The SU.VI.MAX Study

A Randomized, Placebo-Controlled Trial of the Health Effects of Antioxidant Vitamins and Minerals

Serge Hercberg, MD, PhD; Pilar Galan, MD, PhD; Paul Preziosi, MD; Sandrine Bertrais, PhD; Louise Mennen, PhD; Denis Malvy, MD, PhD; Anne-Marie Roussel, PhD; Alain Favier, PhD; Serge Briançon, MD

Background: It has been suggested that a low dietary intake of antioxidant vitamins and minerals increases the incidence rate of cardiovascular disease and cancer. To date, however, the published results of randomized, placebo-controlled trials of supplements containing antioxidant nutrients have not provided clear evidence of a beneficial effect. We tested the efficacy of nutritional doses of supplementation with a combination of antioxidant vitamins and minerals in reducing the incidence of cancer and ischemic cardiovascular disease in the general population.

Methods: The Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) study is a randomized, double-blind, placebo-controlled primary prevention trial. A total of 13,017 French adults (7,876 women aged 35-60 years and 5,141 men aged 45-60 years) were included. All participants took a single daily capsule of a combination of 120 mg of ascorbic acid, 30 mg of vitamin E, 6 mg of beta carotene, 100 µg of selenium, and 20 mg of zinc, or a placebo. Median follow-up time was 7.5 years.

Results: No major differences were detected between the groups in total cancer incidence (267 [4.1%] for the study group vs 295 [4.5%] for the placebo group), ischemic cardiovascular disease incidence (134 [2.1%] vs 137 [2.1%]), or all-cause mortality (76 [1.2%] vs 98 [1.5%]). However, a significant interaction between sex and group effects on cancer incidence was found ($P = .004$). Sex-stratified analysis showed a protective effect of antioxidants in men (relative risk, 0.69 [95% confidence interval {CI}, 0.53-0.91]) but not in women (relative risk, 1.04 [95% CI, 0.85-1.29]). A similar trend was observed for all-cause mortality (relative risk, 0.63 [95% CI, 0.42-0.93] in men vs 1.03 [95% CI, 0.64-1.63] in women; $P = .11$ for interaction).

Conclusions: After 7.5 years, low-dose antioxidant supplementation lowered total cancer incidence and all-cause mortality in men but not in women. Supplementation may be effective in men only because of their lower baseline status of certain antioxidants, especially of beta carotene.

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Experimental studies have demonstrated that free radicals can induce numerous pathological processes, and it has been suggested that nutrients such as beta carotene, ascorbic acid, vitamin E, selenium, and zinc may prevent such harmful effects because of their antioxidant capacity.1-3 Epidemiological data from cross-sectional, case-control, and prospective studies have indeed shown a strong relationship between the intake of antioxidant vitamins and minerals, or of foods rich in these nutrients, and the risks of cancer and ischemic cardiovascular disease (CVD).4-8 However, randomized, placebo-controlled, primary prevention trials in which antioxidant micronutrients, single or in pairs, were taken at high doses over long periods have not confirmed this potential beneficial effect,9-14 and 2 of these10,11 even suggested harmful effects. The seemingly contradictory results between the observational studies and these randomized trials can be explained by the fact that the doses used in clinical trials were much higher than the highest levels found in ordinary dietary intake—levels associated with the lowest risk of cancer and CVD. In fact, the only trial that observed a beneficial effect on total mortality and cancer incidence used nutritional doses of a combination of several vitamins and minerals and was performed on a Chinese population with very low baseline micronutrient status because of poor life conditions.9

The objective of the Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) study was to test, in a randomized, placebo-controlled trial, whether an adequate and well-balanced intake of antioxidant nutrients reduces the inci-
idence of cancers and ischemic CVD in a middle-aged general population.

METHODS

The design, methods, and rationale of the study were reported elsewhere and are briefly presented below.

PARTICIPANTS, RANDOMIZATION, AND TREATMENT

From March to July 1994, information on the objectives and outline of the study was presented in various public media, along with a call for volunteers living in France (women aged 35–60 years or men aged 45–60 years). The lower age in women was determined by the incidence of breast and uterine cancers and the female-to-male ratio of 1.5:1 by the lower incidence of ischemic CVD among women. Candidates responded by telephone or mail. A comprehensive information package on the scientific and practical features of the study was sent to those who responded. They were expected to return a signed informed consent form and a completed screening questionnaire to be eligible. Further eligibility criteria were lack of disease likely to hinder active participation or threatened 5-year survival; acceptance of the possibility to be given a placebo and acceptance of the constraints of participation; lack of previous regular supplementation with any of the vitamins or minerals in the supplement provided; and absence of extreme beliefs or behavior regarding diet. Eligible individuals were invited to an enrollment visit during which they received an instruction manual as well as forms to be completed electronically or on paper during follow-up and were randomly allocated to receive either a combination of antioxidants (120 mg of ascorbic acid, 30 mg of vitamin E, 6 mg of beta carotene, 100 µg of selenium [as selenium-enriched yeast], and 20 mg of zinc [as gluconate]) or a matching placebo in a single daily capsule. Capsules were prepared in 52 weekly packages of 7 capsules and delivered each year in a box labeled with the participant’s number and a 10-digit lot number. Random treatment allocation was performed by block-sequence generation stratified by sex and age group. Randomization was concealed from subjects and all investigators except for the few who were in charge of capsule labeling. The absence of an easy way to distinguish antioxidant from placebo capsules was tested in a pilot study. The protocol was approved by a medical ethics committee and the National Committee for the Protection of Privacy and Civil Liberties.

FOLLOW-UP

At enrollment and at 12- to 18-month intervals, participants were invited to visit a mobile medical unit or a preventive health center for the following tests: at years 0, 2, 5, and 7, a fasting venous blood sample was obtained to measure serum cholesterol and fasting glucose levels in each participant, as well as antioxidant concentrations in an unselected subsample. Vitamin C status was evaluated by serum ascorbic acid determination using an automated method based on the principle of continuous flow segmented by air bubbles. Serum levels of retinol, beta carotene, and tocopherol were measured by high-performance liquid chromatography using the Biotek-Kontron HPLC system (Biotek-Kontron, Montigny-le-Bretonneux, France); serum levels of zinc and selenium were determined using the flame atomic absorption spectrometers Perkin Elmer 3110 (for zinc and selenium) and Perkin Elmer 4100 ZL (for selenium) (Perkin Elmer, Norwalk, Conn) and total cholesterol and fasting glucose levels were measured by an enzymatic method using a Technicon flow analysis device (Technicon DAX-24; Bayer Diagnostic, Pittsburgh, Pa).

At years 1, 3, and 7, the visit included physical examination, anthropometric measurements, blood pressure assessment, electrocardiogram, a fecal occult blood test for individuals older than 45 years, and a Papanicolaou test for women. A screening mammogram was also performed in women older than 50 years who had not had one in the past 2 years. Participants received a summary letter of their health status for their physician, and a medical report was sent to the coordinating center. Participants were asked to complete a monthly questionnaire summarizing treatment compliance and health events via Minitel (a French telephone-based terminal), the Internet, or mail. If there was no contact with a participant for a long period, or if a participant did not appear at the yearly visit, an investigation was launched to determine the reasons. If necessary, an inquiry was made with the participant’s neighbors and/or physician.

Whatever the sources of information, once a possible adverse event was suspected, all relevant records, including results of diagnostic tests and procedures, were collected from the physicians and hospitals involved or directly from the participants. Primary outcomes were major fatal and nonfatal ischemic cardiovascular events (International Classification of Diseases, 10th Revision, Clinical Modification [ICD-10-CM] codes 120-125, 163, 165, 166, 170, 171, 174) and cancer of any kind (ICD-10-CM codes C00-C07, D00-D09, D37-D48), except for basal cell carcinoma of the skin (ICD-10-CM codes C44 and M809-M811). Secondary outcome was all-cause mortality. All data were reviewed by expert committees blinded for supplementation assignment. Cancers were validated by histologic reports; ischemic CVDs were confirmed by radiologic reports or when meeting a combination of clinical, biological, and electrocardiographic criteria, as appropriate. Causes of death were confirmed by information from relatives or physicians. At the end of follow-up, vital status of all subjects and causes of death were verified with the national death registry.

STATISTICAL ANALYSIS

Baseline characteristics of participants were compared using the t or Pearson tests, as appropriate.

As prespecified in the study protocol, data were summarized as Kaplan-Meier incidence curves depicting the proportion of subjects remaining free of adverse events since randomization. Thus, all participants, including those lost to follow-up and those who withdrew their consent, contributed to the analysis for the duration of their follow-up. Outcome analysis consisted of log-rank comparisons based on the first occurrence of each selected outcome and Cox proportional hazard regression to control for age and sex and to test for a sex × group interaction. All randomized participants contributed to the analysis in the originally allocated group.

The number of participants was expected to allow detection of a 25% difference in incidence of cancer and mortality and 33% in incidence of CVD (1-tailed α = 5%; 1-tailed β = 90%).

Plasma concentrations of antioxidants during follow-up were compared by 2-way (time × subject) analysis of variance with Bonferroni adjustment for multiple mean comparisons.

RESULTS

ENROLLMENT

Among the 79,976 candidates who volunteered after the media campaign, 14,412 were eligible and invited to en-
Of the 13017 who were seen for an enrollment visit between October 1994 and June 1995 and were randomized (Figure 1), 270 withdrew consent within 3 days because they could not accept the constraints of participation, and 6 were found to be outside the age range and declared ineligible. Thus, 12741 participants (6364 randomized to the intervention and 6377 to the placebo group) contributed data for our analyses. The follow-up period ended September 1, 2002. The median follow-up time was 7.54 years, ranging from 2 days to 7.89 years, for a total of 89441 person-years (44866 in the intervention and 44574 in the placebo group). The study sample included 7713 women (mean ± SD age, 46.6±6.6 years) and 5028 men (mean ± SD age, 51.3±4.7 years). Baseline characteristics did not differ between groups (Table 1).

COMPLIANCE

Among the 12741 participants, 739 (5.8%) withdrew consent during the study. Of these, 343 (5.4%) were in the intervention group (mean follow-up time, 2.0±1.5 years) and 396 (6.2%) in the placebo group (mean follow-up time, 1.9±1.5 years). Of 736 individuals (5.8%) lost to follow-up (6.0% of the women and 5.5% of the men), 367 were in the intervention group (follow-up time, 5.1±2.2 years) and 369 in the placebo group (follow-up time, 5.0±2.3 years). Within each sex, there were no differences between the intervention and placebo groups regarding the percentages of individuals who withdrew consent or were lost to follow-up.

At the end of follow-up, 74% of the participants reported having taken at least two thirds of the capsules. There were no differences in capsule consumption between the groups (mean percentage of capsules taken, 79% in each group). Compliance was confirmed for the intervention group by statistically significant increases in all biochemical markers of supplementation after 2 years and after 7 years for beta carotene, vitamin C, and selenium. Furthermore, statistically significant differences between the intervention and placebo groups were observed for all markers at 2 years, which were maintained at 7 years for beta carotene, vitamin C, zinc, and selenium (Table 2).

CANCER, CVD, AND BASELINE VITAMIN AND MINERAL STATUS

When the placebo group was divided into quintiles of baseline serum beta carotene concentration, the incidence of cancer among men was higher in the lowest than in the highest quintile (relative risk [RR] in the highest quintile, 0.55; 95% confidence interval [CI], 0.30-0.99). A similar pattern was seen for ischemic CVD (RR for the highest quintile, 0.57; 95% CI, 0.29-1.00). These effects were not seen among women in the placebo group (RRs in the highest quintile were 0.98 [95% CI, 0.54-1.08] for cancer and 0.48 [95% CI, 0.09-2.60] for ischemic CVD). No relation between baseline concentration of the other nutrients studied and cancer or ischemic CVD was observed in the placebo group.

CANCER INCIDENCE

Among the 562 cancers that occurred, 504 were invasive and 58 were in situ. There was no significant difference of overall cancer incidence between the groups (267 cases in the intervention group vs 295 in the placebo group).
group). However, a sex × group interaction was observed, indicating a significant difference between treatment effects according to sex (Table 3). A significant protective effect of antioxidant supplementation was found in men, whereas no effect was seen in women (Figure 2). Specific cancer locations are shown in Figure 3.

INCIDENCE OF ISCHEMIC CVD

In total, 271 subjects developed ischemic CVD during the study, 134 in the intervention group and 137 in the placebo group (Table 3). There were no differences in the incidence of ischemic CVD between the groups, and no sex × group interaction was detected.

MORTALITY

Altogether, 174 deaths (103 in men and 71 in women) occurred during the trial, 76 in the intervention group and 98 in the placebo group. No overall significant difference was observed in all-cause mortality between groups. Again, a sex × group interaction was observed, showing a significant protective effect of antioxidants in men (Table 3).

Our study, performed in individuals not selected for risk factors, indicates that a 7.5-year low-dose antioxidant supplementation lowered total cancer incidence in men but not in women. A similar tendency was observed for all-cause mortality. This supplementation did not result in any major effect on ischemic CVD incidence in men or women.

One difficulty in our study is that no national cancer or CVD registry exists in France; the inability to find information on subjects whom we could not trace explains the high number of subjects lost to follow-up compared with other trials. Furthermore, the relatively high number of individuals who withdrew their consent during the study may be related to the lack of a run-in phase or to the recruitment method. Subjects were not invited to participate and be followed up by health staff already in charge of their care; rather, they were volunteers who had to play an active part in their follow-up. Furthermore, the difference in withdrawal rates between the groups is unlikely to have occurred by chance alone, but no explanation was found. Although there was no simple
way to distinguish between antioxidant and placebo capsules, it is possible that some participants had their capsules analyzed. Even if the results from chemical assays caused some individuals in the placebo group to withdraw from the study and convinced a similar number of individuals in the intervention group to go on with the study, the breach to the protocol would have been limited and could not have induced a false protective effect on cancer incidence in men.

The main difference between ours and the previous primary prevention trials that did not find a positive effect (the Physicians’ Health Study12 and the Women’s Health Study13) or even found a deleterious effect (the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study,10 and the Beta-Carotene and Retinol Efficacy Trial11) of antioxidant supplementation on cancer incidence is due to the doses and kinds of antioxidant used, the recruitment methods, the selection criteria, and the character-

### Table 2. Average Plasma Concentrations of Antioxidants During Follow-up*

<table>
<thead>
<tr>
<th>Antioxidant</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo Group (n = 339)</td>
<td>Intervention Group (n = 325)</td>
</tr>
<tr>
<td>Serum beta carotene, µg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>37.7 ± 25.2</td>
<td>40.4 ± 36.5</td>
</tr>
<tr>
<td>2 y</td>
<td>41.5 ± 28.4†</td>
<td>68.9 ± 55.0‡§</td>
</tr>
<tr>
<td>7 y</td>
<td>57.4 ± 39.8‡</td>
<td>91.5 ± 55.4†§</td>
</tr>
<tr>
<td>Serum vitamin E, mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.4 ± 0.2</td>
<td>1.4 ± 0.4</td>
</tr>
<tr>
<td>2 y</td>
<td>1.4 ± 0.3</td>
<td>1.5 ± 0.4‡§</td>
</tr>
<tr>
<td>7 y</td>
<td>1.3 ± 0.3‡</td>
<td>1.4 ± 0.3‡</td>
</tr>
<tr>
<td>Serum vitamin C, mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.0 ± 0.3</td>
<td>1.1 ± 0.5</td>
</tr>
<tr>
<td>2 y</td>
<td>1.1 ± 0.4</td>
<td>1.3 ± 0.4‡§</td>
</tr>
<tr>
<td>7 y</td>
<td>1.1 ± 0.4‡</td>
<td>1.3 ± 0.3‡§</td>
</tr>
<tr>
<td>Selenium, µg/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>92.8 ± 1.9</td>
<td>84.4 ± 14.4</td>
</tr>
<tr>
<td>2 y</td>
<td>89.2 ± 15.7</td>
<td>132.5 ± 21.3‡§</td>
</tr>
<tr>
<td>7 y</td>
<td>199.9 ± 18.9†</td>
<td>146.7 ± 290‡</td>
</tr>
<tr>
<td>Zinc, µg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>87.2 ± 9.1</td>
<td>83.6 ± 12.2</td>
</tr>
<tr>
<td>2 y</td>
<td>87.3 ± 11.2</td>
<td>96.0 ± 23.7†</td>
</tr>
<tr>
<td>7 y</td>
<td>75.3 ± 7.9‡</td>
<td>79.5 ± 9.6</td>
</tr>
</tbody>
</table>

SI conversion factors: See Table 1.
*Values are given as mean ± SD.
†P<.05 compared with baseline.
‡P<.001 compared with baseline.
§P<.001 compared with the placebo group.
¶P<.01 compared with baseline.
#P<.05 compared with the placebo group.

### Table 3. Effect of Antioxidants on Main Outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention Group, No. (%)</th>
<th>Placebo Group, No. (%)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic cardiovascular disease incidence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall effect</td>
<td>134 (2.1)</td>
<td>137 (2.1)</td>
<td>0.97 (0.77-1.20)</td>
<td>.80</td>
</tr>
<tr>
<td>Sex × group interaction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effect in women</td>
<td>27 (0.7)</td>
<td>23 (0.6)</td>
<td>1.17 (0.67-2.05)</td>
<td>.57</td>
</tr>
<tr>
<td>Effect in men</td>
<td>107 (4.2)</td>
<td>114 (4.6)</td>
<td>0.82 (0.71-1.20)</td>
<td>.54</td>
</tr>
<tr>
<td>Cancer incidence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall effect</td>
<td>267 (4.2)</td>
<td>295 (4.6)</td>
<td>0.90 (0.76-1.06)</td>
<td>.19</td>
</tr>
<tr>
<td>Sex × group interaction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effect in women</td>
<td>179 (4.7)</td>
<td>171 (4.4)</td>
<td>1.04 (0.85-1.29)</td>
<td>.53</td>
</tr>
<tr>
<td>Effect in men</td>
<td>88 (3.5)</td>
<td>124 (4.9)</td>
<td>0.69 (0.53-0.91)</td>
<td>.008</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall effect</td>
<td>76 (1.2)</td>
<td>98 (1.5)</td>
<td>0.77 (0.57-1.00)</td>
<td>.09</td>
</tr>
<tr>
<td>Sex × group interaction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effect in women</td>
<td>36 (0.9)</td>
<td>35 (0.9)</td>
<td>1.03 (0.64-1.63)</td>
<td>.92</td>
</tr>
<tr>
<td>Effect in men</td>
<td>40 (1.6)</td>
<td>63 (2.5)</td>
<td>0.63 (0.42-0.93)</td>
<td>.02</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.
eral antioxidant nutrients at nutritional doses. Mechanistic studies have provided many arguments in favor of the safety of nutritional doses and the potential adverse effects of high doses of antioxidants with respect to cancer risk. Antioxidants and free radicals both appear to be ambiguous compounds, with a wide range of benefits but also a range of toxicity. Second, our trial was carried out in a general population, in contrast to the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, and the Beta-Carotene and Retinol Efficacy Trial, which included individuals at high risk for cancer (heavy smokers and occupationally exposed individuals). The population of the nutrition intervention trials in Linxian, China, had a very low baseline micronutrient status because of poor life conditions. High doses of beta carotene supplementation may be deleterious in individuals with no clinical symptoms but in whom the initial phase of cancer development has already started and could be ineffective in well-nourished individuals with adequate antioxidant status. The latter possibility may explain the difference between men and women observed in our study.

Our study results are concordant with those of all primary prevention trials and most of the secondary prevention trials that have evaluated the effects of different antioxidant supplementations on CVD. Only the Cambridge Heart Antioxidant Study, reported a slight decrease in recurrent CVD after high doses of vitamin E supplementation.

In conclusion, our results suggest that an adequate and well-balanced supplementation of antioxidant nutrients, at doses that might be reached with a healthy diet that includes a high consumption of fruits and vegetables, had protective effects against cancer in men. Baseline beta carotene and vitamin C status was lower in men than in women. The ineffectiveness of supplementation in women may be due to a higher intake; however, in the case of beta carotene, we cannot exclude the effect of hormonal differences or differences between the sexes in lipid and nutrient transport.

An inverse relationship between baseline serum beta carotene levels and cancer risk has been noted in many observational studies. We observed this relationship in men but not women in the placebo group, probably because of their lower baseline beta carotene concentrations. After 7.5 years of supplementation, serum level of beta carotene increased in men to reach the serum level of the women in the placebo group. The efficiency of supplementation in reducing cancer incidence may be related to the ability to correct antioxidant status with an adequate dose of antioxidant nutrients in individuals with a suboptimal antioxidant status (as the men in our study). This hypothesis is supported by results from the Linxian trial, which was conducted in a general population with a very low baseline micronutrient status and using a combination of nutritional doses of antioxidants, including beta carotene. This is the only trial that found a statistically significant reduction in total and specific cancer incidence and overall mortality.

We were not able to analyze differences in site-specific cancers between men and women because of low statistical power. However, our results do not seem to support the presence of a main effect on cancers affecting only men. We cannot exclude sex-specific explanations as part of the overall assessment of the difference in cancer incidence that we observed between men and women.

In conclusion, our results suggest that an adequate and well-balanced supplementation of antioxidant nutrients, at doses that might be reached with a healthy diet that includes a high consumption of fruits and vegetables, had protective effects against cancer in men. Baseline beta carotene and vitamin C status was lower in men than in women. The ineffectiveness of supplementation in women may be
due to their better baseline antioxidant status. The improved antioxidant status achieved by supplementation in men, which proved protective against cancer, confirms the results of other prospective observational studies on the benefits of consuming fruits and vegetables. The present study reinforces the general recommendations of a lifelong diversified diet that includes an abundance of foods rich in antioxidant nutrients. Further investigations are needed to better understand the causes of the sex differences observed in our study.

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Author Affiliations: Institut National de la Santé et de la Recherche Médicale (INSERM) Unité de Recherche Médicale INSERM/Institut National de la Recherche Agronomique/Conservatoire National des Arts et Métiers (CNAM) (Drs Hercberg, Galan, Preziosi, Bertrais, and Mennen), and Unité de Surveillance et d’Épidémiologie Nutritionnelle (Drs Hercberg and Mennen), InVS/CNAM, Paris, France; Center René-Labusquière, Université Victor Segalen, Bordeaux, France (Dr Malvy); Laboratoires Nutrition, Vieillissement et Maladies Cardiovasculaires (Dr Roussel) and Lésions des Acides Nucléiques (Dr Favier), Université Joseph Fourier, Grenoble, France; and Département d’Épidémiologie Clinique, École de Santé Publique, Faculté de Médecine, Centre Hospitalier Universitaire (CHU) Nancy, Nancy, France (Dr Briançon).

Correspondence: Serge Hercberg, MD, PhD, U577 INSERM and Unité de Surveillance et d’Épidémiologie Nutritionnelle, 5 rue Verbois, 75003 Paris, France.

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Correspondence: Judith P. Kelly, MS, Slone Epidemiology Center, Boston University School of Public Health, 1010 Commonwealth Ave, Boston, MA 02215 (jkelly@slone.bu.edu).
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REFERENCES


Correction

Errors in Table Values. In the Original Investigation by Hercberg et al titled “The SU.VI.MAX Study: A Randomized, Placebo-Controlled Trial of the Health Effects of Antioxidant Vitamins and Minerals,” published in the November 22 issue of the ARCHIVES (2004;164: 2335-2342), several mean ± SD plasma levels of selenium were incorrectly reported in Table 2. In women, values at 7 years should have read 90.9 ± 18.9 µg/L in the placebo group and 146.7 ± 29.0 µg/L in the intervention group. In men, values at baseline should have read 94.6 ± 15.5 µg/L in the placebo group and 142.8 ± 24.4 µg/L in the intervention group; values at 2 years should have read 142.8 ± 24.4 µg/L in the intervention group; and values at 7 years should have read 170.6 ± 34.1 µg/L in the intervention group.