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Antioxidant Supplementation and Risk of Incident Melanomas: Results from a Large Prospective Cohort Study

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Abstract

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 Antioxidant (SUVIMAX) study which reported a four-fold higher melanoma risk among women who were randomized to a supplement with nutritionally appropriate doses of antioxidants.

Design—Prospective study (VITamins And Lifestyle (VITAL) cohort).

Setting—Population-based study targeting supplement users recruited from Western Washington State.

Participants—69,671 men and women who self-reported intake of multivitamins and supplemental antioxidants including selenium and beta-carotene over the past 10 years as well as 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 regression models were used to estimate multivariate relative risks (RR) and 95% confidence intervals (CI) for multivitamins, supplemental selenium and supplemental beta-carotene use. After adjusting for melanoma risk factors, we did not detect a significant association between multivitamins and melanoma risk for women (RR=1.14, CI = 0.78–1.66) or men (RR=1.09, CI =0.83–1.43). Moreover, we did not observe increased melanoma risk for supplemental beta-carotene (RR=0.87, CI=0.48, 1.56) or selenium (RR=0.98, CI=0.69–1.41) at doses comparable to the SUVIMAX study.

Conclusion—Antioxidants in nutritional doses do not appear to increase the melanoma risk.

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A recent, randomized, primary prevention trial testing the efficacy of antioxidants in reducing cancer incidence in the general population (Supplementation in Vitamins and Mineral Antioxidants Study, SUVIMAX) found that oral daily supplementation with a combination of antioxidants (120 mg vitamin C, 30 mg vitamin E, 6 mg beta-carotene, 100 μg selenium, and 20 mg zinc) for a median follow-up time of 7.5 years increased the incidence of melanoma for women (adjusted HR = 4.31, CI=1.23, 15.13, p = 0.02) but not for men.[1] These results suggested that "regular intake of such nutrients may be associated with harmful effects"[2] which is alarming given that an estimated 48–55% of US adults use vitamins and/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 50–76 years residing in western Washington recruited in the VITAL study between 2000 and 2002. The goal of VITAL 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] 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.

Exclusions

Participants were excluded if they reported a melanoma diagnosis at baseline (n=1,557), or were nonwhite or did not report their race (n=6,491), leaving 69,671 participants.

Supplement Use

We examined self-reported use of the five 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 SUVIMAX corresponded to amounts found in a standard multivitamin. In SUVIMAX, the beta-carotene and selenium doses were several times greater than those in a standard multivitamin, therefore, we conducted further analyses on supplemental use of those two nutrients.

Individuals were queried about multivitamin use in the past 10 years, including duration (years), frequency (days/week), and lifetime use after age 21 (years). Dose was calculated as "pills years" (duration × pills per week/7). Detailed information on use of single nutrient supplements over 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 over individual supplements and micronutrient dose in participant-reported multivitamins.

Covariates

We obtained information on suspected or established risk factors for melanoma including age at baseline (years), gender (female, male), education (high school or less, some college, advanced degree), first degree family history melanoma (no, yes), personal history of non-melanoma skin cancer (no, yes), ever had moles removed (no, yes), freckles between ages 10–20 years (no, yes), had ≥ 3 severe sunburns between ages 10–20 years (no, yes), natural red/

blond hair between ages 10–20 years (no, yes), and reaction to one-hour in strong sunlight (tan or no sunburn, mild burning, painful sunburn, severe sunburn with blistering).

Melanoma Ascertainment

Through linkage with SEER between October 2000 and December 2006, we identified 461 incident cases of cutaneous melanoma using the coding of the International Classification of Diseases for Oncology (ICD-O-2). These included melanoma in situ, malignant melanoma NOS, 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 SEER to ensure that registry data is accurate and complete.

Statistical Analysis

Cox proportional hazards models were used to estimate age- and multivariate-adjusted RR and 95% CI for melanoma risk. Participants were followed from the date of their baseline questionnaire until melanoma diagnosis or 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 State death files); or moved from 13-county catchment area of the SEER registry (5.4% as identified by linkage to the National Change of Address System and by follow-up letters and phone calls). In multivariate models, we adjusted for all melanoma risk factors defined as covariates as noted in the Tables. For all analyses, missing indicators were created for each non-continuous covariate so participants with a missing value could be included in the analyses. Statistical tests were two-sided. All statistical analyses were performed using SAS, version 9.1, (SAS Institute Inc., Cary, NC).

RESULTS

Most participants (66%) were either current or past users of multivitamins. The associations between multivitamin use and incidence of melanoma after adjusting for melanoma risk factors are summarized in Table 1. None of the multivitamin exposures 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 were associated with melanoma risk. Specifically, in our highest dose category of multivitamins, which is comparable to the doses of vitamin E, vitamin C and zinc in SUVIMAX, there was no increased risk of melanoma. Results were similar for men (RR 1.09, CI 0.83–1.43) and women (RR 1.14, CI 0.78–1.66, p interaction 0.93).

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

DISCUSSION

In this prospective study, we found no evidence for an association between use of supplemental antioxidants and melanoma risk, and the results did not vary by sex. Our doses were comparable to that of SUVIMAX and our duration of follow-up was similar (7.5 years vs. 5.0 average, maximum 6 years). Consistent with our results, case-control studies examining serologic levels of beta-carotene, vitamin E and selenium did not find any association with subsequent risk of melanoma.[4–6] Moreover, the Nurses' Health Study reported no association between intake of

vitamins A, C, E and melanoma risk among 162,000 women during more than 1.6 million person-years of follow-up.[7]

The association between the SUVIMX supplement and melanoma risk among women could be explained by methodologic short-comings.[8] Their analysis was limited to a sub-sample of participants who agreed to answer a single question on their lifetime sun exposure "How would you describe the intensity of yours 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 not included in their multivariate analysis. Although their multivariate model found a HR of 4.31 for women, the CI was wide (1.23–15.13) as the analysis was based on only 16 cases. The study identified a small number of incident melanomas, possibly due to inaccurate case ascertainment, which may explain the five-fold lower rates of incident melanomas in the SUVIMAX trial (25 cases/100,000 person-years) compared to the VITAL Study (120 cases/100,000 person-years).

There are several limitations to our 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, gender, education, family history of melanoma, hair color, sun-sensitivity, sunburns before age 20 and history of freckles and moles, did not alter the risks in the multivariable 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 non-differential measurement error; however, our detailed supplement assessment yielded very good validity and reliability results.[9] Specifically, the reliability of 10-year intake as reported on our baseline questionnaire as compared to 3 months later yielded intraclass correlation coefficients of 0.81, 0.69, and 0.80 for multivitamins, beta-carotene and selenium respectively. Comparison of questionnaire-reported current dose of supplements to an in-home pill bottle inventory yielded Pearson correlation coefficients of 0.58 for beta-carotene and 0.77 for selenium.

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

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Table 1

Association between multivitamin intake and incident melanoma, VITAL cohort (n=69,671) from 2000–2006.

	Total			Women			Men			
	Cohort N (%)	Case N (%)	Multivariate-RR (95% CI)	Cohort N (%)	Case N (%)	Multivariate-RR (95% CI)	Cohort N (%)	Case N (%)	Multivariate-RR (95% CI)	p †
10-year use of multivitamins										
Overall use										
None	22996 (34)	152 (34)	1.00	10048 (29)	44 (27)	1.00	12948 (40)	108 (38)	1.00	
Former	4363 (7)	24 (5)	0.88 (0.57–1.36)	2472 (7)	13 (8)	1.16 (0.63–2.16)	1891 (6)	11 (4)	0.69 (0.37–1.28)	
Current	39636 (59)	275 (61)	1.04 (0.85–1.27)	22007 (64)	108 (65)	1.04 (0.73–1.48)	17629 (54)	167 (58)	1.05 (0.82–1.34)	
P-trend			0.65			0.85			0.67	0.91
Duration (years)										
None	22996 (34)	152 (34)	1.00	10048 (29)	44 (27)	1.00	12948 (40)	108 (38)	1.00	
1–3	8068 (12)	47 (10)	0.91 (0.65–1.27)	4357 (13)	23 (14)	1.14 (0.68–1.91)	3711 (11)	24 (8)	0.77 (0.49–1.20)	
4–6	8082 (12)	55 (12)	1.05 (0.77–1.43)	4443 (13)	18 (11)	0.89 (0.51–1.54)	3639 (11)	37 (13)	1.16 (0.80–1.69)	
≥7	27849 (42)	197 (44)	1.05 (0.85–1.30)	15679 (45)	80 (48)	1.08 (0.75–1.56)	12170 (37)	117 (41)	1.04 (0.80–1.35)	
P-trend			0.55			0.79			0.57	0.88
Pill-years										
None	22996 (34)	152 (34)	1.00	10048 (29)	44 (27)	1.00	12948 (40)	108 (38)	1.00	
>0 – ≤25	10291 (15)	65 (14)	0.99 (0.74–1.33)	5639 (16)	28 (17)	1.07 (0.66–1.73)	4652 (14)	37 (13)	0.94 (0.65–1.37)	
>25 – <50	9392 (14)	52 (12)	0.85 (0.62–1.17)	5166 (15)	19 (12)	0.81 (0.47–1.39)	4226 (13)	33 (12)	0.89 (0.60–1.31)	
≥50	24316 (36)	182 (40)	1.11 (0.89–1.38)	13674 (40)	74 (45)	1.14 (0.78–1.66)	10642 (33)	108 (38)	1.09 (0.83–1.43)	
P-trend			0.44			0.58			0.58	0.93
Lifetime use of multivitamins (since age 21)										
Duration (years)										
None	21483 (31)	136 (30)	1.00	8950 (25)	41 (24)	1.00	12533 (37)	95 (33)	1.00	
1–4	9558 (14)	54 (12)	0.93 (0.67–1.27)	5227 (15)	22 (13)	0.86 (0.51–1.45)	4331 (13)	32 (11)	0.95 (0.64–1.42)	
5–9	9215 (13)	62 (13)	1.09 (0.80–1.47)	4909 (14)	20 (12)	0.84 (0.49–1.43)	4306 (13)	42 (15)	1.23 (0.86–1.77)	
10–14	10784 (16)	82 (18)	1.20 (0.91–1.58)	5812 (16)	30 (18)	1.06 (0.66–1.69)	4972 (15)	52 (18)	1.28 (0.91–1.80)	
≥15	18509 (27)	126 (27)	1.07 (0.84–1.37)	11146 (31)	58 (34)	1.01 (0.68–1.51)	7363 (22)	68 (24)	1.08 (0.79–1.48)	
P-trend			0.30			0.73			0.30	0.75

[*] RRs adjusted for: age at baseline (years), gender (female, male), education (high school or less, some college, advanced degree), 1st degree family history melanoma (no, yes), personal history of non-melanoma skin cancer (no, yes), ever had moles removed (no, yes), freckles between ages 10–20 years (no, yes), had ≥3 severe sunburns between ages 10–20 years (no, yes), natural red/blond hair between ages 10–20 years (no, yes), and reaction to 1-hour in strong sunlight (tan or no sunburn, mild burning, painful sunburn, severe sunburn with blistering). RRs stratified by sex did not have gender in the models.

[†] P for interaction testing whether estimates were different among women vs. men; computed using a Wald test.

Table 2

Association between average daily intakes of supplemental beta-carotene and selenium over 10 years and incident melanoma, VITAL cohort ((n=69,671)) from 2000–2006*

	Cohort N (%)	Case N (%)	Multivariate-RR (95% CI) *
Beta-carotene†			
None	23664 (34)	146(32)	1.00
>0 – ≤600 μg/day	24578 (36)	158(35)	1.07 (0.85–1.34)
>600–<3000 μg/day	18501 (27)	137(30)	1.17 (0.93–1.48)
≥3000 μg/day	2091 (3)	12(3)	0.87 (0.48–1.56)
P-trend			0.38
Selenium†			
None	23855 (34)	152(33)	1.00
>0 – ≤20 μg/day	28613 (41)	195(42)	1.09 (0.88–1.36)
>20–<50 μg/day	11414 (16)	76(17)	1.01 (0.77–1.33)
≥50 μg/day	5392 (8)	37(8)	0.98 (0.69–1.41)
P-trend			0.98

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

† 10-year average mcg/day from individual and multivitamin supplements.