Annals of Internal Medicine | ORIGINAL RESEARCH

# Sunscreen and Prevention of Skin Aging

## A Randomized Trial

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**Background:** Sunscreen use and dietary antioxidants are advocated as preventives of skin aging, but supporting evidence is lacking.

**Objective:** To determine whether regular use of sunscreen compared with discretionary use or β-carotene supplements compared with placebo retard skin aging, measured by degree of photoaging.

**Design:** Randomized, controlled, community-based intervention. (Australian New Zealand Clinical Trials Registry: ACTRN12610000086066).

**Setting:** Nambour, Australia (latitude 26° S).

**Patients:** 903 adults younger than 55 years out of 1621 adults randomly selected from a community register.

**Intervention:** Random assignment into 4 groups: daily use of broad-spectrum sunscreen and 30 mg of β-carotene, daily use of sunscreen and placebo, discretionary use of sunscreen and 30 mg of β-carotene, and discretionary use of sunscreen and placebo.

**Measurements:** Change in microtopography between 1992 and 1996 in the sunscreen and β-carotene groups compared with controls, graded by assessors blinded to treatment allocation.

**Results:** The daily sunscreen group showed no detectable increase in skin aging after 4.5 years. Skin aging from baseline to the end of the trial was 24% less in the daily sunscreen group than in the discretionary sunscreen group (relative odds, 0.76 [95% CI, 0.59 to 0.98]). β-Carotene supplementation had no overall effect on skin aging, although contrasting associations were seen in subgroups with different severity of aging at baseline.

**Limitation:** Some outcome data were missing, and power to detect moderate treatment effects was modest.

**Conclusion:** Regular sunscreen use retards skin aging in healthy, middle-aged men and women. No overall effect of β-carotene on skin aging was identified, and further study is required to definitively exclude potential benefit or potential harm.

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Preservation of a youthful complexion has been the goal of aging humans for thousands of years (1). Today, many billions of dollars are spent annually on creams and lotions that purport to treat or protect against skin wrinkling (2). Most changes associated with skin aging are due to photoaging after cumulative sun exposure, superimposed on chronologic aging (3).

Photoaging describes the clinical and histologic skin changes induced by sun exposure. Affected skin loses elasticity and appears dry, wrinkled, and patchily pigmented and often has dilated superficial blood vessels and actinic keratoses (4–6). Histologic changes include epidermal thickening, atypical keratinocytes, and reduced collagen in the dermis with abundant abnormal elastin ("dermal elastosis") (7).

Ultraviolet (UV) A and B components of solar radiation are implicated in photoaging of the skin (8). Apart from unwanted cosmetic effects, photoaging is a strong risk factor for skin cancer (9). Ultraviolet radiation damages nucleic acids and proteins in epidermal cells directly and through reactive oxygen species (10), resulting in impaired collagen and elastin homeostasis, local immune suppression, altered differentiation of keratinocytes, and ultimately tumor development (8, 10, 11).

Although dermal elastosis is considered definitive confirmation of photoaging, several noninvasive techniques can also assess its presence and severity: visual analog scoring (12), skin extensibility (13), pulsed ultrasonography of skin (14), and silicone impressions of skin surface topography (15, 16). We have previously shown that severity of dermal elastosis (17, 18) is predicted by standard grading of the microtopography of the skin surface (19, 20), which provides a valid measure of skin photoaging up to age 70 years (21).

Among myriad creams, drugs, and "cosmeceuticals" available over the counter or by prescription, several preventive and therapeutic agents for photoaged skin are believed to be efficacious, the most common being sunscreen (22). However, experimental evidence showing that sunscreen protects against aging (23) is not matched by human evidence. A trial in 35 patients with a history of skin cancer randomly assigned to sunscreen or placebo for 2 years showed no significant difference in dermal elastosis with sunscreen use (24).

No known randomized studies in humans have evaluated the effect of sunscreen on surface changes associated with skin aging. We performed a randomized, controlled trial to examine whether daily sunscreen use could prevent progression of skin aging in adults younger than 55 years (25). In addition, in view of experimental evidence that oral antioxidants can reduce signs of oxidative skin damage

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***Context***

Whether sunscreen or β-carotene protects against skin aging has not been established.

***Contribution***

After 4 years, participants randomly assigned to daily application of sunscreen showed less skin aging than those instructed to use sunscreen on a discretionary basis. No difference in skin aging was shown with daily β-carotene compared with placebo.

***Caution***

Power was limited; although results suggest no effect, a beneficial or harmful effect of β-carotene cannot be confidently excluded.

***Implication***

Daily sunscreen use protects against skin aging. Although no effect on aging was seen with β-carotene use, these findings need confirmation before firm conclusions can be made.

*—The Editors*

and wrinkling due to sun exposure (26), we evaluated whether β-carotene supplements could protect against skin aging.

## METHODS

### Design Overview

The Nambour Skin Cancer Prevention Trial was a randomized, community-based trial in Nambour, Australia (latitude 26 °S). Aims, methods, and results have been fully documented elsewhere (25, 27–29). In brief, the study was conducted from 1992 to 1996 in 1621 randomly selected adults and evaluated whether daily application of broad-spectrum sunscreen or dietary supplementation with β-carotene could reduce skin cancer and retard actinic keratosis and photoaging (25). The Queensland Institute of Medical Research Ethics Committee (Queensland, Australia) approved the study, and participants provided written informed consent.

### Setting and Participants

Per the protocol, this study was restricted to participants younger than 55 years because their skin aging is caused predominantly by photoaging rather than by photoaging and growing old. Persons receiving vitamin supplements containing β-carotene or applying sunscreen on a strict daily basis were ineligible. Height and weight were measured, and personal information, including skin color, skin reaction to sun exposure, outdoor behavior, sunburn history, and smoking status, were obtained at baseline by using standardized questionnaires.

### Randomization and Interventions

Using a 2 × 2 factorial design, one of our study investigators, who had no knowledge of the participants, randomly assigned them by using a computer-generated randomized list to daily application of sunscreen labelled "sun-protection factor 15+," containing 8% (by weight) 2-ethylhexyl-*p*-methoxycinnamate and 2% (by weight) 4-*tert*-butyl-4' methoxy-4-dibenzoylmethane (Ross Cosmetics, Melbourne, Victoria, Australia), or discretionary sunscreen use (placebo sunscreen was considered unethical) and to 30 mg of β-carotene or placebo supplements daily. Those allocated to daily sunscreen use were asked to apply the intervention sunscreen to their head, neck, arms, and hands every morning, with reapplication after heavy sweating, bathing, or spending more than a few hours outdoors.

### Outcomes and Follow-up

The primary outcome was change in photoaging from 1992 to 1996 in those in the intervention groups compared with their respective controls. To assess photoaging, trained personnel obtained skin surface replicas from the back of the left hand by using silicone-based impression material (SilFlo, Flexico, Potters Bar, United Kingdom), avoiding scarred areas. Participants were asked to not use moisturizer or sunscreen the day that the replicas were taken.

Experienced assessors who were unaware of treatment allocation graded replicas by using the Beagley and Gibson scale of microtopography grades (15, 16). Grades increase from 1 (undamaged skin with fine lines evenly spaced in a 2-directional network) to 6 (increasing severity of changes characterized by surface flattening, deepening of horizontal lines, and loss of vertical lines). Intra- and intergrader repeatability of assessors was high, with weighted κ statistics of 0.81 and 0.86, respectively (19).

Every 3 months, adverse effects were assessed and adherence was evaluated by measured weights of returned sunscreen bottles for the daily sunscreen group and remaining tablet counts. Biennially, application frequency in all participants was assessed by questionnaire, dermal β-carotene was assessed by photometric measurement (28), and sun exposure and smoking habits were updated.

### Statistical Analysis

The number of trial participants younger than 55 years who were eligible for study was determined by the original random sample drawn from the Nambour community (25). Thus, our sample size was determined by practical constraints rather than a priori power calculations.

Data were analyzed according to treatment as randomly allocated. Change in photoaging was assessed by comparing change in microtopography grades from baseline to the end of the trial among intervention and control groups by ordinal logistic regression using generalized estimating equations (GEEs) (30). The GEE model is based on generalized linear regression and allows dependence be-

tween repeated outcome measurements (30). It adjusts for within-person correlation of outcomes over time and accounts for the magnitude of differences in categories of aging (rather than simply the odds of more aging, yes or no) and the changes in odds of higher grades of skin aging over time.

This method gives effect estimates in terms of the odds of having higher microtopography grades in 1996 relative to 1992 for each category of sunscreen and β-carotene intervention and the relative odds, assumed constant from 1 grade to the next (proportional odds assumption), comparing these. The effects of treatments on microtopography grades over time were estimated by specifying an interaction between trial allocation and time in the model. Three effect estimates (with 95% CIs using robust SEs) were calculated for each intervention (that is, daily sunscreen and β-carotene): change in microtopography grade over time in the intervention and control groups and relative change over time in microtopography between the 2 groups. All estimates for the sunscreen intervention were adjusted for the β-carotene intervention and its interaction with time, and vice versa. Models were fitted using the REPOLR procedure (31), specifying exchangeable correlation between repeated measures of microtopography grades to obtain an estimate of relative change over time in the microtopography intervention and control groups, supplemented with a contrast function written by an investigator to obtain an estimate of change in microtopography grade over time in the 2 groups (R, version 2.13.2; R Foundation for Statistical Computing, Vienna, Austria). The score test was used to assess adherence to proportional odds assumption.

The chi-square test was used to assess whether baseline photoaging grade was associated with missing follow-up grade. To test for possible differences in the final study sample, characteristics of the participants with 2 photoaging grades were compared with those with only 1 by using multiple logistic regressions applying a GEE. A binary variable for data completeness was created for both time points and used as the outcome variable, with time and the characteristic being analyzed as the explanatory variables. Analyses of the effects of intervention were repeated, including factors that were significantly associated with having 1 missing microtopography grade.

To assess consistency of effect according to baseline characteristics (age, sex, education, body mass index, smoking status, phenotype, sun exposure, and history of skin cancer), we performed subgroup analyses using ordinal logistic regression applying a GEE and incorporating an interaction among time, treatment allocation, and the previously cited factors to detect heterogeneity of effects. Effect estimates for each subgroup were obtained using the REPOLR procedure in R specifying an exchangeable correlation structure, as described earlier. Because assessment of the overall significance of the third-order interaction (to test heterogeneity of effect) is not available using REPOLR, *P* values for the interactions were estimated from the score test in the GEE model by using the PROC GENMOD procedure (SAS, version 9.2; SAS Institute, Cary, North Carolina), assuming independent correlation among repeated measurements of microtopography grades. Because of the high positive correlation among repeated measurements (0.63 to 0.81), these *P* values were smaller than if dependency among repeated measures were considered.

We conducted 2 sensitivity analyses: We reanalyzed the data only on participants with complete photoaging grades, then we imputed values for missing photoaging grades and covariates by using multiple imputation by the logistic regression method with 10 iterations (32). To assess whether treatment effects differed by preexisting level of photoaging, we conducted separate exploratory analyses for participants with baseline grades 3 to 4 and 5 to 6. All *P* values were 2-sided; a *P* value less than 0.05 was considered significant.

### Role of the Funding Source

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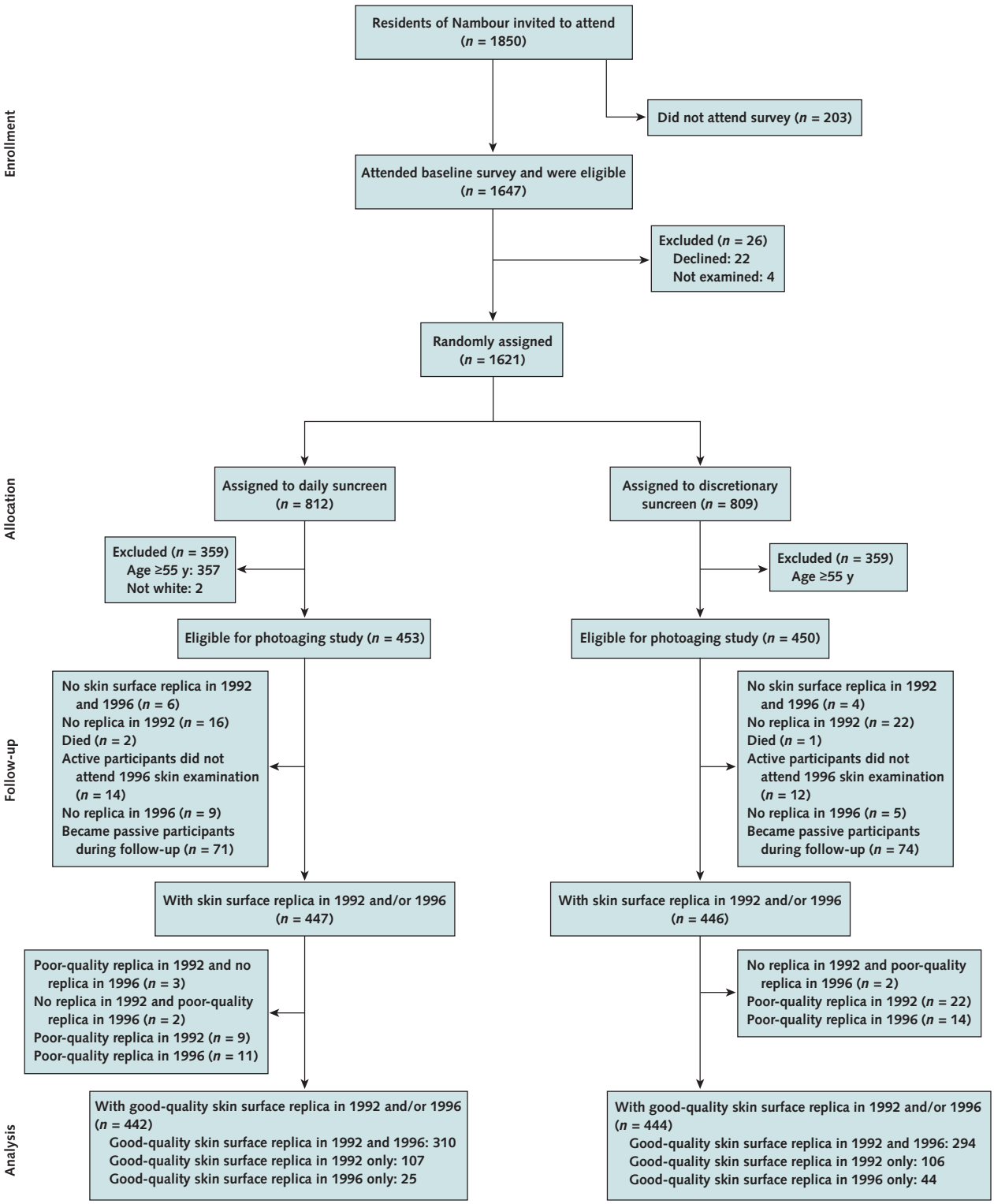
## RESULTS

Of the 1621 Nambour residents enrolled in the trial, 903 were younger than 55 years and eligible for the study (**Figure 1** and **Appendix Figure**, available at www.annals.org). Good-quality replicas of the back of the hand were obtained from 817 participants at baseline and 673 in 1996, and 886 participants (98% of 903) (mean age, 39 years [SD, 7]; 58% women) had at least 1 good-quality skin replica. Of these, 604 contributed replicas in 1992 and 1996, 213 in 1992 only, and 69 in 1996 only. Compared with those with 2 replicas, participants who contributed only 1 ($n = 282$) were more likely to have severe photoaging of the neck and 2 to 5 total sunburns. Having a missing microtopography grade in 1996 was not associated with baseline microtopography grade.

Most participants were fair-skinned, and more than 90% burned on acute sun exposure. One half worked mainly indoors; around 43% ever smoked regularly. There were no differences in phenotype, sun exposure, or pretrial sunscreen use between the intervention and control groups at baseline, although slightly more people were randomly assigned to β-carotene than to placebo ($P = 0.06$) (**Table 1**). Reported sun exposure was similar between the daily and discretionary sunscreen groups during the trial (78% of the daily sunscreen group and 76% of the discretionary sunscreen group spent <50% of weekend time outdoors) ($P = 0.25$). Use of sun-protection measures other than sunscreen was also similar (54% of the daily sunscreen

*Figure 1.* **Study flow diagram of the Nambour sunscreen use and photoaging study, 1992–1996.**




group and 53% of the discretionary sunscreen group usually sought shade, and 63% of the daily sunscreen group and 67% of the discretionary sunscreen group usually wore a hat).

In 1992, 58% of participants had moderate photoaging (grades 3 and 4); in 1996, the corresponding proportion was 49% (**Tables 2** and **3**). When the odds of having higher microtopography grades in 1996 compared with

*Table 1.* **Participant Characteristics at Baseline in 1992, According to Sunscreen and β-Carotene Allocation***

| Characteristic | Intervention, *n* (%) | | | |
|---|---|---|---|---|
| | Daily Sunscreen (*n* = 442) | Discretionary Sunscreen (*n* = 444) | β-Carotene (*n* = 447) | Placebo (*n* = 439) |
| **Sex** | | | | |
| Men | 189 (42.8) | 185 (41.7) | 185 (41.4) | 189 (43.1) |
| Women | 253 (57.2) | 259 (58.3) | 262 (58.6) | 250 (57.0) |
| **Age** | | | | |
| 25 to <40 y | 226 (51.1) | 220 (49.6) | 239 (53.5) | 207 (47.2) |
| 40 to <55 y | 216 (48.9) | 224 (50.4) | 208 (46.5) | 232 (52.9) |
| **Country of birth†** | | | | |
| Australia/New Zealand | 409 (92.5) | 405 (91.4) | 409 (91.5) | 405 (92.5) |
| Other | 33 (7.5) | 38 (8.6) | 38 (8.5) | 33 (7.5) |
| **Education†** | | | | |
| High school | 187 (52.4) | 185 (49.7) | 192 (50.5) | 180 (51.4) |
| Higher education | 170 (47.6) | 187 (50.3) | 188 (49.3) | 170 (48.6) |
| **Skin color†** | | | | |
| Fair | 257 (58.1) | 248 (56.0) | 260 (58.2) | 245 (55.9) |
| Medium | 161 (36.4) | 172 (38.8) | 160 (35.8) | 173 (39.5) |
| Dark | 24 (5.4) | 23 (5.2) | 27 (6.0) | 20 (4.6) |
| **Skin reaction to acute sun†** | | | | |
| Burn, never tan | 94 (21.3) | 92 (20.8) | 97 (21.7) | 89 (20.3) |
| Burn, then tan | 326 (73.8) | 318 (71.8) | 322 (72.0) | 322 (73.5) |
| Only tan | 22 (5.0) | 33 (7.5) | 28 (6.3) | 27 (6.2) |
| **Previous occupations†** | | | | |
| Mainly outdoors | 82 (18.6) | 73 (16.5) | 77 (17.2) | 78 (17.8) |
| Indoors and outdoors | 130 (29.4) | 147 (33.2) | 146 (32.7) | 121 (29.9) |
| Mainly indoors | 230 (52.0) | 223 (50.3) | 224 (50.1) | 229 (52.3) |
| **Sunburns†** | | | | |
| 0 | 25 (5.7) | 18 (4.1) | 22 (4.9) | 21 (4.8) |
| 1 | 53 (12.0) | 48 (10.8) | 56 (12.5) | 45 (10.3) |
| 2–5 | 218 (49.3) | 230 (51.9) | 227 (50.8) | 221 (50.5) |
| >5 | 146 (33.0) | 147 (33.2) | 142 (31.8) | 151 (34.5) |
| **Nevi on back†** | | | | |
| 0 | 55 (12.7) | 51 (11.7) | 55 (12.6) | 51 (11.9) |
| 1–10 | 285 (65.8) | 283 (65.1) | 287 (65.5) | 281 (65.4) |
| ≥11 | 93 (21.5) | 101 (23.2) | 96 (21.9) | 98 (22.8) |
| **History of skin cancer** | | | | |
| No | 379 (85.8) | 379 (85.4) | 385 (86.1) | 373 (85.0) |
| Yes | 63 (14.3) | 65 (14.6) | 62 (13.9) | 66 (15.0) |
| **Clinical photoaging of neck†** | | | | |
| None | 158 (35.8) | 146 (33.0) | 157 (35.2) | 147 (33.6) |
| Low to moderate | 220 (49.9) | 218 (49.2) | 226 (50.7) | 212 (48.4) |
| Severe | 63 (14.3) | 79 (17.8) | 63 (14.1) | 79 (18.0) |
| **Body mass index†** | | | | |
| <25.0 kg/m$^2$ | 170 (50.5) | 166 (46.4) | 176 (48.1) | 160 (48.6) |
| 25.0–29.9 kg/m$^2$ | 112 (33.2) | 140 (39.1) | 130 (35.5) | 122 (37.1) |
| ≥30.0 kg/m$^2$ | 55 (16.3) | 52 (14.5) | 60 (16.4) | 47 (14.3) |
| **Sunscreen use outdoors before randomization†** | | | | |
| Never | 71 (16.1) | 77 (17.4) | 72 (16.1) | 76 (17.4) |
| >50% of the time | 197 (44.6) | 181 (40.9) | 194 (43.4) | 184 (42.0) |
| ≥50% of the time | 150 (33.9) | 157 (35.4) | 155 (34.7) | 152 (34.7) |
| Always | 24 (5.4) | 28 (6.3) | 26 (5.8) | 26 (5.9) |

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*Table 1*—Continued

| Characteristic | Intervention, *n* (%) | | | |
|---|---|---|---|---|
| | Daily Sunscreen (*n* = 442) | Discretionary Sunscreen (*n* = 444) | β-Carotene (*n* = 447) | Placebo (*n* = 439) |
| **Recreational activity†** | | | | |
| None | 127 (35.6) | 122 (32.9) | 131 (34.6) | 118 (33.8) |
| Low | 94 (26.3) | 83 (22.4) | 97 (25.6) | 80 (22.9) |
| Moderate | 50 (22.4) | 93 (25.1) | 84 (22.2) | 89 (25.5) |
| High | 56 (15.7) | 73 (19.7) | 67 (17.7) | 62 (17.8) |
| **Smoking status†** | | | | |
| Never smoker | 225 (58.0) | 219 (54.9) | 234 (57.5) | 210 (55.3) |
| Former smoker | 107 (27.6) | 123 (30.8) | 110 (27.0) | 120 (31.6) |
| Current smoker | 56 (14.4) | 57 (14.3) | 63 (15.5) | 50 (13.2) |
| **β-Carotene allocation** | | | | |
| Placebo | 233 (52.7) | 206 (46.4) | – | – |
| β-Carotene | 209 (47.3) | 238 (53.6) | – | – |
| **Sunscreen allocation** | | | | |
| Daily sunscreen | – | – | 238 (53.2) | 206 (46.9) |
| Discretionary sunscreen | – | – | 209 (46.8) | 233 (53.1) |

* Numbers and percentages show distribution of 886 respondents by sunscreen and β-carotene allocation independently to demonstrate numbers used in analyses.
† Missing responses for country of birth, skin color, skin reaction to acute sun, previous occupations, sunburns, sunscreen use before randomization ($n = 1$), education ($n = 156$), nevi on back ($n = 18$), clinical photoaging of the neck ($n = 2$), body mass index ($n = 191$), recreational activity ($n = 158$), and smoking status ($n = 99$).

1992 were examined after adjustment for sunburns and photoaging of the neck, only the daily sunscreen group showed no detectable increase in microtopography grade (model 2 in **Table 4**). Compared with discretionary sunscreen users, persons randomly assigned to daily sunscreen were 24% less likely to show increased aging (relative odds, 0.76 [95% CI, 0.50 to 0.98]).

There was no difference in increases in microtopography grades among persons allocated to β-carotene and placebo (relative odds, 0.95 [CI, 0.74 to 1.22]) (model 2 in **Table 4**), and odds were consistent across photoaging levels (score test $P = 0.51$). Results were not materially different from models without these covariates (model 1 in **Table 4**) and were consistent with results using only those participants with complete photoaging grades ($n = 604$) and with results incorporating multiple imputations of missing data.

*Table 2.* **Change in Skin Aging Grades From 1992 to 1996 Among Participants, by Sunscreen Allocation**

| Skin Aging Grade in 1992 | Participants, by Skin Aging Grade in 1996, *n* (%)* | | | | |
|---|---|---|---|---|---|
| | No Grade | 3 | 4 | 5 | 6 |
| **Daily sunscreen** | | | | | |
| No grade | 0 (0.0) | 1 (4.0) | 9 (36.0) | 9 (36.0) | 6 (24.0) |
| 3 | 8 (28.6) | 8 (28.6) | 10 (35.7) | 2 (7.1) | 0 (0.0) |
| 4 | 52 (24.9) | 11 (5.3) | 113 (54.1) | 28 (13.4) | 5 (2.4) |
| 5 | 22 (20.0) | 1 (0.9) | 16 (14.6) | 62 (56.4) | 9 (8.2) |
| 6 | 25 (35.7) | 0 (0.0) | 2 (2.9) | 6 (8.6) | 37 (52.9) |
| **Discretionary sunscreen** | | | | | |
| No grade | 0 (0.0) | 0 (0.0) | 10 (22.7) | 18 (40.9) | 16 (3.6) |
| 3 | 13 (38.2) | 6 (17.7) | 14 (41.2) | 1 (2.9) | 0 (0.0) |
| 4 | 45 (22.2) | 7 (3.5) | 108 (53.2) | 38 (18.7) | 5 (2.5) |
| 5 | 18 (19.2) | 2 (2.1) | 9 (9.6) | 46 (48.9) | 19 (20.2) |
| 6 | 30 (43.5) | 0 (0.0) | 3 (4.4) | 8 (11.6) | 28 (40.6) |

* The percentage is the number of participants/number of participants who had a skin aging grade in 1992 × 100.

With regard to long-term self-reported treatment adherence, by 1996 a total of 77% of daily sunscreen users were applying sunscreen at least 3 to 4 days per week compared with 33% of discretionary users. Supplement adherence (defined as taking at least 80% of the prescribed tablets) was 68% in the β-carotene group and 67% in the placebo group. The β-carotene group had significantly greater mean skin reflectance (measured in integers of 3 to 11 with an SE of 0.04 at baseline) on the palm at follow-up than at baseline (6.2 vs. 6.0; $P < 0.001$, paired *t* test), and their follow-up values were greater than those of the placebo group (5.3; $P < 0.001$).

Effect of sunscreen did not vary according to baseline characteristics of participants (**Figure 2**). Exploratory analysis of effects of sunscreen and β-carotene according to baseline microtopography grades suggested stronger and inverse associations with both treatments in those with less severe skin aging at baseline. For participants with microtopography grades of 3 or 4 at baseline, skin aging was reduced among those in the daily sunscreen (odds ratio [OR], 0.77 [CI, 0.48 to 1.23]) and β-carotene (OR, 0.52 [CI, 0.32 to 0.84]) groups than in their respective comparison groups. For those with baseline microtopography grades 5 or 6, daily sunscreen use was not associated with a change in skin aging (OR, 0.90 [CI, 0.44 to 1.87]), whereas the β-carotene group tended to experience more

skin aging (OR, 1.38 [CI, 0.66 to 2.88]) than the placebo group.

The main reported symptoms relating to use of sunscreen were contact allergy or skin irritation (3%), greasiness (1%), and interference with perspiration or stinging eyes after facial perspiration (0.8%) (28).

## DISCUSSION

In this community-based, randomized, controlled trial, we have shown that regular application of sunscreen by people younger than 55 years for 4.5 years significantly retarded aging of the skin. This difference does not seem to be due to changes in outdoor behavior or sun protection by the intervention compared with the control group. Long-term β-carotene supplementation did not seem to influence progressive skin aging, although we could not rule out a small decrease or increase in skin aging as a result of supplementation.

Despite the widespread belief that by screening out solar UV radiation implicated in skin aging (8), sunscreen application can diminish its severity in young and middle-aged adults as they grow older (22), to date there has been evidence of this only in hairless mice (23, 33). A search of relevant English-language papers in MEDLINE (1980 to November 2012) using the terms "sunscreen" (and "beta-carotene") and "photoaging," "skin aging," or "skin wrinkling" identified a single trial involving 35 patients with past skin cancer that evaluated the effect of sunscreen on histologic skin aging. The study showed no difference in dermal elastosis between sunscreen and placebo groups after analysis during which repeated measurements were accounted for (24). To our knowledge, whether sunscreen protects humans against visible rather than histologic premature skin aging has not previously been tested.

These results have important clinical implications. In our data, a unit increase in microtopography grade is significantly related to visible deterioration in skin texture (coarser skin and increased wrinkling) and an increase in visible small blood vessels and comedones on the face (as assessed by dermatologists [4]). More important, a unit increase in microtopography significantly correlates with risk for actinic keratoses and skin cancer (16, 34). A reduction in the highly prevalent aging changes among middle-aged adults by regular application of sunscreen will therefore be associated with cosmetic benefit (prevention of visible aging changes and hence more youthful appearance) and reduced risk for skin cancer.

The cost-effectiveness of promoting daily sunscreen use based on skin cancer prevention alone (35) is probably substantially higher after accounting for the additional prevention of skin photoaging. Whether our results would have differed with a sunscreen with a higher sun-protection factor or one with greater absorption in the UVA spectrum is debatable, because the overriding factor in achieving ad-

*Table 3.* **Change in Skin Aging Grades From 1992 to 1996 Among Participants, by β-Carotene Allocation**

| Skin Aging Grade in 1992 | Participants, by Skin Aging Grade in 1996, *n* (%)* | | | | |
|---|---|---|---|---|---|
| | No Grade | 3 | 4 | 5 | 6 |
| **β-Carotene** | | | | | |
| No grade | 0 (0.0) | 1 (2.4) | 15 (36.6) | 14 (34.2) | 11 (26.8) |
| 3 | 12 (33.3) | 8 (22.2) | 16 (44.4) | 0 (0.0) | 0 (0.0) |
| 4 | 43 (20.5) | 8 (3.8) | 130 (61.9) | 27 (12.9) | 2 (1.0) |
| 5 | 22 (22.2) | 1 (1.0) | 8 (8.1) | 53 (53.5) | 15 (15.2) |
| 6 | 19 (31.2) | 0 (0.0) | 4 (6.6) | 4 (6.6) | 34 (55.7) |
| **Placebo** | | | | | |
| No grade | 0 (0.0) | 0 (0.0) | 4 (14.3) | 13 (46.4) | 11 (39.3) |
| 3 | 9 (34.6) | 6 (23.1) | 8 (30.8) | 3 (11.5) | 0 (0.0) |
| 4 | 54 (26.7) | 10 (5.0) | 91 (45.1) | 39 (19.3) | 8 (4.0) |
| 5 | 18 (17.1) | 2 (1.9) | 17 (16.2) | 55 (52.4) | 13 (12.4) |
| 6 | 36 (46.2) | 0 (0.0) | 1 (1.3) | 10 (12.8) | 31 (39.7) |

* The percentage is the number of participants/number of participants who had a skin aging grade in 1992 × 100.

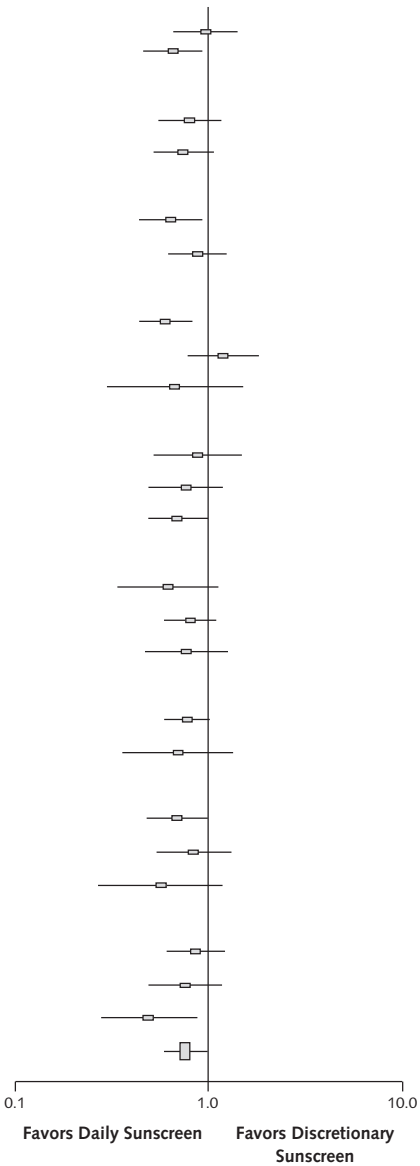
*Table 4.* **Odds of Having Higher Microtopography Grades in 1996 Relative to 1992, by Sunscreen and β-Carotene Intervention***

| Intervention | Model 1 | | Model 2 | |
|---|---|---|---|---|
| | Odds of 1996 Compared With 1992 (95% CI)† | *P* Value | Odds of 1996 Compared With 1992 (95% CI)† | *P* Value |
| **Sunscreen‡** | | | | |
| Daily sunscreen | 1.19 (1.00–1.41) | 0.046 | 1.18 (0.99–1.39) | 0.060 |
| Discretionary sunscreen | 1.56 (1.29–1.88) | <0.001 | 1.54 (1.28–1.86) | <0.001 |
| Relative odds, daily sunscreen/discretionary sunscreen | 0.76 (0.59–0.98) | 0.033 | 0.76 (0.59–0.98) | 0.033 |
| **β-Carotene§** | | | | |
| β-Carotene | 1.32 (1.12–1.55) | 0.001 | 1.31 (1.11–1.55) | 0.001 |
| Placebo | 1.40 (1.16–1.70) | <0.001 | 1.38 (1.14–1.67) | <0.001 |
| Relative odds, β-carotene/placebo | 0.94 (0.73–1.20) | 0.61 | 0.95 (0.74–1.22) | 0.69 |

* Represents 1490 records across 886 persons.
† Odds ratios derived from generalized estimating equation models.
‡ In model 1, the analysis was adjusted for the β-carotene intervention; in model 2, the analysis was also adjusted for factors associated with missing photoaging grade (number of sunburns and clinical photoaging of the neck).
§ In model 1, the analysis was adjusted for the sunscreen intervention; in model 2, the analysis was also adjusted for factors associated with missing photoaging grade (number of sunburns and clinical photoaging of the neck).

*Figure 2.* **Effect of sunscreen intervention on photoaging, according to baseline characteristics.**

| Variable | Odds Ratio (95% CI) | | Relative Odds (95% CI) | Approximate *P* Value for Interaction* |
|---|---|---|---|---|
| | Daily Sunscreen | Discretionary Sunscreen | | |
| **Sex** | | | | |
| Male | 1.35 (1.05–1.75) | 1.39 (1.05–1.86) | 0.97 (0.66–1.42) | |
| Female | 1.10 (0.86–1.39) | 1.67 (1.30–2.15) | 0.66 (0.46–0.93) | 0.30 |
| **Age** | | | | |
| 25 to <40 y | 1.24 (0.96–1.60) | 1.55 (1.17–2.05) | 0.80 (0.55–1.17) | |
| 40 to <55 y | 1.07 (0.83–1.37) | 1.43 (1.10–1.87) | 0.74 (0.52–1.07) | 0.79 |
| **Education** | | | | |
| High school | 1.01 (0.79–1.28) | 1.58 (1.19–2.11) | 0.64 (0.44–0.93) | |
| Higher education | 1.49 (1.17–1.91) | 1.71 (1.32–2.20) | 0.88 (0.62–1.24) | 0.22 |
| **Skin color** | | | | |
| Fair | 1.04 (0.85–1.29) | 1.73 (1.35–2.22) | 0.60 (0.44–0.83) | |
| Medium | 1.58 (1.16–2.15) | 1.33 (0.99–1.78) | 1.19 (0.78–1.83) | |
| Dark | 0.95 (0.58–1.55) | 1.42 (0.67–2.99) | 0.67 (0.30–1.51) | 0.106 |
| **Previous occupations** | | | | |
| Mainly outdoors | 1.16 (0.87–1.53) | 1.32 (0.84–2.06) | 0.88 (0.52–1.49) | |
| Indoors and outdoors | 1.21 (0.88–1.66) | 1.58 (1.15–2.17) | 0.77 (0.49–1.19) | |
| Mainly indoors | 1.21 (0.96–1.54) | 1.75 (1.36–2.27) | 0.69 (0.49–0.98) | 0.49 |
| **Nevi on back** | | | | |
| 0 | 0.82 (0.56–1.21) | 1.33 (0.84–2.12) | 0.62 (0.34–1.13) | |
| 1–10 | 1.27 (1.04–1.57) | 1.58 (1.25–1.98) | 0.81 (0.59–1.10) | |
| ≥11 | 1.22 (0.87–1.72) | 1.58 (1.09–2.30) | 0.77 (0.47–1.27) | 0.95 |
| **History of skin cancer** | | | | |
| No | 1.20 (1.00–1.44) | 1.54 (1.26–1.90) | 0.78 (0.59–1.02) | |
| Yes | 1.14 (0.69–1.87) | 1.63 (1.05–2.50) | 0.70 (0.36–1.34) | 0.89 |
| **Body mass index** | | | | |
| <25.0 kg/m$^2$ | 1.17 (0.91–1.50) | 1.68 (1.29–2.19) | 0.69 (0.48–1.00) | |
| 25.0–29.9 kg/m$^2$ | 1.21 (0.90–1.64) | 1.44 (1.02–2.02) | 0.84 (0.54–1.32) | |
| ≥30.0 kg/m$^2$ | 1.02 (0.64–1.63) | 1.79 (1.01–3.17) | 0.57 (0.27–1.19) | 0.66 |
| **Smoking status** | | | | |
| Never smoker | 1.17 (0.93–1.48) | 1.36 (1.05–1.77) | 0.86 (0.61–1.22) | |
| Former smoker | 1.21 (0.91–1.61) | 1.59 (1.14–2.23) | 0.76 (0.49–1.18) | |
| Current smoker | 1.35 (0.88–2.08) | 2.74 (1.85–4.06) | 0.49 (0.28–0.88) | 0.197 |
| **Overall** | 1.18 (0.99–1.39) | 1.54 (1.28–1.86) | 0.76 (0.59–0.98) | |




* *P* values for heterogeneity of effects were derived using score tests from generalized estimating equations, assuming independent correlations between repeated measures of skin microtopography grades.

equate skin protection is application of a liberal quantity of sunscreen; the sun-protection factor or precise shape of the sunscreen-absorption spectrum is far less important (36, 37). The effect of sunscreen may vary depending on other risk factors associated with skin aging, namely increasing age (38), UV-susceptible phenotypes (fair skin and an inability to tan), male sex, smoking, and body mass index (4, 18, 39–44); however, our data did not support this theory.

Our null result for β-carotene contrasts with the only relevant clinical study identified, which involved 29 Korean women in whom photoaging measures (skin elasticity, depth of skin wrinkling assessed by digitized images of replicas of "crow's feet" skin near the eyes, and immunohistochemical assessment of buttock skin samples) were taken before and after a 3-month period of daily β-carotene supplementation (15 women received 30-mg capsules and 14 received 90-mg capsules) (45). After 3

months, the authors reported a decrease in crow's feet wrinkles in the 15 women randomly assigned to 30-mg capsules. However, because of this study's (45) methodological limitations, including very small sample size, short duration, lack of controls, and possible confounding by sunscreen use, its findings are difficult to interpret and cannot be compared with those from our long-term controlled trial. Our results show a lack of effect of β-carotene and are unlikely to be explained by nonadherence to tablet consumption, because photometric measurements of skin color confirmed that the group receiving supplements maintained significantly higher amounts of dermal β-carotene than the placebo group.

Our study has limitations. One third of the participants had only 1 microtopography grade (mostly baseline). A standard repeated-measures analysis would remove these participants and reduce power, whereas a GEE optimizes power by using all available data. Although photoaging on the neck and sunburns were associated with having only 1 microtopography grade, these factors are unlikely to have affected trial findings because treatment allocation was not associated with missing grades; moreover, these factors were controlled for in the statistical model. Baseline grade was unrelated to missing follow-up grade and a complete case analysis, and estimates from multiple imputation replicated the results presented in **Table 4**. Measurement error occurred in study variables, including sun exposure by questionnaire and assessment of microtopography grades; however, it seemed to be nondifferential with respect to treatment groups, particularly for microtopography, because assessors were blinded to allocations.

Our sample size was determined by practical constraints. Although our estimate of the effect of β-carotene relative to placebo was 0.95 and was bounded by reasonably tight and symmetrical confidence limits implying no effect, the lack of precision around this estimate leaves open the possibility of β-carotene supplementation having either a protective effect (in the less severely aged subgroup) or a small but harmful effect (in the severely aged subgroup) on skin aging. Future research is needed to verify the effect of β-carotene in persons with varying levels of skin aging at baseline.

We conclude that regular sunscreen use by young and middle-aged adults younger than 55 years can retard skin aging. Although our study did not identify an effect of β-carotene supplementation on skin aging, a small slowing or accelerating effect cannot be ruled out.

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*Appendix Figure.* **Study flow diagram of the Nambour β-carotene and photoaging study, 1992–1996.**