Antioxidant Supplementation and Risk of Incident Melanomas

Results of a Large Prospective Cohort Study

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Objective: To examine whether antioxidant supplement use is associated with melanoma risk in light of recently published data from the Supplementation in Vitamins and Mineral Antioxidants (SUVIMAX) study, which reported a 4-fold higher melanoma risk in women randomized to receive a supplement with nutritionally appropriate doses of antioxidants.


Setting: Western Washington State.

Participants: A total of 69,671 men and women who self-reported (1) intake of multivitamins and supplemental antioxidants, including selenium and beta carotene, during the past 10 years and (2) melanoma risk factors on a baseline questionnaire.

Main Outcome Measure: Incident melanoma identified through linkage to the Surveillance, Epidemiology, and End Results (SEER) cancer registry.

Results: Cox proportional hazards regression models were used to estimate multivariable relative risks (RRs) and 95% confidence intervals (CIs) for multivitamin, supplemental selenium, and supplemental beta carotene use. After adjusting for melanoma risk factors, we did not detect a significant association between multivitamin use and melanoma risk in women (RR, 1.14; 95% CI, 0.78-1.66) or in men (RR, 1.09; 95% CI, 0.83-1.43). Moreover, we did not observe increased melanoma risk with the use of supplemental beta carotene (RR, 0.87; 95% CI, 0.48-1.56) or selenium (RR, 0.98; 95% CI, 0.69-1.41) at doses comparable with those of the SUVIMAX study.

Conclusion: Antioxidants taken in nutritional doses do not seem to increase melanoma risk.

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A RECENT RANDOMIZED, PRIMARY PREVENTION TRIAL TESTING THE EFFICACY OF ANTIOXIDANTS IN REDUCING THE CANCER INCIDENCE IN THE GENERAL POPULATION (SUPPLEMENTATION IN VITAMINS AND MINERAL ANTIOXIDANTS [SUVIMAX] STUDY)\(^1\) found that oral daily supplementation with a combination of antioxidants (120 mg of vitamin C, 30 mg of vitamin E, 6 mg of beta carotene, 100 µg of selenium, and 20 mg of zinc) for a median of 7.5 years increased the incidence of melanoma in women (adjusted hazard ratio, 4.31; 95% confidence interval [CI], 1.23-15.13; \(P = .02\)) but not in men. These results suggest that “regular intake of such nutrients may be associated with harmful effects,”\(^2\) which is alarming given that an estimated 48% to 55% of US adults use vitamin or mineral supplements regularly.\(^3\) We sought to confirm these findings by examining melanoma incidence in the Vitamins and Lifestyle (VITAL) study, a large population-based prospective cohort study designed to examine the association of supplement use with cancer risk.

METHODS

STUDY POPULATION

Participants were 37,382 men and 40,337 women aged 50 to 76 years residing in the western part of the state of Washington who were recruited into the VITAL study between October 1, 2000, and December 31, 2002. The goal of the VITAL study was to investigate the association between dietary supplement use and cancer risk. Participants answered a 24-page self-administered questionnaire about lifestyle factors, health history, dietary intake, supplement use, personal characteristics, and cancer risk factors. Further details regarding study design, recruitment, and study implementation have been published previously.\(^3\)

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This study was approved by the Fred Hutchinson Cancer Research Center institutional review board. The Declaration of Helsinki protocols were followed, and patients gave their written informed consent. Participants were excluded if they reported a melanoma diagnosis at baseline (n=1357) or were non-white or did not report their race (n=6491), leaving 69,671 participants.

## SUPPLEMENT USE

We examined self-reported use of the 5 supplements used in the SUVIMAX trial—vitamin C, vitamin E, beta carotene, selenium, and zinc—in the 10 years before baseline. The doses of vitamin C, vitamin E, and zinc supplements used in the SUVIMAX study corresponded to the amounts found in a standard multivitamin. In the SUVIMAX study, the beta carotene and selenium doses were several times greater than those in a standard multivitamin; therefore, we conducted further analyses on the supplemental use of these 2 nutrients.

Individuals were queried about multivitamin use in the past 10 years, including duration (years), frequency (days per week), and lifetime use after age 21 years (years). Dose was calculated as “pill-years” (duration × [pills per week/7]). Detailed information on the use of single-nutrient supplements during the past 10 years, including beta carotene and selenium, was also obtained. Average supplemental intake of each nutrient was calculated as (dose per day) × (days per week/7) × (years/10), summed across individual supplements and micronutrient doses in participant-reported multivitamins.

## COVARIATES

We obtained information on suspected or established risk factors for melanoma, including age at baseline (years), sex (female or male), education (high school or less, some college, or advanced degree), first-degree family history of melanoma (no or yes), personal history of nonmelanoma skin cancer (no or yes), ever had moles removed (no or yes), freckles between ages 10 and 20 years (no or yes), natural red or blond hair between ages 10 and 20 years (no or yes), and reaction to 1 hour in strong sunlight (tan or no sunburn, mild sunburn, painful sunburn, or severe sunburn with blistering). The RR for melanoma was stratified by sex and did not have sex in the models.

## MELANOMA ASCERTAINMENT

Through linkage with the Surveillance, Epidemiology, and End Results (SEER) cancer registry between October 1, 2000, and December 31, 2006, we identified 461 incident cases of cutaneous melanoma using the coding of the International Classification of Diseases for Oncology. These cases included melanoma in situ, malignant melanoma not otherwise specified, superficial spreading melanoma, lentigo maligna melanoma, nodular melanoma, and other subtypes, including melanoma.
within a junctional nevus, spindle cell melanoma, acral lentiginous melanoma, and desmoplastic melanoma. Extensive quality control procedures have been implemented by the SEER registry to ensure that registry data are accurate and complete.

STATISTICAL ANALYSIS

Cox proportional hazards regression models were used to estimate age- and multivariable-adjusted relative risks (RRs) and 95% CIs for melanoma risk. Participants were observed from the date of their baseline questionnaire until melanoma diagnosis or the end of follow-up on December 31, 2006. Participants were censored at an earlier date if they withdrew from the study (0.03%), died (4.6% identified from Washington death files), or moved from the 13-county catchment area of the SEER cancer registry (5.4% as identified by linkage to the National Change of Address System and by follow-up letters and telephone calls). In the multivariable models, we adjusted for all the melanoma risk factors defined as covariates, as noted in Table 1 and Table 2. For all analyses, missing indicators were created for each noncontinuous covariate so that participants with a missing value could be included in the analyses. Statistical tests were 2-sided. All statistical analyses were performed using a software program (SAS version 9.1; SAS Institute Inc, Cary, North Carolina).

RESULTS

Most participants (66%) were either current or past users of multivitamins. Associations between multivitamin use and the incidence of melanoma after adjusting for melanoma risk factors are summarized in Table 1. None of the multivitamin exposure variables, whether expressed as overall use, duration of use in the past 10 years, dose in pill-years, or years of use since age 21 years, were associated with melanoma risk. Specifically, in the highest dose category of multivitamins, which is comparable with the doses of vitamin E, vitamin C, and zinc in the SUVIMAX study, there was no increased risk of melanoma. Results were similar in men (RR, 1.09; 95% CI, 0.78-1.51) and women (RR, 1.14; 95% CI, 0.78-1.66; P = .93 for interaction).

We also examined the risk of melanoma associated with long-term use of supplemental beta carotene and selenium (from multivitamins plus individual supplements) at doses similar to those used in the SUVIMAX trial (daily dose of 100 µg of selenium and 6000 µg of beta carotene). We defined the highest category of beta carotene starting at 3000 µg (6000 µg/d used 7 d/wk for 5 years) and of selenium use starting at 50 µg/d on average (100 µg/d used 7 d/wk for 5 years). There was no increased risk of melanoma associated with these supplemental nutrients at these doses (Table 2).

COMMENT

In this prospective study, we found no evidence of an association between use of supplemental antioxidants and melanoma risk, and the results did not vary by sex. These doses were comparable with those of the SUVIMAX study, as was duration of follow-up (7.5 years vs a mean of 3.0 years and a maximum of 6.0 years). Consistent with the present results, case-control studies examining sero-

Table 1. Baseline Characteristics of Participants in the VITAL Cohort, 2000-2006

Table 2. Association Between Average Daily Intakes of Supplemental Beta Carotene and Selenium Across 10 Years and Incident Melanoma, VITAL Cohort, 2000-2006

<table>
<thead>
<tr>
<th>Participants, No. (%) (N=69 671)</th>
<th>Multivariable RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta carotene, µg/d</strong></td>
<td><strong>Cohort</strong></td>
</tr>
<tr>
<td>0</td>
<td>23 664 (34)</td>
</tr>
<tr>
<td>&gt;0 to ≤600</td>
<td>24 578 (36)</td>
</tr>
<tr>
<td>&gt;600 to &lt;3000</td>
<td>18 501 (27)</td>
</tr>
<tr>
<td>≥3000</td>
<td>2091 (3)</td>
</tr>
<tr>
<td><strong>Selenium, µg/d</strong></td>
<td><strong>Cohort</strong></td>
</tr>
<tr>
<td>0</td>
<td>23 855 (34)</td>
</tr>
<tr>
<td>&gt;0 to ≤20</td>
<td>28 613 (41)</td>
</tr>
<tr>
<td>&gt;20 to &lt;50</td>
<td>11 414 (17)</td>
</tr>
<tr>
<td>≥50</td>
<td>5392 (8)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk; VITAL, Vitamins and Lifestyle.

The RRs are adjusted for age at baseline (years), sex (female or male), education (high school or less, some college, or advanced degree), first-degree family history of melanoma (no or yes), personal history of nonmelanoma skin cancer (no or yes), ever had moles removed (no or yes), freckles between ages 10 and 20 years (no or yes), had 3 or more sunburns between ages 10 and 20 years (no or yes), natural red or blond hair between ages 10 and 20 years (no or yes), and reaction to 1 hour in strong sunlight (tan or no sunburn, mild sunburn, painful sunburn, or severe sunburn with blistering).

Ten-year average from individual and multivitamin supplements.

logic levels of beta carotene, vitamin E, and selenium did not find any association with subsequent risk of melanoma. Moreover, the Nurses’ Health Study reported no association between intake of vitamins A, C, and E and melanoma risk in 162 000 women during more than 1.6 million person-years of follow-up.

The association between the SUVIMAX supplement and melanoma risk in women could be explained by methodological shortcomings. Their analysis was limited to a subsample of participants who agreed to answer a single question on their lifetime sun exposure (“How would you describe the intensity of your skin’s exposure to the sun during your lifetime?”), which could introduce selection bias and limit generalizability. Also, the response to that question, which was the only melanoma risk factor ascertained other than age, current smoking status, and latitude of residence, was excluded from their multivariable analysis. Although their multivariable model found a hazard ratio of 4.31 for women, the 95% CI was wide (1.23-15.13) because the analysis was based on only 16 cases. The study identified few incident melanomas, possibly owing to inaccurate case ascertainment, which may explain the 5-fold lower rates of incident melanomas in the SUVIMAX trial (25 cases per 100 000 person-years) compared with the VITAL study (120 cases per 100 000 person-years).

There are several limitations to this study, including the absence of detailed information on some known melanoma risk factors, such as sunlight exposure at early ages and number of nevi. However, adjusting for the major melanoma risk factors, including age, sex, education, family history of melanoma, color of hair between ages 10 and 20
years, sensitivity to sun, the number of sunburns before age 20 years, and history of freckles and moles, did not alter the risks in the multivariate model. Thus, it is unlikely that including more refined estimates of melanoma risk factors would appreciably change the results. Also, this study relied on self-reported use of antioxidant supplements, and no physiologic measures, such as serum levels, were obtained. Use of self-reported exposure information likely led to some attenuation of the results due to nondifferential measurement error; however, the detailed supplement assessment yielded very good validity and reliability results. Specifically, the reliability of 10-year intake as reported on the baseline questionnaire compared with 3 months later yielded intraclass correlation coefficients of 0.81 for multivitamins, 0.69 for beta carotene, and 0.80 for selenium. Comparison of questionnaire-reported current dose of supplements with an in-home pill bottle inventory yielded Pearson correlation coefficients of 0.58 for beta carotene and 0.77 for selenium. Comparison of questionnaire-reported current dose of supplements with an in-home pill bottle inventory yielded Pearson correlation coefficients of 0.58 for beta carotene and 0.77 for selenium.

In summary, these data suggest no association between self-reported multivitamin use and supplemental selenium and beta carotene use similar to doses used in the SUVIMAX study and melanoma risk. Strengths of this investigation include its prospective design, its large cohort size (>450 cases), and the availability of baseline information on major potential confounding factors. The results of the SUVIMAX study should be interpreted with caution.

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Author Contributions: All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Asgari, Kushi, and White. Acquisition of data: White. Analysis and interpretation of data: Asgari, Maruti, Kushi, and White. Drafting of the manuscript: Asgari. Critical revision of the manuscript for important intellectual content: Asgari, Maruti, Kushi, and White. Statistical analysis: Maruti and White. Obtained funding: Asgari and White. Administrative, technical, or material support: Asgari and White. Study supervision: Asgari and White.

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REFERENCES