive	3	11	0.27	0.08 to 0.97	.045
II: in papillary dermis	3	4			
III: filling papillary dermis	0	1			
IV: reticular dermis	0	5			

**P* values were calculated from Cox regression that used sunscreen and beta carotene as main effects.

No significant interactions with any baseline characteristics were found (Fig 3). Sun exposure was similar between the daily and discretionary sunscreen groups during the trial (79% and 77%, respectively, spent less than 50% of weekend time outdoors[23]) or after the trial (3.8 and 3.9 hours each day, respectively, spent outdoors on weekdays [$P = .46$]; 4.6 and 4.7 hours each day, respectively, spent outdoors on weekends [$P = .79$]). Use of sun protection measures other than sunscreen was similar during the trial (approximately 60% of both groups usually sought shade; around 75% usually wore a hat) and after the trial (at midpoint of follow-up, 40% and 67% usually sought shade and wore a hat in the sun, respectively).

DISCUSSION

Long-term follow-up of this randomized trial showed that, among adults age 25 to 75 years, regular application of SPF 15+ sunscreen in

	Sunscreen Intervention	No Sunscreen Intervention	Hazard Ratio (95% CI)	*P* for Interaction
Sex				
Male	3/356 (0.8)	10/354 (2.8)	0.66 (0.27 to 1.63)	
Female	8/456 (1.7)	12/455 (2.6)	0.30 (0.08 to 1.08)	.31
Age, years				
Less than 50	5/446 (1.1)	11/442 (2.5)	0.54 (0.16 to 1.29)	
50-59	4/166 (2.4)	3/164 (1.8)	1.34 (0.30 to 5.98)	
60 years or more	2/200 (1.0)	8/203 (3.9)	0.25 (0.05 to 1.19)	.30
Skin Cancer History				
No	7/169 (1.2)	13/598 (2.2)	0.53 (0.21 to 1.33)	
Yes	4/207 (1.9)	9/211 (4.3)	0.46 (0.14 to 1.49)	.85
Reaction to Sun				
Burn, no tan	3/171 (1.8)	7/169 (4.9)	0.41 (0.11 to 1.59)	
Burn, then tan	7/552 (1.3)	15/547 (2.7)	0.46 (0.19 to 1.13)	
Tan	1/88 (1.1)	0/92 (0.0)		.99
Skin Color				
Light	8/453 (1.8)	14/442 (3.2)	0.55 (0.23 to 1.32)	
Medium	2/299 (0.7)	6/315 (1.9)	0.35 (0.07 to 1.75)	
Dark	1/59 (1.7)	2/51 (3.9)	0.43 (0.04 to 4.76)	.89
Occupation				
Mainly outdoors	2/165 (1.2)	5/138 (3.6)	0.33 (0.06 to 1.70)	
Indoors/outdoors	4/283 (1.4)	7/318 (2.2)	0.64 (0.19 to 2.18)	
Mainly indoors	5/363 (1.4)	10/352 (2.8)	0.49 (0.17 to 1.43)	.82
Leisure Activities				
Mainly outdoors	6/333 (1.8)	12/336 (3.6)	0.50 (0.19 to 1.34)	
Indoors/outdoors	2/350 (0.6)	8/352 (2.3)	0.25 (0.05 to 1.17)	
Mainly indoors	3/127 (2.4)	2/118 (1.7)	1.45 (0.24 to 8.66)	.34
History of Burns				
Never	3/97 (3.1)	2/88 (2.3)	1.44 (0.24 to 8.59)	
Once	0/131 (0.0)	2/144 (1.4)		
2-5 times	4/362 (1.1)	12/354 (3.4)	0.32 (0.10 to 0.99)	
More than 5 times	4/220 (1.8)	6/222 (2.7)	0.67 (0.19 to 2.37)	.55
Naevi on Back				
None	1/134 (0.8)	3/127 (2.4)	0.32 (0.03 to 3.06)	
1-10	8/537 (1.5)	12/526 (2.3)	0.65 (0.27 to 1.59)	
11 or more	2/123 (1.6)	7/135 (5.2)	0.32 (0.07 to 1.52)	.66
Overall	**11/812 (1.3)**	**22/809 (2.7)**	**0.50 (0.24 to 1.02)**	

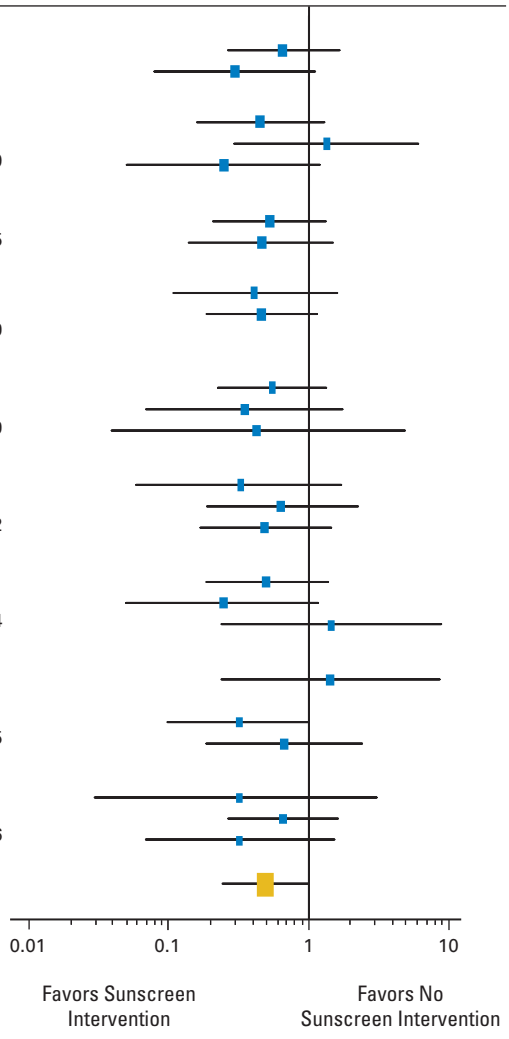

Fig 3. Effect of sunscreen intervention on melanoma according to baseline characteristics. Hazard ratios are for melanoma in a comparison of the sunscreen intervention and control groups. Hazard ratios, 95% CIs, and *P* values were calculated by using Cox regression that incorporated a subgroup interaction term to detect heterogeneity of effects.

a 5-year period appeared to reduce the incidence of new primary melanomas for up to 10 years after trial cessation. A protective effect was also evident for invasive melanoma, which showed a 73% decrease in those randomly assigned to daily sunscreen after approximately 15 years of follow-up. This result for the invasive subgroup was an exploratory finding, however, and should be interpreted cautiously. The apparent decrease in melanoma across all body sites, not only prescribed application sites, likely reflected the ongoing tendency of more participants in the daily than the discretionary sunscreen group to apply sunscreen regularly to the trunk and lower limbs.[21,22] Intensity of application also tended to be higher in the intervention group.[21]

There was no evidence to suggest that the observed difference could be explained by a difference in sun exposure in the intervention group relative to the control group, because outdoor behavior was similar during[23] and after the trial. Similarly, there were no differences in active completion of follow-up questionnaires with self-reports (later validated) of all new skin cancers, including melanomas. Without reference to treatment groups, we attempted to capture all melanomas diagnosed between 1993 and 2006 among passive trial participants (except for two who withdrew consent for follow-up) from the Queensland Cancer Registry as well as from the pathology laboratories. Ultimately, however, the final diagnosis of each melanoma reported during or after the trial was determined by the two reviewing dermatopathologists (one who was highly experienced in melanoma diagnosis) who were unaware of allocated treatment groups. There were technical limitations of the histopathologic review, because it was based on the slides available and because much of the material was archival. Even when tissue blocks were available, the remaining tissue might not have been representative of the tumor as a whole. We had no information on presence of ulceration or mitotic figures; definitive assessment of thickness of these study melanomas required reference to original diagnostic pathology reports, because original slides or tissue blocks no longer existed in many cases. Level of invasion also may have been subject to some uncertainty, though not

differentially according to sunscreen, because the dermatopathologists had no knowledge of treatment allocation.

With regard to the beta carotene intervention, we found no evidence of harmful effect on melanoma or other health outcomes (mortality overall or as a result of other cancers). Although we observed fewer deaths in the intervention than in the control group on follow-up, we observed no specific beneficial effect on cancer outcomes, which is in agreement with two other randomized trials of beta carotene supplementation with follow-up[24,25] and with a recent meta-analysis.[26]

Though this community-based skin cancer prevention trial is the only one of its kind, its findings that suggest the general preventability of melanoma after the regular application of broad-spectrum sunscreen have been predicted.[11,16] They accord with those of a trial of sunscreen to prevent melanocytic nevus development in children,[12] despite the limited number of children involved and the brief follow-up.[27] The results are consistent with the knowledge that excessive sun exposure causes melanoma,[5] notwithstanding the evidence that solar UV carcinogenesis may operate by different pathways to cause melanomas on different body sites.[28,29] Results also accord with background experimental data in mice,[9] including prevention of p53 mutations in UV-irradiated skin by sunscreen.[30] In addition, in people with sun-sensitive skin types, daily-care sunscreen can inhibit clinical, cellular, and molecular damage caused by daily suberythemal solar-simulating radiation.[31]

Given the importance of early-life sun exposure in the genesis of melanoma,[32] a long-term sunscreen intervention among children and adolescents may yield even greater benefits in cancer prevention[33] than did this intervention in adults. The adult participants in Nambour would have experienced relatively high ambient sun exposure for years, so skin carcinogenesis may already have been initiated in many of them; only the promoting effects of ongoing adult sun exposure would have been targeted by this intervention.

In conclusion, our findings provide reassurance in view of the widespread uncertainty to date about sunscreen's ability to prevent melanoma.[7,34] Although the results are directly relevant to people who live in sunny climates like Australia's and who receive relatively high levels of ambient sun exposure as a matter of course, they also have implications for white people living in temperate climates in North America and Europe[35] who are at increased risk of melanoma because of increased solar UV exposure caused by the predilection for holidays in sunny places.[5,36]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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AUTHOR CONTRIBUTIONS

Conception and design: Adèle C. Green, Gail M. Williams
Financial support: Adèle C. Green
Administrative support: Adèle C. Green, Valerie Logan
Provision of study materials or patients: Adèle C. Green, Valerie Logan, Geoffrey M. Strutton
Collection and assembly of data: Adèle C. Green, Gail M. Williams, Valerie Logan
Data analysis and interpretation: Adèle C. Green, Gail M. Williams, Geoffrey M. Strutton
Manuscript writing: All authors
Final approval of manuscript: All authors

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