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Incidence of skin cancers during 5-year follow-up after stopping antioxidant vitamins and mineral supplementation ☆

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ABSTRACT

Context: In the SU.VI.MAX study, antioxidant supplementation for 7.5 years was found to increase skin cancer risk in women but not in men.
Objective: To investigate the potential residual or delayed effect of antioxidant supplementation on skin cancer incidence after a 5-year post-intervention follow-up.
Design, setting and participants: Assessment of skin cancer including melanoma and non-melanoma during the post-intervention follow-up (September 2002–August 2007). The SU.VI.MAX study was a double-blind, placebo-controlled, randomised trial, in which 12,741 French adults (7713 women aged 35–60 years and 5028 men aged 45–60 years) received daily a placebo or a combination of ascorbic acid (120 mg), vitamin E (30 mg), β-carotene (6 mg), selenium (100 μg) and zinc (20 mg), from inclusion in 1994 to September 2002.
Main outcome measures: Total skin cancer incidence, including melanoma, squamous cell carcinoma and basal cell carcinoma.
Results: During the post-intervention period, 10 melanomas appeared in women and 9 in men (26 and 18, respectively, for the total period of supplementation + post-supplementation). Six squamous cell carcinomas were found in women and 15 in men (10 and 25, respectively, for the total period). Finally, 40 basal cell carcinomas appeared in women and 36 in men (98 and 94, respectively, for the total period). Regarding potential residual or delayed effects of supplementation in women, no increased risk of melanoma was observed during the post-intervention follow-up period. No delayed effects, either on melanoma or non-melanoma skin cancers, were observed for either gender.

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Conclusions: The risk of skin cancers associated with antioxidant intake declines following interruption of supplementation. This supports a causative role for antioxidants in the evolution of skin cancers.

1. Introduction

Skin cancers (SC) are the most common malignancies occurring in Caucasian populations.[1–3] During the last decades, the steadily increasing incidence of skin cancers has brought much attention to the process by which these tumours develop and how they can be prevented. Skin is constantly exposed to ultraviolet (UV) radiation as well as to an array of environmental pollutants, such as components of cigarette smoke, which lead to the production of reactive oxygen species (ROS).[4] This phenomenon is responsible for accelerated sun-induced cutaneous changes (photoaging) in the areas exposed to UV radiation. Moreover, ROS are considered as potent inducers of structural alterations in DNA leading to mutations, the first step in tumour development.[5] Consequently, agents that inhibit ROS formation or activity may potentially enhance endogenous defence systems and thus prevent or reverse photodamage. Although clinical trials have provided contradictory findings concerning their efficacy, oral antioxidant pills have been proposed for the prevention of sunburn and for their supposed photoprotective properties.[6]

However, in contrast with this hypothesis, the results of the SU.VI.MAX study indicated a significantly higher incidence of total skin cancers and melanomas in the group of women receiving a combination of antioxidants compared to placebo after a median follow-up time of 7.5 years. Conversely, in men, no significant differences were found between the treatment groups.[7] In order to investigate possible residual or delayed effects of antioxidant supplementation on skin cancer incidence, the SU.VI.MAX cohort was followed-up 5 years after the end of the double-blind supplementation period.

2. Patients and methods

2.1. Study design and population

The study rationale, design, methods, study sample, endpoint ascertainment and initial findings of the SU.VI.MAX trial have been reported elsewhere.[8,9] Briefly, the target population was a sample of adults aged at inclusion between 35 and 60 years for women and between 45 and 60 years for men recruited from the French general population in France. The SU.VI.MAX study used a randomised, double-blind, placebo-controlled design. The participants were randomised 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, in a single daily oral capsule. A total of 13,017 volunteers, 7876 women and 5141 men, were included and randomly allocated. The participants entered the trial between 12th October 1994 and 30th April 1995. Of these, 270 subjects (2%: 115 in the antioxidant group and 155 in the placebo group) withdrew their written consent within 3 d of enrolment because they could not meet the constraints of the protocol. In addition, six subjects were excluded from the study as they did not fall within the specified age range. Thus, 12,741 subjects (7713 women aged 46.6 ± 6.6 years and 5028 men aged 51.3 ± 4.7 years) contributed to the analyses. The primary analyses were performed on outcome events validated on 1st September 2002 (median follow-up time of 7.5 years). At the end of the intervention phase, the participants were informed of the results of the trial. No recommendations were given concerning the use of supplements, but about having a balanced diet with at least five fruits or vegetables daily. Participants who were still alive at the end of the supplementation period (1st September 2002) and who had not dropped out of the study or been lost to follow-up (n = 11 054) were asked to participate in the post-supplementation follow-up. Subjects have now been followed up for an additional 5 years (until the 1st September 2007), up to a total period of 13 years since beginning enrolment.

The protocol was approved by a medical ethics committee and the National Committee for the Protection of Privacy and Civil Liberties.

2.2. Follow-up during the post-intervention period

During the post-intervention follow-up, all major health events were identified from the 6-monthly questionnaires returned by the participants and from all additional information provided spontaneously by participants or their kin. Once a possible skin cancer was suspected, all relevant records, including results of diagnostic tests, procedures and pathology reports, were collected from the physicians and hospitals involved, or directly from the participants. End-points were validated only after review of all relevant information by a committee of specialised physicians who were blinded for supplementation assignment.

2.3. Study outcomes

The outcomes considered in the present analysis were all-stage melanoma, squamous cell carcinoma (SCC) of the skin, basal cell carcinoma (BCC) and other types of SC (International Classification of Diseases, 10th revision, Clinical Modification [ICD-10-CM], codes C43, C44, D03, D04). Moreover, all possible SC were removed surgically and evaluated by histopathology to ascertain the diagnosis. The pathologist's reports were subsequently reviewed by an expert committee of dermatologists, who were unaware of the treatment assignment. Whatever the original source of information, 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.

2.4. Statistical methods

Statistical analyses were performed using SAS® software version 9.1.3 (SAS Institute Inc., Cary, NC).

Separate analyses were performed for each type of SC (BCC, SCC and melanoma). A subject with more than one cancer of a specific type was taken into account only once (only the first cancer occurrence), but if two different types of SC were identified, the subject was included for each type of cancer in the analysis. The duration of follow-up for each participant was defined as the time from randomisation until the occurrence of the first event (diagnosis of skin cancer, death or date of last contact). The analysis was conducted under the intention to treat principle. Due to the differential effects of antioxidant supplementation according to gender found during the intervention period,[7,9] all subsequent analyses were performed by gender.

The frequency of SC was described by treatment group (antioxidant group and placebo group) using the FREQ procedure, option CHISQ or EXACT.[10] The proportion of volunteers remaining event-free since randomisation was described using Kaplan–Meier survival analysis and compared between groups using the log-rank test.[11] These descriptive analyses were performed for both the intervention period and total period.

To test the effect of possible confounding factors (smoking status, dwelling latitude, sunburn during childhood,

Table 1 – Characteristics of the study population.

n	Women			Men		
	Placebo	Antioxidant	*p*	Placebo	Antioxidant	*p*
	3964	3912		2572	2569	
Age, mean (SD), years	47.1 (6.6)	47.1 (6.6)	1.00	51.8 (4.7)	51.8 (4.6)	0.99
Dwelling latitude, mean (SD), °	47.1 (1.9)	47.1 (1.9)	0.77	47.0 (2.0)	47.0 (2.0)	0.73
Body mass index, mean (SD), kg/m^2	22.9 (3.6)	22.8 (3.5)	0.44	25.2 (3.0)	25.2 (3.0)	0.84
Smoking status, %			0.89			0.83
Never	54.7	54.5		34.5	33.6	
Former	29.1	28.9		50.2	50.9	
Current	16.1	16.5		15.3	15.4	
Phototype[a] (I and II *versus* III and IV), %	34.3	33.9	0.77	17.1	19.1	0.13
Severe lifetime sun exposure[b] (yes *versus* no), %	11.1	11.6	0.54	12.1	12.5	0.74
Severe sunburn during childhood[c] (yes *versus* no), %	29.1	28.2	0.46	29.9	29.5	0.79
Severe sunburn during adulthood[c] (yes *versus* no), %	28.9	29.6	0.57	24.7	24.4	0.85

[a] Fitzpatrick classification[13]; data were available for 5432 women and 3668 men.
[b] Data were available for 5428 women and 3693 men.
[c] Data were available for 5542 women and 3751 men for sunburn during childhood and for 5010 women and 3426 men for sunburn during adulthood.

Table 2 – Occurrence of skin cancers by gender and treatment group.

Cancer type	Women		p^c	Men		p^c
	Placebo N = 3964	Antioxidant N = 3912		Placebo N = 2572	Antioxidant N = 2569	
Basal cell carcinoma						
Intervention period[a]	24 (0.6%)	34 (0.9%)	0.17	32 (1.2%)	26 (1.0%)	0.43
Post-intervention period[b]	21 (0.6%)	19 (0.6%)	0.75	15 (0.7%)	21 (0.9%)	0.40
Total period[b]	45 (1.1%)	53 (1.4%)	0.38	47 (1.8%)	47 (1.8%)	1.00
Squamous cell carcinoma						
Intervention period[a]	3 (0.1%)	1 (<0.1%)	0.62	6 (0.2%)	4 (0.2%)	0.75
Post-intervention period[b]	3 (0.1%)	3 (0.1%)	1.00	6 (0.3%)	9 (0.4%)	0.60
Total period[b]	6 (0.2%)	4 (0.1%)	0.75	12 (2.1%)	13 (2.3%)	0.84
Melanoma						
Intervention period[a]	3 (0.1%)	13 (0.3%)	0.0114	6 (0.2%)	3 (0.1%)	0.51
Post-intervention period[b]	6 (0.2%)	4 (0.1%)	0.54	4 (0.2%)	5 (0.2%)	1.00
Total period[b]	9 (0.2%)	17 (0.4%)	0.11	10 (0.4%)	8 (0.3%)	0.64

[a] Number of cases (% of study group participants).
[b] Number of cases (% of follow-up participants).
[c] Probability value (χ^2 test or Fisher's exact test, as appropriate).

phototype, self-assessed lifetime sun exposure on the outcomes), a series of Cox regression models adjusted for age was performed using the PHREG procedure. Age-adjusted hazard ratios (adjusted HR) with their 95% confidence intervals (95% CI) were estimated from these models.

A possible residual or delayed effect of antioxidant supplementation during the post-intervention period was tested using multivariate Cox regression models with treatment as a time-dependent variable adjusted for confounding variables according to the following equation[12]:

$$h(t) = h_0(t) * \exp(\beta_1^* \text{ treatment}(t) + \beta_2^* \text{ group} + \beta_i^* Z)$$

In the model, the 'Treatment(t)' variable was defined as antioxidant supplementation (yes or no) and the 'Group' variable as the original randomisation group (antioxidant or placebo group). The 'Treatment(t)' variable was always equal to 0 for the subjects in the placebo group whatever the period, whereas, for the subjects in the antioxidant group, it was equal to 1 during the intervention period and equal to 0 during the post-intervention period. The variable 'Group' was equal to 1 for the subjects in the antioxidant group and was equal to 0 for the placebo group. Thus, the relative risk of the variable 'Group' corresponds to the residual or late effect of the supplementation during the post-intervention period. The term 'Z' was the set of possible confounding factors. The results are expressed as relative risks (RR), adjusted for confounders, together with their 95% CI.

3. Results

3.1. Study sample characteristics

As described previously,[9] the antioxidant and placebo groups were balanced for most baseline variables, notably smoking habits, body mass index (BMI), Fitzpatrick phototype[13] and items related to sun exposure (Table 1).

During the post-intervention phase, 271 subjects withdrew consent or were lost to follow-up (follow-up time: 1.4 ± 1.6 years) and 158 subjects died. The median follow-up time was 12.5 years for a total of 138,616 person–years (68,576 in the antioxidant group and 70,040 in the placebo group).

3.2. Incidence of BCC

The frequency of BCC is presented in Table 2. At the end of the intervention period, 116 subjects, 58 women and 58 men, presented a validated case of BCC. In women, the frequency of BCC was 0.9% in the antioxidant group, compared to 0.6% in the placebo group. Five years later, the total number of subjects with a BCC had increased by 76–192 subjects (98 women and 94 men). The cumulative incidence of BCC according to treatment group and gender is presented in Fig. 1A and B. During the post-intervention period, the cumulative incidence curve for the antioxidant group remained above the placebo group in both genders, although the inter-group difference appeared to decrease after 5 years of follow-up. The between-group effect over the total period (1994–2007) was not significant for either gender (log-rank tests: $p = 0.47$ for women and $p = 0.87$ for men). Table 3 presents the results of the Cox regression analysis. For both genders, no significant residual or delayed effect of supplementation was found on the risk of BCC during the post-intervention period (RR = 0.70 [95% CI: 0.48–1.65] for women; 1.22 [0.64–2.33] for men).

3.3. Incidence of SCC

Fourteen subjects (4 women and 10 men) presented a SCC at the end of the intervention period, and 35 subjects (10 women and 25 men), at the end of the post-intervention period

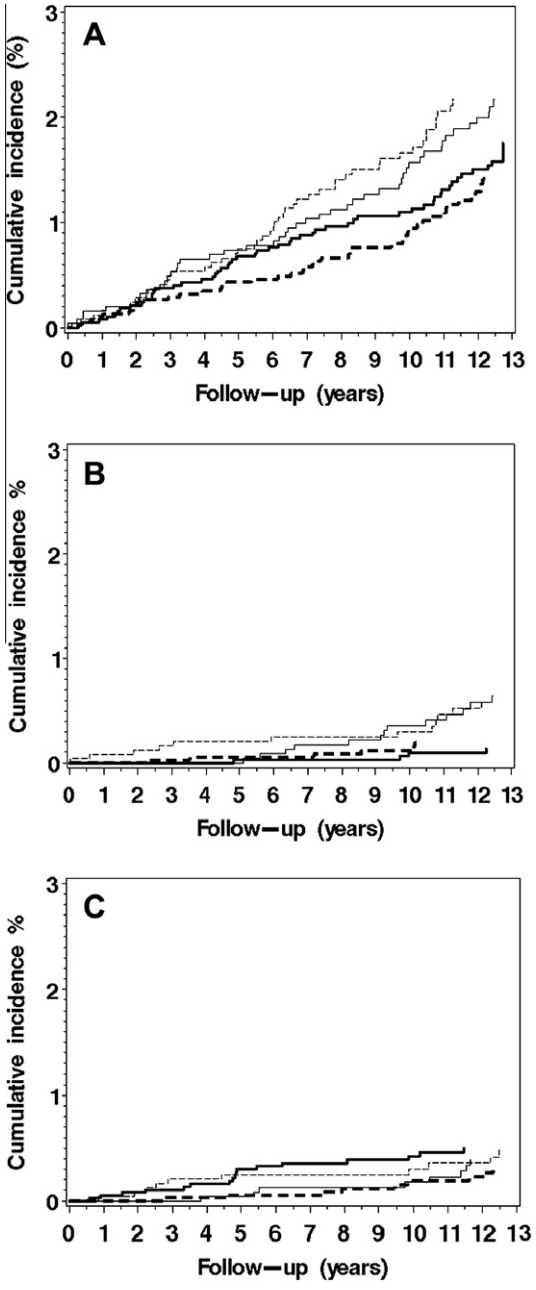

Fig. 1 – Cumulative incidence over the entire study period (intervention and post-intervention) of: (A) basal cell carcinoma; (B) squamous cell carcinoma of the skin, and (C) melanoma.

Table 3 – Residual or delayed effect of antioxidant supplementation during the post-intervention period for each skin cancer, by gender.

Cancer type	Placebo *n*	Antioxidant *n*	Relative risk (95% CI)	*p*
Basal cell carcinoma				
Men	47	47	1.22 (0.64–2.33)	0.54
Women	45	53	0.70 (0.48–1.65)	0.70
Squamous cell carcinoma				
Men	12	13	1.38 (0.49–3.84)	0.54
Women	6	4	0.95 (0.19–4.67)	0.95
Melanoma				
Men	10	8	1.15 (0.31–4.27)	0.83
Women	9	17	0.64 (0.18–2.27)	0.49

Relative risks refer to the residual treatment effect during the post-intervention period as described in Section 2.

(Table 2). The cumulative incidence curves of the antioxidant group and the placebo group are presented in Fig. 1C and D. These curves crossed over during the follow-up period for both genders. The between-group effect for the total period (1994–2007) was not significant for either gender (log-rank test: $p = 0.50$ for women, $p = 0.93$ for men). No significant effect of supplementation was found on the risk of SCC during the post-intervention period for either gender (RR = 0.95 [95% CI = 0.19–4.67] for women; 1.38 [0.49–3.84] for men) (Table 3).

3.4. *Incidence of melanoma*

At the end of the intervention period, the total number of subjects with a melanoma was 25 (16 women and 9 men). In women, the frequency of melanoma was significantly higher in the antioxidant group than in the placebo group (Table 2). At the end of the post-intervention study, the total number of subjects with a melanoma skin cancer was 44 (26 women and 18 men) and, for women, the frequency of melanoma was higher in the antioxidant group than in the placebo group, although this difference was not significant. Fig. 1E and F present the cumulative incidence of melanoma. In women, the difference between the treatment groups increased over time, with a numerically, but not significantly, higher incidence in the antioxidant group (log-rank test: $p = 0.13$), whereas the incidence was comparable in men (log-rank test: $p = 0.57$). A significant residual or delayed effect of supplementation on the risk of melanoma during the post-intervention period was not seen for either gender (RR = 0.64 [95% CI = 0.18–2.27] for women and 1.15 [0.31–4.27] for men) (Table 3).

4. Discussion

In the original analysis of skin cancer risk in the SU.VI.MAX trial, an excess risk of skin cancers was found in the antioxidant treatment group in women.[7] The present analysis shows that this elevated risk recedes when antioxidant supplementation is stopped. This observation argues in favour of a causative role of supplementation in the appearance of skin cancers reported in the original study. In addition, the post-intervention follow-up period did not reveal any delayed protective effects of supplementation on skin cancer.

Our results are at least partly consistent with previous lung cancer prevention trials performed in a community setting, which have assessed the impact of supplementation with antioxidants and conducted a follow-up post-intervention extension.[14,15] Both for these lung cancer studies, and for skin cancer in the SU.VI.MAX study, the rapidity with which tumour incidence rises following initiation of vitamin or antioxidant supplementation, suggests an effect on the growth of pre-clinical tumours, rather than induction of *de novo* tumours.[16] Indeed, it is unlikely that tumours of the skin may develop over a time period as short as the supplementation periods of these trials.[4] This is particularly the case for melanoma, whose earliest pathogenetic events are believed to occur early in life with a very long subclinical silent period. Moreover, in all these studies, the elevated risk of cancer declined after stopping the supplementation, over a 4-year period in the lung cancer trials and over 5 years in the SU.VI.MAX trial.

Our findings of risk differences between men and women should be interpreted with caution because of the relatively small number of events within subgroups of skin cancer. However, in a recent review it has been proposed that gender differences in oxidative stress caused by radical oxygen species (ROS) may underlie survival differences between male and female for melanoma as it is firmly recognised that males express lower amounts of anti-oxidant enzymes, resulting in more oxidative stress than females.[17] Other hypotheses to explain this difference are that women may have more skin fat tissue in which antioxidants and vitamins are stored[4,18] as well as hormonal factors may also influence susceptibility to skin cancers.[19,20]

Despite a large body of knowledge on cell-culture systems and in animal models demonstrating substantial efficacy,[21] previous studies of prevention strategies based on the administration of antioxidants to restore free-radical homeostasis, have so far failed to provide unequivocal evidence that any antioxidant agent or strategy is effective in preventing oxidative injury-mediated carcinogenesis in human populations.[9,15,21–23]

A recent meta-analysis of randomised clinical trials concluded that there was no evidence to support a preventive effect of antioxidant supplementation on cancer and cautioned that this may in certain cases be harmful.[24] One possible explanation for the contradictory results in such trials is that the genetic background may be a confounding factor for cancer development.[19,25] In light of these disappointing findings, it was subsequently shown in studies assessing the growth of various tumour cells *in vitro* that the efficacy of certain antitumoural drugs was actually diminished in the presence of antioxidants.[26] Hence, most drugs used for the treatment of cancers proceed through the production of ROS.[27] It is possible that for cancers with a long preclinical development period, such as melanoma, antioxidants interfere with scavenging of pre-clinical tumour cells by macrophages releasing ROS. Further research on ROS containing pathways, genetic susceptibility, pharmacokinetics, skin bioavailability and concentrations are issues still to be addressed in order to elucidate the overall impact of ROS pathways on carcinogenesis.

The principal limitation of this study is the relatively low number of events, due to the low overall incidence of melanoma,[28] which compromises the precision with which the risk can be determined. A further limitation that should be noted is that the analysis of the incidence rates of confirmed BCC was performed *post hoc*. Finally, we have no explicit data on any possible voluntary antioxidant intake during the post-intervention follow-up period, even though this was not encouraged by the study investigators at the end of the SU.VI.MAX trial.

In conclusion, the current study demonstrated that the risk of skin cancers associated with antioxidant intake declined following interruption of supplementation. This supports a causative role for antioxidants in the evolution of skin cancers. Systematic antioxidant supplementation should be avoided in at-risk individuals for skin cancers, such as those with a lifetime history of excessive sun exposure, since it may be harmful to them.

Author contributions

Dr.(s)/Pr.(s) Ezzedine, Hercberg, Galan, Kesse-Guyot, Malvy had full access to all of the data in the study and take(s) full responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Dr.(s)/Pr.(s) Ezzedine, Hercberg, Galan, Guinot, Malvy

Acquisition of the data: Dr.(s)/Pr.(s) Ezzedine, Hercberg, Galan.

Analysis and interpretation of the data: Dr.(s)/Pr.(s) Ezzedine, Latreille, Kesse-Guyot, Galan, Hercberg, Guinot, Malvy.

Drafting of the manuscript: Dr.(s)/Pr.(s) Ezzedine, Malvy, Guinot.

Critical revision of the manuscript for important intellectual content: Dr.(s)/Pr.(s) Hercberg, Galan, Kesse-Guyot.

Statistical analysis: Dr.(s)/Pr.(s) Guinot, Latreille, Ezzedine, Malvy.

Obtained funding: Dr.(s)/Pr.(s) Hercberg, Galan.

Administrative, technical, or material support: Pr. Hercberg.

Study supervision: Pr. Hercberg.

Conflict of interest statement

None declared.

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