Antioxidant Supplementation Increases the Risk of Skin Cancers in Women but Not in Men

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Abstract
This research aimed to test whether supplementation with a combination of antioxidant vitamins and minerals could reduce the risk of skin cancers (SC). It was performed within the framework of the Supplementation in Vitamins and Mineral Antioxidants study, a randomized, double-blinded, placebo-controlled, primary prevention trial testing the efficacy of nutritional doses of antioxidants in reducing incidence of cancer and ischemic heart disease in the general population. French adults (7876 women and 5141 men) were randomized to take an oral daily capsule of antioxidants (120 mg vitamin C, 30 mg vitamin E, 6 mg β-carotene, 100 μg selenium, and 20 mg zinc) or a matching placebo. The median time of follow-up was 7.5 y. A total of 157 cases of all types of SC were reported, from which 25 were melanomas. Because the effect of antioxidants on SC incidence varied according to gender, men and women were analyzed separately. In women, the incidence of SC was higher in the antioxidant group [adjusted hazard ratio (adjusted HR) = 1.68; P = 0.03]. Conversely, in men, incidence did not differ between the 2 treatment groups (adjusted HR = 0.69; P = 0.11). Despite the small number of events, the incidence of melanoma was also higher in the antioxidant group for women (adjusted HR = 4.31; P = 0.02). The incidence of nonmelanoma SC did not differ between the antioxidant and placebo groups (adjusted HR = 1.37; P = 0.22 for women and adjusted HR = 0.72; P = 0.19 for men). Our findings suggest that antioxidant supplementation affects the incidence of SC differentially in men and women. J. Nutr. 137: 2098–2105, 2007.

Introduction
Melanoma and nonmelanoma skin cancers (SC),10 namely squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), are the most common forms of malignancy in the Caucasian population (1) and sun exposure is thought to be the main established risk factor for all 3 types of tumor (2). An aging population, estimated at 23% of the population in 2010 in France, would increase the incidence of skin malignancy (3). Accumulation of mutations in tumor suppressor genes (4) and the potential protective effect of antioxidants (4). Formation of free radicals in the skin can be enhanced by UV radiation. The cutaneous system has a very efficient interlinked antioxidant defense system for counteracting UV-induced oxidative stress. However, excessive exposure to sunlight or other sources of UV light can overwhelm the skin’s antioxidant capacity. A potentially interesting strategy for preventing UV exposure damage could be to boost the endogenous antioxidant system by oral intake of antioxidant vitamins and minerals. Although clinical trials have showed contradictory findings (5–7), oral antioxidant pills have been recommended for the prevention of sunburns and for their supposed photoprotective properties.

In particular, it has been suggested that nutrients such as β-carotene, ascorbic acid, vitamin E, selenium, and zinc may prevent such harmful effects of UV exposure because of their antioxidant ability (8). Clinical trials testing the impact of supplementation with high doses of antioxidants over long periods have, however, failed to reveal beneficial effects on the incidence of SC (9,10). For example, the Nutritional Prevention of Cancer trial, a double-blind, randomized clinical trial, was designed to test whether selenium (200 μg/d) could prevent nonmelanoma SC (NMSC) in 1312 individuals with an individual

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10 Abbreviations used: BCC, basal cell carcinoma; HR, hazard ratio; MSC, melanoma skin cancer; NMSC, nonmelanoma skin cancer; SC, skin cancer; SCC, squamous cell carcinoma; SU.VI.MAX, Supplémentation en Vitamines et Minéraux Antioxydants study.

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history of SC recruited in the eastern United States. The initial analysis, which was conducted after 6.4 y of intervention, showed a significant inverse association between supplementation and all types of cancer incidence (10). However, a subsequent analysis found the protective effect of selenium supplementation on all types of cancer incidence to be attenuated (11). Surprisingly, the last analysis conducted after 13 y of supplementation suggested a link between selenium supplementation and an increased risk of NMSC (12).

There is some evidence that a combination of antioxidants may have a more powerful free radical scavenging effect than individual molecules, due to complementarity and synergy in their mechanism of action (13). In addition, metabolic interrelations also exist between antioxidant nutrients with beneficial mutual protection and regeneration.

The Supplementation in Vitamins and Mineral Antioxidants (SU.VI.MAX) study was a primary-prevention trial designed to assess whether a daily supplementation with antioxidant vitamins and minerals, at nutritional doses, could reduce the incidence of the most prevalent chronic diseases in industrialized countries causing premature death, cancer, and ischemic heart disease in middle-aged men and women. A double-blind, randomized, placebo-controlled design was used to compare medium-term outcome (5–10 y) in subjects receiving antioxidant supplementation or not. The framework of the SU.VI.MAX study allowed data to be collected relating to markers of oxidative stress and thus provided an opportunity to study the relationship between antioxidant effects relating to the intervention and cancer incidence.

Our aim was to test, in the context of the SU.VI.MAX study, the impact of a combination of antioxidant nutrients on the incidence of melanoma and NMSC in a large sample of middle-aged individuals from the French general population.

Subjects and Methods

Setting and study design. Details concerning the study rationale, design, methods, and study sample of the SU.VI.MAX trial have been reported previously (14,15). Briefly, the target population was a sample of adults aged 35–60 y for women and 45–60 y for men recruited from the French general population in France. The sample was thus not restricted to high-risk subjects. Enrolled subjects had to “declare themselves free of any severe pathology that might limit participation for 8 y including cancers and cardiovascular disease.” The SU.VI.MAX study used a randomized, double-blind, placebo-controlled design. The participants were randomized to take a capsule containing a combination of antioxidants [120 mg vitamin C (sodium ascorbate), 30 mg vitamin E (dl-α-tocopherol), 6 mg β-carotene, 100 μg selenium (selenium-enriched yeast), and 20 mg zinc (zinc gluconate)] or a matching placebo.

Evaluation of antioxidant supplement was performed by block-sequence generation stratified by gender and age group. Subjects were treated throughout the follow-up period.

The SU.VI.MAX study was approved by a medical ethics committee (Comité Consultatif pour la Protection des Personnes participant à la Recherche Biomédicale n°706) of Paris-Cochin, and the National Committee for the Protection of Privacy and Civil Liberties Comité National Informatique et Liberté (n°334641), which advocates that all medical information be confidential and anonymous. The participants signed an informed consent form allowing the investigators to perform screening tests to identify cancer or cardiovascular disease and to communicate the results to their physician.

Follow-up of the participants. The participants underwent a yearly medical visit, which consisted in alternate years either of taking a blood sample or of a clinical examination (physical examination, electrocar-diogram, blood pressure measurement, visual acuity examination, anthropometrical measurements, fecal occult blood testing for subjects over 45 y, smear test for all women, and a screening mammogram for women over 50 y). Moreover, the participants were also expected to provide monthly information on treatment compliance, dietary intake, and any health event by completing computerized questionnaires. In the absence of monthly contact for >6 mo, or if the participant missed the yearly visit, an investigation was launched to determine the reasons and to resume contact. If necessary, an inquiry was conducted among neighbors and the participant’s physician. Causes of death were provided by families, physicians, or hospitals. At the end of the interventional trial (September 1, 2002), vital status and possible causes of death were confirmed through the National Death Registry.

Antioxidant status. At baseline and every 2 y, 35 mL of venous blood samples after 12-h fasting were taken from each participant. Serum antioxidant concentrations were measured on a randomized sub-sample of 1134 subjects stratified by sex, age, treatment group, and geographic location. All biochemical analyses were performed in the same reference laboratory. Vitamin C status was evaluated by serum ascorbic acid (ascorbate) determination using an automated method based on the principle of continuous flow segmented by air bubbles (16). Serum levels of retinol, β-carotene, and α-tocopherol were measured by HPLC using the Biotek-Kontron HPLC system (17). Serum levels of zinc and selenium were determined using flame atomic absorption spectrometry (Perkin Elmer 3110 for zinc and selenium and Perkin Elmer 4100 ZL for selenium) (18,19).

Endpoints of the SU.VI.MAX trial. Whatever the source of information (see paragraph above on follow-up), once an event was suspected, all relevant records, including results of diagnostic tests and procedures, were collected from physicians, hospitals, or directly from the participants. The primary outcomes of the SU.VI.MAX trial were first fatal and nonfatal major ischemic cardiovascular events and first cancer events during the follow-up. However, BCC and SCC of the skin were not considered in the cancer outcomes as defined in the study protocol. Each event was reviewed by expert committees who were unaware of the treatment assignment. In the case of cancer events, these were ascertained by pathologist reports and reviewed by a committee of oncologists [details in (14)].

Endpoints of the analysis of SC. The outcomes of the present analysis were first event of melanoma at any stage, SCC and BCC of the skin, and other types of SC (International Classification of Diseases, 10th revision, Clinical Modification, codes C43, C44, D03, D04). Moreover, all SC, which were ascertained by pathologist reports, were also reviewed by an expert committee of dermatologists, who were unaware of the treatment assignment.

Assessment of sun exposure. Two questionnaires on sun exposure were administered to participants in 1997 and 2001. The content of the 2 questionnaires was similar, with one part that investigated sun exposure and protection over the past year and another part that assessed lifetime sun exposure and protection (20). Over 64% of the questionnaires of the first survey were returned (4824 women and 3260 men). Following the next survey, we collected 1332 additional questionnaires (800 women and 532 men). The final analysis was conducted on a sub-sample of 9293 participants (3925 women and 5368 men). The outcomes of the present analysis were first event of melanoma at any stage, SCC and BCC of the skin, and other types of SC (International Classification of Diseases, 10th revision, Clinical Modification, codes C43, C44, D03, D04). Moreover, all SC, which were ascertained by pathologist reports, were also reviewed by an expert committee of dermatologists, who were unaware of the treatment assignment.

Statistical methods. All subjects who participated in the SU.VI.MAX study were evaluated in the present analysis. Statistical analyses were performed using SAS software version 8.2 (SAS Institute). Descriptive analysis was performed by gender and treatment group (UNIVARIATE and FREQ procedures). Quantitative variables were expressed as mean ± SD.
Baseline characteristic means were compared using ANOVA (GLM procedure). Relationships between antioxidant levels at baseline were assessed using Pearson correlation coefficients (CORR procedure). Percentages of individuals lost to follow-up in each treatment group were compared using the Pearson test (FREQ procedure, option CHISQ) (21).

The duration of follow-up for each participant was defined as the time from randomization until the occurrence of the first event (diagnosis of SC, death, or date of last contact). The analysis was conducted under the assumption that the event of interest was independent of the subject's survival status at that time point. In these subjects, plasma levels of the biochemical markers β-carotene, vitamin C, and selenium significantly increased in the antioxidant group 2 and 7 y after randomization. Furthermore, the 2 treatment groups differed significantly 2 and 7 y after randomization. In addition, interaction terms between levels of each antioxidant at baseline and treatment group were also tested. Furthermore, to estimate the effect of antioxidant levels at baseline on each outcome in the antioxidant and the placebo groups, each multivariate Cox model obtained at the last step was rebuilt within each treatment group.

The number of participants was expected to allow detection of a 25% difference in incidence of the outcome (1-tailed α = 5%; 1-tailed β = 90%).

Results

Study sample characteristics. A total of 13,017 volunteers, 7876 women and 5141 men, were randomized to take the capsule containing a combination of antioxidants or a matching placebo. The participants entered the trial between October 12, 1994 and April 30, 1995. Subsequently, 270 subjects (2%; 115 in the antioxidant group and 155 in the placebo group) withdrew their written consent on the very day of the enrollment visit or within the next 3 d, because they could not meet the constraints of the protocol. In addition, 6 subjects were excluded from the study because they did not fall within the specified age range. The flow of participants by treatment group is shown in Figure 1. The median follow-up time was 7.5 y for a total of 89,441 person-years (44,866 in the antioxidant group and 44,574 in the placebo group).

The 2 treatment groups did not differ with respect to capsule intake, which was 79% in each treatment group. Compliance was confirmed on a random sub-sample of ~1000 participants. In these subjects, plasma levels of the biochemical markers β-carotene, vitamin C, and selenium significantly increased in the antioxidant group 2 and 7 y after randomization. Furthermore, the 2 treatment groups differed significantly 2 and 7 y after randomization with respect to all markers except serum zinc [details in (14,15)].

The antioxidant and placebo groups were balanced for most baseline variables, notably smoking habits, alcohol consumption,
occupational status, education level, marital status, and BMI (14). The treatment groups were also balanced for self-assessed lifetime sun exposure. In women, the frequency of severe exposure was 11.2% in the placebo group and 11.1% in the antioxidant group, whereas in men, it was 11.8% in the placebo group and 12.2% in the antioxidant group.

Within each gender, the ages of the treatment groups were comparable, with women being 47.1 ± 6.6 y old and men being 51.8 ± 4.7 y old. Serum levels of antioxidants did not differ between the treatment groups at baseline, except for selenium (Table 1). However, serum levels of antioxidants at baseline differed significantly between genders. Serum β-carotene concentrations were correlated with serum levels of vitamin C ($r = 0.26; P < 0.0001$) and vitamin E ($r = 0.24; P < 0.0001$).

Incidence of SC. Overall, 157 validated cases of SC occurred in 81 women and 76 men. These corresponded to 25 melanoma SC (MSC) in 16 women and 9 men. The remaining 132 NMSC were represented by 115 BCC in 57 women and in 58 men, 13 SCC in 4 women and in 9 men, and 4 cases of other types of SC, namely Bowen disease in 4 women (Table 2).

The overall incidence rate of SC did not differ between the treatment groups ($P = 0.35$). However, when segregated by gender, the frequency of SC in women was higher in the antioxidant group ($P = 0.02$). Fifty-one women developed SC in the antioxidant group compared with 30 in the placebo group. There was no such difference in the frequency of SC between treatment groups in men (43 cases in the placebo group and 33 in the antioxidant group; $P = 0.25$).

The incidence of melanoma did not differ between the treatment groups in men (6 cases in the placebo group and 3 cases in the antioxidant group; $P = 0.51$) but was higher in the antioxidant group in women (3 cases in the placebo group and 13 cases in the antioxidant group; $P = 0.01$).

The incidence of NMSC did not differ between treatment groups in either men (37 cases in the placebo group and 30 cases in the antioxidant group; $P = 0.39$) or women (27 cases in the placebo group and 38 cases in the antioxidant group; $P = 0.15$).

Due to the differential effects of antioxidant supplementation according to gender, all subsequent analyses were performed by gender.

Variables associated with the incidence of all SC. According to actuarial survival analysis of the cumulative incidence of SC, the difference between the treatment groups increased regularly over time in women, with a higher incidence in the antioxidant group (logrank test, $P = 0.02$) (Fig. 2A). Among men, the incidence of SC did not differ between the treatment groups (logrank test, $P = 0.22$). This differential effect according to gender was confirmed by a Cox proportional hazard regression model, in which there was a significant interaction between gender and treatment group ($P = 0.01$) in addition to

![FIGURE 2](https://academic.oup.com/jn/article-abstract/137/9/2098/4664864)
gender and treatment group effects (data not shown). Therefore, subsequent analyses were conducted for each gender separately. Univariate and multivariate Cox proportional hazard regression models were generated for the number of cases of all SC (Table 3). In the univariate model, antioxidant treatment group (HR = 1.70; P = 0.02), older age (HR = 1.06; P = 0.0005), and greater lifetime sun exposure (HR = 2.23; P = 0.006) were associated with a higher probability of developing SC in women. Treatment group (adjusted HR = 1.68; P = 0.02) and age (adjusted HR = 1.06; P = 0.001) were retained as independent variables associated with cancer risk in the multivariate model. In men, age was the only variable associated with increased cancer risk identified in either the univariate or the multivariate analysis (HR = 1.08; P = 0.001 in both cases).

Variables associated with the incidence of melanoma. Actuarial survival analysis of the cumulative incidence of melanoma was also performed (Fig. 2C). In women, the difference between the treatment groups increased regularly over time, with a higher incidence in the antioxidant group (logrank test, P = 0.01), whereas the incidence of SC in men did not differ between groups (logrank test, P = 0.31). In women, antioxidant treatment group was the only variable associated with a higher probability of developing melanoma in both the univariate (HR = 4.32; P = 0.02) and multivariate (adjusted HR = 4.31; P = 0.02) Cox proportional hazard regression models (Table 4). No such association was identified in men.

Variables associated with the incidence of NMSC. According to the actuarial survival analysis, the 2 treatment groups did not differ in terms of the cumulative incidence of NMSC in either women (logrank test, P = 0.17) or men (logrank test, P = 0.36) (Fig. 2B). In the univariate Cox proportional hazard regression model, older age (HR = 1.09; P = 0.0001) and greater lifetime sun exposure (HR = 2.19; P = 0.01) were significantly associated with a higher probability of developing SC in women, as was older age in men (HR = 1.08; P = 0.003) (Table 5). In the multivariate model, only age was retained as an associate variable (adjusted HR = 1.09; P = 0.0001 in women and HR = 1.08; P = 0.004 in men).

### Table 3: Cox proportional hazard regression models for SC occurrence by gender

<table>
<thead>
<tr>
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<th>Women, n = 7876</th>
<th></th>
<th>Men, n = 5141</th>
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<tbody>
<tr>
<td></td>
<td>n1</td>
<td>HR (95% CI)</td>
<td>P3</td>
</tr>
<tr>
<td>Univariate analysis</td>
<td></td>
<td></td>
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<tr>
<td>Treatment group</td>
<td>7876</td>
<td>1.70 (1.08; 2.67)</td>
<td>0.021</td>
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<tr>
<td>Age, y</td>
<td>7874</td>
<td>1.06 (1.03; 1.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoking</td>
<td>7361</td>
<td>1.05 (0.56; 1.91)</td>
<td>0.87</td>
</tr>
<tr>
<td>Dwelling latitude, degree</td>
<td>7711</td>
<td>0.99 (0.88; 1.10)</td>
<td>0.80</td>
</tr>
<tr>
<td>Lifetime sun exposure</td>
<td>5542</td>
<td>2.23 (1.26; 3.95)</td>
<td>0.006</td>
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<td>Multivariate analysis</td>
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<td></td>
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<tr>
<td>Treatment group</td>
<td>1.68 (1.08; 2.65)</td>
<td>0.027</td>
<td>0.69 (0.43; 1.10)</td>
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<td>Age, y</td>
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<td>0.001</td>
<td>1.08 (1.03; 1.13)</td>
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<td>Current smoking</td>
<td>1.21 (1.06; 2.21)</td>
<td>0.53</td>
<td>0.96 (0.49; 1.87)</td>
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<td>Dwelling latitude, degree</td>
<td>0.97 (0.87; 1.09)</td>
<td>0.57</td>
<td>0.98 (0.88; 1.10)</td>
</tr>
</tbody>
</table>

1 Data were missing to a variable extent for each variable (up to 29% for lifetime sun exposure) and the actual sample size is therefore indicated for each variable.
2 The multivariate analysis was only conducted on the 12,004 subjects for whom data on all relevant variables were available.
3 Probability values were calculated with the Wald test.

### Table 4: Cox proportional hazard regression models for melanoma occurrence by gender

<table>
<thead>
<tr>
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<th>Women, n = 7876</th>
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<th>Men, n = 5141</th>
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<tbody>
<tr>
<td></td>
<td>n1</td>
<td>HR (95% CI)</td>
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<tr>
<td>Univariate analysis</td>
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</tr>
<tr>
<td>Treatment group</td>
<td>7876</td>
<td>4.32 (1.23; 15.18)</td>
<td>0.02</td>
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<tr>
<td>Age, y</td>
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<td>0.95 (0.87; 1.02)</td>
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</tr>
<tr>
<td>Current smoking</td>
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<td>1.75 (0.56; 5.43)</td>
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<td>Dwelling latitude, degree</td>
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<td>1.12 (0.85; 1.48)</td>
<td>0.42</td>
</tr>
<tr>
<td>Lifetime sun exposure</td>
<td>5542</td>
<td>2.36 (0.65; 8.56)</td>
<td>0.19</td>
</tr>
<tr>
<td>Multivariate analysis</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Treatment group</td>
<td>4.31 (1.23; 15.13)</td>
<td>0.02</td>
<td>0.49 (0.12; 1.97)</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.95 (0.88; 1.03)</td>
<td>0.19</td>
<td>1.08 (0.95; 1.13)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1.53 (0.49; 4.89)</td>
<td>0.46</td>
<td>3.05 (0.76; 12.23)</td>
</tr>
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<td>Dwelling latitude, degree</td>
<td>1.12 (0.85; 1.49)</td>
<td>0.42</td>
<td>0.98 (0.68; 1.47)</td>
</tr>
</tbody>
</table>

1 Data were missing to a variable extent for each variable (up to 29% for lifetime sun exposure) and the actual sample size is therefore indicated for each variable.
2 The multivariate analysis was only conducted on the 12,004 subjects for whom data on all relevant variables were available.
3 Probability values were calculated with the Wald test.
and the presence of a larger reservoir of subcutaneous adipose tissue due to a higher intake of dietary vitamin C and women tend to have higher concentrations of antioxidants in the skin may also contribute to the effect of antioxidant tumor biology (25).

It has been hypothesized that the relative importance of low selenium status as a risk factor for cancer might differ between men and women due to sex- or gender-related factors that influence hormone-sensitive expression of genes coding for cellular transporters of vitamins and antioxidants involved in the metabolism of carcinogens or in regulation of the cell cycle. For example, it has been hypothesized that the relative importance of low selenium status as a risk factor for cancer might differ between men and women receiving antioxidant supplementation, although this difference did not reach statistical significance. This may reflect underpowering of the study for the detection of differences in the incidence of relatively rare events such as SC.

Our results show that the effect of antioxidant supplementation on the incidence of SC varies according to gender. The incidence of all types of SC and melanomas was higher in the group of women receiving antioxidant supplementation compared with the placebo group. Such an effect was not observed in men. These results can be compared with the main results of the principal analysis of the SU.VI.MAX trial (14), which showed that antioxidant supplementation was associated with a significant reduction in the overall incidence of all-site cancers in men with no effect in women. It should, however, be noted that, in the present analysis, the incidence of SC was lower in the men receiving antioxidants, although this difference did not reach statistical significance. This may reflect underpowering of the study for the detection of differences in the incidence of relatively rare events such as SC.

Our findings may be attributed in part to gender differences in nutrient metabolism. Although the molecular basis for this metabolic difference is poorly characterized, it may result from hormone-sensitive expression of genes coding for cellular transporters of vitamins and antioxidants involved in the metabolism of carcinogens or in regulation of the cell cycle. For example, it has been hypothesized that the relative importance of low selenium status as a risk factor for cancer might differ between men and women due to sex- or gender-related factors that influence tumor biology (25).

Gender-dependent differences in the handling of antioxidants in the skin may also contribute to the effect of antioxidant supplementation on SC incidence in women. For example, women tend to have higher concentrations of antioxidants in the skin due to a higher intake of dietary vitamin C and β-carotene and the presence of a larger reservoir of subcutaneous adipose tissue in which to store lipophilic antioxidants such as β-carotene (26). In our study, men had significantly lower average serum levels of several antioxidants, particularly β-carotene, than women. This may be related to the capacity of circulating β-carotene to reflect recent or current carotenoid intake from dietary fruits and vegetables (14,27), which may be lower in men.

The discrepancy between our results and experimental data in animals that has suggested an anticarcinogenetic effect of antioxidants with respect to SC may be explained by differences in the timing of the intervention. In animal models of cutaneous carcinogenesis, the diet is enriched in antioxidants prior to irradiation with UV-A or UV-B, leading to a predominantly beneficial effect of treatment on DNA protection. In contrast, in the SU.VI.MAX trial and related primary prevention studies, antioxidants are given only after many years of exposure to sunlight or other risk factors. At this stage, it may be too late for antioxidants to prevent DNA damage, whereas increased antioxidant exposure might exert a negative influence on antitumoral immunity, angiogenesis, or apoptosis. For example, antioxidants have been reported to interfere with the ability of natural killer lymphocytes to destroy tumor cells in animal models (28). This detrimental effect late in the disease process might explain why we observed a more pronounced effect upon melanoma, which requires a longer time frame over which to develop compared with other SC types and is presumed to be mainly induced by exposure to solar radiation during infancy. For other SC types, a protective effect of antioxidants with respect to sun exposure during the time of the study could counterbalance a detrimental effect on the development of preexisting precancerous lesions induced before the trial began, which could explain the absence of effect of antioxidant supplementation observed in our study.

Previous observational surveys, which have evaluated the relationship between antioxidant status, estimated by serum biomarkers, and the risk of SC have yielded contradictory results. Some studies reported a negative association between serum levels of α-tocopherol, carotenoids, or selenium and the risk of melanoma or NMSC (29–31), whereas others did not find any such protective effect (32–35). In contrast, a recent Italian study of a community-based cohort reported that the incidence rate of melanoma was nearly 4 times higher in individuals exposed to a high selenium intake (provided by tap water) than in unexposed individuals (36). Several large randomized trials evaluating the impact of β-carotene supplementation did not

### TABLE 5  
Cox proportional hazard regression models for NMSC occurrence by gender

<table>
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<td>n1</td>
<td>HR (95% CI)</td>
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<td>Univariate analysis</td>
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<tr>
<td>Treatment group</td>
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<td>1.41 (0.86; 2.30)</td>
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<td>5025</td>
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<td>Lifetime sun exposure</td>
<td>5542</td>
<td>2.19 (1.16; 4.16)</td>
<td>0.01</td>
<td>3751</td>
</tr>
<tr>
<td>Multivariate analysis2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment group</td>
<td>7876</td>
<td>1.37 (0.83; 2.28)</td>
<td>0.220</td>
<td>5141</td>
</tr>
<tr>
<td>Age, y</td>
<td>7874</td>
<td>1.09 (1.05; 1.13)</td>
<td>0.0001</td>
<td>5141</td>
</tr>
<tr>
<td>Current smoking</td>
<td>7361</td>
<td>0.89 (0.44; 1.81)</td>
<td>0.75</td>
<td>4815</td>
</tr>
<tr>
<td>Dwelling latitude, degree</td>
<td>7711</td>
<td>0.96 (0.95; 1.08)</td>
<td>0.50</td>
<td>5025</td>
</tr>
</tbody>
</table>

1 Data were missing to a variable extent for each variable (up to 29% for lifetime sun exposure) and the actual sample size is therefore indicated for each variable.
2 The multivariate analysis was only conducted on the 12,004 subjects for whom data on all relevant variables were available.
3 Probability values were calculated with the Wald test.
reveal any beneficial effect on the development of SC in community-based populations (9,32–34,37,38) or in patients with antecedents of NMSC (39).

In addition, some trials have evaluated gender effects with respect to the potential benefits of dietary supplementation with individual antioxidants. For example, in the Nutritional Prevention of Cancer study, the initial data analysis showed that the beneficial effect of supplementation with selenium on the incidence of all types of cancer was restricted to men, specifically to those with the lowest baseline serum selenium concentrations (12). This differential effect of selenium supplementation according to gender is consistent with the results of previous case-control studies (40) and prospective studies conducted on all types of cancers (41).

There are several methodological limitations to the present study. For example, BCC occurrence was not considered as a primary endpoint within the framework of the SU.VI.MAX core trial and our analysis thus corresponds to a post hoc analysis. In addition, the pertinence of the analysis of the incidence of melanoma is limited by the small number of cases.

In conclusion, our findings suggest that dietary supplementation with vitamins and trace element antioxidants may not always provide beneficial effects. This issue is important, given the vast quantities of antioxidant pills that are sold in certain countries. This is particularly true among sunseekers and women in northern countries, where the use of such pills is reputed to prevent solar damage to the skin. In this respect, our study indicates that regular intake of such nutrients, especially at doses taken by consumers of supplements in northern countries, may be associated with harmful effects. Clearly, high doses of specific nutrients given to middle-aged adults over a period of several years do not have an equivalent biological impact to the lifelong intake of a broad palette of nutrients from a well-balanced diet. It therefore appears crucial to better define the safety profile of such nutrients to be able to assess accurately the risk-benefit relationship associated with their use as dietary supplements.

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Literature Cited


