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Association of Vitamin A and Carotenoid Intake with Melanoma Risk in a Large Prospective Cohort

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Abstract

Laboratory data suggest that intake of vitamin A and carotenoids, may have chemopreventive benefits against melanoma, but epidemiologic studies examining the association have yielded conflicting results. We examined whether dietary and supplemental vitamin A and carotenoid intake was associated with melanoma risk among 69,635 men and women who were participants of the Vitamins and Lifestyle (VITAL) cohort study in Western Washington. After an average of 5.84 years of follow-up, 566 incident melanomas were identified. Cox proportional hazards regression models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for risk of melanoma associated with dietary, supplement and total vitamin A and carotenoid intake after adjusting for melanoma risk factors. Baseline use of individual retinol supplements was associated with a significant reduction in melanoma risk (HR: 0.60, 95% CI: 0.41–0.89). High-dose (>1200 ug/day) supplemental retinol was also associated with reduced melanoma risk (HR: 0.74, 95% CI: 0.55–1.00), as compared to non-users. The reduction in melanoma risk was stronger in sun-exposed anatomic sites. There was no association of melanoma risk with dietary or total intake of vitamin A or carotenoids. Retinol supplementation may have a preventative role in melanoma among women.

INTRODUCTION

Melanoma is the sixth most common cancer in the United States (American Cancer Society Fact and Figures, 2010) and its lifetime incidence is rising (Statbite, 2011). It is estimated that one out of every 45 Americans born in 2010 will be diagnosed with melanoma during their lifetime (American Cancer Society Fact and Figures, 2010). The rising incidence of

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CONFLICT OF INTEREST

The authors state no conflict of interest.

melanoma and its poor prognosis in advanced stages (Criscione and Weinstock, 2010) are compelling reasons to identify novel chemopreventive agents. There is accumulating evidence that vitamin A and its derivatives may play a chemoprotective role in melanoma.

Vitamin A (retinol) is a fat-soluble, organic compound that cannot be synthesized by humans, yet is necessary for normal physiologic function, and thus, is classified an essential nutrient. Retinol belongs to a class of compounds called retinoids that includes the naturally occurring relatives of retinol, retinaldehyde and retinoic acid, as well as over 1000 synthetic compounds (van Berkel et al, 2009). The main source of vitamin A in the diet are from retinyl esters, mostly from animal products such as eggs, milk, and liver; and plant-based pro-vitamin A carotenoids (α-carotene, α-carotene, β-cryptoxanthin) that can be converted to retinol in the intestine. Carotenoids constitute a large group of over 563 compounds (http://ods.od.nih.gov/factsheets/VitaminA-HealthProfessional, accessed 11 August 2011), fewer than 10% of which can be converted to vitamin A. The vast majority of carotenoids are non-pro-vitamin A, and include substances such as lutein, zeaxanthin, and lycopene.

Retinoids have powerful effects on cell differentiation and proliferation and inhibits malignant transformation (Goodman 1984). They have been shown to inhibit the proliferation of human melanoma cell lines (Niu et al, 2005, Meyskens and Salmon 1979, Meyskens and Fuller, 1980) and have been shown to inhibit tumor invasion using *in vitro* models (Wood et al, 1990). *In vivo*, murine models have shown that retinoids decrease tumor size and improve survival in melanoma (Weinzweig et al, 2003, Liu et al, 2008). The pro-vitamin A carotenoids have also been shown to exert anti-melanoma activity through alternate pathways including anti-angiogenic effects by altering cytokine profiles and nuclear translocation of transcription factors in melanoma cell lines (Guruvayoorappan and Kuttan, 2007, Palozza et al, 2003). Some non pro-vitamin A carotenoids have also been shown to have chemopreventative effects *in vitro* (Philips et al, 2007).

Epidemiologic studies on the association of vitamin A/carotenoid intake and melanoma risk have largely been case-control studies and have yielded mixed results (Bain et al, 1993, Naldi et al, 2003; Millen et al, 2004, Kirkpatrick et al, 1994, Stryker et al, 1990, Le Marchand et at, 2006, Osterlind et al, 1988, Vinceti et al, 2005). A recently published systematic review and meta-analysis of randomized controlled trials found no association between β-carotene use and melanoma risk (relative risk (RR)=0.98; 95% confidence interval (CI): 0.65–1.46) (Druesne-Pecollo et al, 2010). These findings were supported by previously published data using the VITamins And Lifestyle (VITAL) cohort (RR, 0.87; 95% CI: 0.48–1.56) (Asgari et al, 2010). In contrast to the lack of association noted with β-carotene use and melanoma risk, data from a large prospective study using two Nurses' Health Study cohorts of women found that retinol intake from foods plus supplements appeared protective within a subgroup of low-risk (RR=0.39, 95% CI: 0.22–0.71), (Feskanich et al, 2003). Thus, β-carotene and retinol appear to have differential effects on melanoma risk.

We sought to explore the association between melanoma risk and dietary, supplemental, and total intake of retinol and carotenoids (including β-carotene, lutein, and lycopene) using the

VITAL cohort, the only large prospective study specifically designed to investigate the association between dietary supplements and cancer risk.

RESULTS

The average age of participants was 62 years (range: 50–76), and slightly more than half of the participants were female (52%). Most individuals had some college or an advanced degree (80%), and were overweight or obese (63%). Cohort members that developed primary cutaneous melanoma during the follow-up period were more likely to be male, have attained higher education, and to have fair skin phenotype (childhood freckling, ≥ 3 severe sunburns, natural red or blond hair, and have a tendency to burn with exposure to sunlight) (Table 1). They were also more likely to have had a personal history of skin cancer, a family history of melanoma, and have had moles removed. Cases and non-cases did not significantly differ in risk of a common indication for vitamin A supplementation, namely history of macular degeneration.

Of the 566 incident melanomas, there were 257 in-situ, and 309 invasive tumors. The break-down of histopathologic subtype of the invasive tumors was n= 144 melanoma not otherwise specified, n=88 superficial spreading, n= 38 lentigo maligna, n= 21 nodular, and n= 13 rare subtypes (including 5 melanomas arising in a junctional nevus, 4 spindle cell, 3 acral lentiginous and 1 desomplastic melanoma). There were 5 cases who had no information on subtype available. There were only 16 invasive melanomas that developed among supplement users, so our cell sizes for the subtype variable were too small to permit meaningful analysis of supplement use by melanoma histopathologic subtype.

The results of supplement and dietary intake of retinol, β-carotene, total vitamin, lutein and lycopene and associated melanoma risk are shown in Table 2. Relative to non-use, current (HR 0.60, 95% CI: 0.41–0.89) but not former (HR 0.90, 95% CI: 0.57–1.43) use of individual retinol supplements at baseline was associated with a decreased risk of melanoma. Intake of supplemental retinol greater than the amount that can be obtained from common multivitamin formulations (>1200 ug/d) was of borderline statistical significance (HR: 0.74, 95% CI: 0.55–1.00); however the association was not linear (*P*-trend=0.25). Retinol intake from food, and the combination of supplement and dietary intake were not associated with melanoma risk.

β-carotene, whether from supplement use or dietary intake, was not associated with melanoma risk. Similarly, total vitamin A intake and intake of pro-vitamin A carotenoids was also not associated with melanoma risk. Among participants who used individual lutein or lycopene supplements, very few developed melanoma (n<10), so our cohort was underpowered to detect an association with regard to supplemental intake of the non-pro-vitamin A carotenoids. Although there was a trend for increased melanoma risk with dietary intake of lutein, the effect was no longer statistically significant in adjusted models of dietary intake of the non-proretinoid carotenoids.

In examining the associations between retinol use and melanoma risk stratified by gender (Table 3), the association of current use of retinol supplements was largely driven by a

marked risk reduction in melanoma risk among women (HR: 0.27, 95% CI: 0.11–0.66) but not men (HR: 0.83, 95% CI: 0.54–1.27; *P*-interaction=0.64). Inverse associations for high doses of retinol supplements and melanoma were similar among men (HR 0.77, 95% CI: 0.53–1.12) and women (HR 0.71, 95% CI: 0.43–1.16), although neither achieved statistical significance. Similar to unstratified findings, there were no clear associations or differences by gender for retinol exposure from diet or total retinol, irrespective of source (data not shown).

Table 4 shows the association of retinol supplement use with melanoma by anatomic site. In comparing current users to non-users, the reduction in melanoma risk with retinol use appeared to be stronger in sun-exposed areas such as the limbs (HR 0.44, 95% CI: 0.22–0.89), and the head and neck (HR 0.49, 95% CI: 0.21–1.10) as compared to the trunk (HR 0.94, 95% CI: 0.52–01.70).

We examined the association between retinol (both current use and dose) and tumor invasiveness and Breslow depth as proxies for tumor progression (Table 5). In comparing insitu to invasive melanomas, or invasive melanomas with Breslow depth <1.0 mm to those >1.0 mm, there was no differential association with retinol use. With regard to dose, low-dose users appeared to have a slightly increased risk of thin (<1.0 mm) melanoma as compared to nonusers (HR 1.44, 95% CI: 1.04–2.00), but this mildly increased risk in low-dose retinol users did not manifest for thicker melanomas (>1.0 mm).

DISCUSSION

In this prospective study, we found an inverse association between supplemental intake of retinol and melanoma risk. The risk reduction was statistically significant for current supplemental retinol users and not significant for former users (as compared to non-users). The association remained stable after adjusting for age and gender, as well as melanoma-specific risk factors. The association was largely driven by a marked risk reduction in females; while the risk reduction in males did not achieve statistical significance. The underlying reason for the differential effect by gender may be chance (spurious association), however, gender differences in melanoma outcomes, with females having more favorable outcomes, has been previously reported (Scoggins et al, 2006).

Multivariable adjustment of the association between dose of supplemental retinol on melanoma risk revealed that the risk reduction was borderline significant only for high-dose supplemental retinol users (>1,200 μg/d). Retinol users in the mid-dose category (19.3–1,200 μg/d), who were largely multivitamin users, did not experience a lower reduction in melanoma risk. Thus, the effect appears to be limited to retinol users who take retinol in doses in excess of that available in a standard multivitamin. There was no clear association of intake of retinol from food sources with melanoma risk.

Intake of beta-carotene (from supplements, diet or total), was not associated with melanoma risk. Given that the vitamin A activity of beta-carotene in foods is 1/12 that of retinol (IOM 2000), the lack of association of melanoma risk with beta-carotene appears consistent with a high dose retinol specific effect. Our findings of a lack of association of melanoma risk and

beta carotene are supported by a recently published meta-analysis of randomized controlled trials reported no effect of beta-carotene supplementation on melanoma risk (RR: 0.98, 95% CI: 0.6–1.46) (Druesne-Pecollo et al, 2010), as well as our previously published findings using the VITAL cohort (RR, 0.87; 95% CI: 0.48–1.56) (Asgari et al, 2010).

Non-pro-vitamin A carotenoids, such as lutein and lycopene, cannot be converted to retinol. We detected no association with lycopene intake, but did find an inverse association with dietary lutein intake and melanoma risk, with higher lutein intake being associated with a higher melanoma risk, a finding which was no longer statistically significant in adjusted models. Dietary intake of lycopene has previously been shown to be associated with a reduction in melanoma risk, with individuals in the highest quintile of lycopene intake having significantly reduced risk of melanoma as compared with the lowest quintile (Millen et al, 2004). However, other studies have failed to find as association between melanoma risk and lycopene intake (Stryker et al, 1990) as well as serum lycopene levels (Breslow et al, 1995; Comstock et al, 1991). The epidemiology literature is also mixed regard the association of melanoma risk with dietary lutein: one case-control study reported non-significant increases in risk for women from dietary lutein, and near significant increases in risk regardless of gender for blood plasma levels of lutein (Le Marchand et al, 2006), whereas another case-control study found a dose-dependent risk reduction with dietary lutein (Millen et al, 2004). The lack of association between melanoma risk and intake of these non-pro-vitamin A carotenoids may have to due with their inability to be converted to retinol, which is the form that appears to be associated with melanoma risk reduction.

Numerous case-control studies have looked at the association of vitamin A intake and melanoma risk, and have reported mixed findings (Bain et al, 1993, Naldi et al, 2003; Millen et al, 2004, Kirkpatrick et al, 1994, Stryker et al, 1990, Le Marchand et at, 2006, Osterlind et al, 1988, Vinceti etl al, 2005). Exposure data in these studies was collected after case diagnosis, making these study potentially vulnerable to recall bias (Austin et al, 1994). Selection bias in case-control studies is also a concern. There has been only one other published large prospective cohort study examining the association of dietary intake of vitamin A and melanoma risk; and upon examining 162,000 women with more than 1.6 million person-years of follow-up, they reported that retinol intake from diet plus supplements appeared protective within a low-risk subgroup of women (RR = 0.39, 95% CI: 0.22–0.71 for >1,800 vs 400 μg/day) (Feskanich et al, 2003). Although they only reported diet and total retinol intake (and not supplemental intake separately), their significant results are limited to total (not dietary) intake, suggesting that supplemental retinol was the key driver behind their findings.

Our data suggest a possible interaction between supplemental retinol use and anatomic site of melanoma, with sun-exposed sites showing a stronger protective effect than sun-protected sites. It may be that retinol's effects may be mediated by sun-light exposure. This intriguing possibility warrants further exploration in future studies.

Strengths of this investigation include the availability of baseline information on major potential confounding factors including constitutional, personal, and family skin cancer history, and the prospective collection of information thereby avoiding recall bias. Other

advantages include the relatively large number of melanoma cases and the high percentage of supplement users recruited into this study. The high test-retest reliability and validity of the VITAL questionnaire in capturing supplement intake over the past 10 years has been documented previously (Satia-Abouta et al, 2003).

There are several limitations to this study. We did not measure serum retinol or carotenoid levels, although serum levels of these fat-soluble vitamins are tightly regulated. Also, this study did not ascertain detailed information on some known melanoma risk factors such as number of nevi, so there is the possibility of residual confounding. We could not define the degree of potential residual confounding, interaction and variations of effect according to these unmeasured variables, such as nevus categories. Furthermore, the lack of a clear dose-response relationship with regard to retinol supplement use perhaps suggests that there may be a threshold for the effect of supplemental retinol, which we were underpowered to further explore. Alternatively, high-dose retinol users may have practiced other health-care behaviors that impacted melanoma risk, which were unmeasured, such as sun-protective behaviors, that could have potentially confounded our results. Finally, although cohort studies are not generally affected by selection bias (because cohort members cannot self-select based on both exposure and future outcome), it is possible that the recruited cohort had certain characteristics, such as high level of education, that may limit the ability to generalize our findings.

In summary, our data, which are based on a large prospective cohort, suggest that retinol intake from individual supplements is associated with a reduction in risk of melanoma, especially among women. Our findings suggest that vitamin A supplementation may hold promise as a chemopreventative agent for melanoma.

MATERIALS AND METHODS

Study Population

Men and women, aged 50 to 76 years at baseline, who lived in the 13-country region of western Washington State covered by the Surveillance, Epidemiology, and End Results (SEER) cancer registry, were eligible to participate. Using names purchased from a commercial mailing list, a baseline 24-page self-administered questionnaire about lifestyle factors, health history, dietary intake, supplement use, personal characteristics, and cancer risk factors were mailed to 364,418 individuals between October 2000 and December 2002. Of these, 77,719 were returned and deemed eligible. Further details regarding study design, recruitment, and study implementation have been published previously (White et al, 2004). This study was approved by the Fred Hutchinson Cancer Research Center Institutional Review Board. The Declaration of Helsinki protocols were followed and subjects gave their written, informed consent.

Participants were excluded if they reported a positive or missing history of melanoma diagnosis at baseline (n=1,558); were of nonwhite race or did not report their race (n=6,489); or for whom a post-baseline diagnosis of melanoma was available only from the death certificate (n=2) without a date of diagnosis. Additional exclusions were made for

participants who were missing baseline information on supplement use (n=35), leaving 69,635 participants available for study.

Supplement Use

Participants reported intake of multivitamins and individual vitamin supplements over the 10 years prior to baseline. For all supplement questions, a close-ended format was used to inquire about current/past use, frequency, duration over the previous 10 years, and usual dose per day for individual supplements and brand or exact nutrient formulation for multivitamins. Current dose (μg/day) of retinol and β-carotene was computed as: Σ(dose per day) × (days per week/7), summed over multivitamin and individual supplement sources. Total vitamin A from supplements was computed in Retinol Activity Equivalents/day (RAE) in which 1 RAE = 1 μg all-trans-retinol. Total supplemental vitamin A in RAE was computed as current dose (μg/day) from retinol + 0.5 × current dose (μg/day) from β-carotene. Current doses of supplemental retinol, β-carotene, and total vitamin A were categorized into non-use, any dose less than or equal to the dose that could be ascertained from daily use of the most commonly taken multivitamin supplement in the cohort (Centrum Silver; Wyeth, Madison, NJ), and doses greater than that could be ascertained from daily use of common formulations of multivitamins alone (retinol: >1,200 μg/d; β-carotene: >600 μg/d; vitamin A: >1,500 RAE/d). Other pro-vitamin A carotenoids were not included because they are not sold in individual supplement form.

Diet and other covariates

Diet over the last year was assessed by a food frequency questionnaire (FFQ) that was an adaptation of FFQs developed for the Women's Health Initiative and other studies (Kristal 1997, Patterson 1999). The FFQ captured intakes of 120 food and beverage items and included adjustment questions on types of foods and preparation techniques. The FFQ analytic program is based on nutrient values from the Minnesota Nutrient Data System. We categorized retinol (μg/d), β-carotene (μg/d), and total vitamin A (RAE/d) from diet and from total intake (diet plus supplements) into quartiles. RAE from food was computed as the sum of (μg/d retinol) + (μg/d β-carotene / 12) + (μg/d other pro-vitamin A carotenoids / 24) (Dietary Reference Intake, 2002). Total lutein intake was calculated as the sum of dietary lutein + zeaxanthin.

The remaining parts of the questionnaire ascertained participants' demographic characteristics, health history, social history (including tobacco and alcohol use), medication use, and cancer risk factors. From these data we calculated body mass index (BMI; kg/m^2). Common melanoma risk factors were also ascertained, including freckles and hair color during ages 10–20 years, sun sensitivity, history of sunburns, family history of melanoma, personal history of non-melanoma skin cancer, and mole removal.

Melanoma Ascertainment

Cohort members were followed for incident melanoma diagnoses from baseline to December 31, 2007. Melanomas were identified though annual linkage of the VITAL cohort database to the western Washington SEER cancer registry, which is maintained by the Fred Hutchinson Cancer Research Center. All incident cancer cases, except non-melanoma skin

cancer, diagnosed within the 13-county area of western Washington State are reported to SEER along with stage, histology, and other tumor characteristics. Between baseline and December 2007, 566 incident cases of melanoma were diagnosed among eligible participants. These included 257 cases of melanoma in-situ, and 309 cases of invasive melanoma.

We ascertained histopathologic subtype as well as anatomic location of the melanomas from the SEER database. The anatomic melanoma location was derived from the SEER ICD-O topography codes to create summary location variables as follows: 1) Skin of the head, neck, and face (including skin of the lip and external ear) (ICD-O 44.0 to 44.4): n=154; 2) Skin of the trunk (ICD-O 44.5): n=164; and 3) Skin of the upper and lower limbs (ICD-O 44.6 to 44.7):n=228. Melanomas arising from the eye, nasal cavity, and unspecified areas (i.e., skin NOS) were excluded.

Follow-up for Censoring

Excluding the 0.8% of the cohort with incident melanoma diagnoses, the remaining participants were right-censored from the analysis at the earliest date of the following events: withdrawal from the study (0.03%); death (5.7%); emigration from the 13 county SEER catchment area (5.5%); or the end of follow-up on December 31, 2007 (88.7%). Deaths occurring in the cohort in Washington State were ascertained by linkage of the VITAL cohort database to the Washington State death file. Emigrations out of the SEER catchment area were identified by linkage to the National Change of Address System and by active follow-up by telephone calls and mailings.

Statistical Analysis

Cox proportional hazards models were used to estimate multivariable-adjusted hazard ratios (HR) and 95% CI for retinol and carotenoid intake and melanoma risk. Age was treated as the time variable with participants entering regression models at their baseline age and exiting at their age at melanoma diagnosis or censor date. All reported *P* values are two-sided. *P* values for trend (*P* trend) were calculated by treating categorical exposures as ordinal in proportional hazards models. We tested the proportionality assumption of regression models, no model violated the assumption.

We selected *a priori* potential confounders including known or suspected melanoma risk factors. Multivariable models were adjusted for age at baseline (years), gender (female, male), education (high school or less, some college, advanced degree), body mass index (kg/m^2: <25.0, 25.0–29.9, ≥30.0), alcohol consumption (drinks/day: 0, <1, 1–1.9, ≥2), 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). Analyses of micronutrients from diet or supplements plus diet were additionally adjusted for energy intake (kcal/day, quartiles). Because vitamin A, lutein, and lycopene supplements are marketed for eye health, all models were additionally adjusted for history of macular degeneration.

In order to assess whether differences in etiology exist in the association between vitamin A exposures and melanoma risk, we stratified models on gender, tumor invasiveness (in situ vs. invasive), and Breslow depth (available for n=272 invasive cases, <0.75 mm vs. ≥0.75mm) as a proxy for tumor progression. All statistical analyses were performed using SAS, version 9.1, (SAS Institute Inc., Cary, NC).

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Abbreviations

VITAL	VITamins and Lifestyle
SEER	Surveillance, Epidemiology, and End Results
RR	relative risks
HR	Hazard ratio
CI	95% confidence intervals

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Table 1

Associations between baseline characteristics and melanoma risk among VITAL participants, (n = 69,635)

Characteristic	Cases (n = 566), n (%)	Non-Cases (n = 69,069), n (%)	Age & Gender-Adjusted HR (95% CI)[1]
Demographics			
Age at baseline (years)			
50.0–54.9	102 (18.0)	15,990 (23.2)	N/A
55.0–59.9	104 (18.4)	15,724 (22.8)	
60.0–64.9	103 (18.2)	12,589 (18.2)	
65.0–69.9	107 (18.9)	11,392 (16.5)	
70.0–76.0	150 (26.5)	13,374 (19.4)	
Gender[2]			
Female	212 (37.5)	35,884 (52.0)	1.00 (reference)
Male	354 (62.5)	33,185 (48.1)	1.82 (1.54–2.16)
Education			
≤High School Graduate	79 (14.0)	13,932 (20.2)	1.00 (reference)
Some College	179 (31.7)	26,348 (38.2)	1.29 (0.99–1.68)
College or Advanced Degree	307 (54.3)	28,624 (41.5)	1.93 (1.50–2.49)
P-trend			<0.0001
Personal Characteristics			
Body mass index (kg/m^2)			
<25.0	204 (36.9)	22,817 (34.3)	1.00 (reference)
25.0–29.9	255 (46.1)	27,400 (41.1)	0.94 (0.78–1.13)
≥30.0	94 (17.0)	16,406 (24.6)	0.65 (0.41–0.83)
P-trend			<0.01
Alcohol (drinks/day)			
0	127 (22.6)	19,276 (28.3)	1.00 (reference)
<1	268 (47.8)	32,496 (47.8)	1.19 (0.96–1.48)
1–1.9	85 (15.2)	8,419 (12.4)	1.33 (1.01–1.76)
≥2	81 (14.4)	7,866 (11.6)	1.28 (0.97–1.70)
P-trend			0.05
Energy intake (kcal/day)			
0–1,287.7	109 (20.7)	15,961 (25.0)	1.00 (reference)
1,287.8–1,728.6	126 (23.9)	15,942 (25.0)	1.04 (0.81–1.35)
1,728.7–2,293.7	139 (26.4)	15,932 (25.0)	1.01 (0.78–1.32)
≥2,293.8	153 (29.0)	15,917 (25.0)	1.00 (0.76–1.31)
P-trend			0.89
Freckles between ages 10 and 20 years			
No	369 (65.9)	54,065 (79.0)	1.00 (reference)
Yes	191 (34.1)	14,383 (21.0)	2.15 (1.80–2.56)
Had ≥3 severe sunburns between ages 10 and 20 years			
No	312 (55.7)	45,669 (66.9)	1.00 (reference)

Characteristic	Cases (*n* = 566), *n* (%)	Non-Cases (*n* = 69,069), *n* (%)	Age & Gender-Adjusted HR (95% CI)[1]
Yes	248 (44.3)	22,553 (33.1)	1.67 (1.41–1.97)
Natural red or blond hair between ages 10 and 20 years			
No	310 (55.1)	46,498 (67.9)	1.00 (reference)
Yes	253 (44.9)	22,026 (32.1)	1.78 (1.50–2.10)
Reaction to 1 hour in strong sunlight			
Tan/No Sunburn	37 (6.7)	8,345 (12.6)	1.00 (reference)
Mild Sunburn then Tan	241 (43.5)	32,084 (48.4)	1.75 (1.24–2.47)
Painful Sunburn with Peeling	228 (41.2)	21,044 (31.8)	2.64 (1.86–3.74)
Severe Sunburn with Blisters	48 (8.7)	4,815 (7.3)	2.54 (1.65–3.90)
P-trend			<0.0001
Multivitamin Use			
Never	183 (32.3)	23,673 (34.3)	1.00 (reference)
Past	41 (7.2)	5,213 (7.6)	1.15 (0.82–1.61)
Current	342 (60.4)	40,173 (58.2)	1.16 (0.97–1.39)
Medical History			
Number of 1st Degree Relatives with Melanoma			
None	515 (92.0)	63,991 (93.9)	1.00 (reference)
1	41 (7.3)	3,860 (5.7)	1.43 (1.04–1.96)
≥2	4 (0.7)	324 (0.5)	1.73 (0.65–4.62)
P-trend			0.02
History of Non-Melanoma Skin Cancer			
No	456 (80.6)	63,836 (92.4)	1.00 (reference)
Yes	110 (19.4)	5,233 (7.6)	2.62 (2.12–3.23)
Had Mole Removed			
No	327 (57.8)	50,734 (73.5)	1.00 (reference)
Yes	239 (42.2)	18,335 (26.6)	2.09 (1.76–2.46)
Macular Degeneration			
No	559 (98.8)	67,934 (98.4)	1.00 (reference)
Yes	7 (1.2)	1,120 (1.6)	0.67 (0.32–1.42)

[1] HR, Hazards Ratio; CI, Confidence Interval

[2] Adjusted for age

Table 2

Associations between retinol and carotenoid intakes and melanoma risk among VITAL participants (*n* = 69,635)

Carotenoid	Cases (*n* = 566), *n* (%)	Non-Cases (*n* = 69,069), *n* (%)	Age & Gender-Adjusted HR (95% CI)	Multivariable-Adjusted HR (95% CI)[1]
Retinol				
Individual supplement use				
Non-User	506 (91.34)	59,557 (87.60)	1.00 (reference)	1.00 (reference)
Former	20 (3.61)	2,655 (3.91)	0.97 (0.62–1.52)	0.90 (0.57–1.43)
Current	28 (5.05)	5,776 (8.50)	0.58 (0.40–0.85)	0.60 (0.41–0.89)
Supplement dose[2]				
Non-User	213 (38.45)	27,434 (40.35)	1.00 (reference)	1.00 (reference)
19.3–1,200 μg/d	279 (50.36)	30,303 (44.57)	1.22 (1.02–1.46)	1.13 (0.93–1.36)
>1,200 μg/d[d]	62 (11.19)	10,246 (15.07)	0.82 (0.62–1.09)	0.74 (0.55–1.00)
P-trend			0.78	0.28
Diet[3]				
≤280.5 μg/d	119 (22.58)	15,951 (25.02)	1.00 (reference)	1.00 (reference)
280.6–424.7 μg/d	118 (22.39)	15,951 (25.02)	0.90 (0.70–1.17)	0.89 (0.68–1.18)
424.8–638.4 μg/d	169 (32.07)	15,902 (24.94)	1.20 (0.94–1.52)	1.24 (0.94–1.63)
>638.4 μg/d	121 (22.96)	15,948 (25.02)	0.81 (0.62–1.05)	0.85 (0.62–1.16)
P-trend			0.42	0.72
Total[2,3]				
≤514.2 μg/d	126 (24.42)	15,694 (25.00)	1.00 (reference)	1.00 (reference)
514.3–1,324.3 μg/d	127 (24.61)	15,693 (25.00)	0.96 (0.75–1.23)	1.00 (0.77–1.30)
1,324.3–1,771.4 μg/d	147 (28.49)	15,673 (24.97)	1.13 (0.89–1.44)	1.10 (0.86–1.42)
>1,771.4 μg/d	116 (22.48)	15,704 (25.02)	0.85 (0.66–1.10)	0.84 (0.64–1.10)
P-trend			0.46	0.33
β-Carotene				
Individual supplement use				
Non-User	502 (90.29)	61,478 (90.04)	1.00 (reference)	1.00 (reference)
Former	24 (4.32)	3,256 (4.77)	0.95 (0.63–1.43)	0.87 (0.57–1.32)
Current	30 (5.40)	3,546 (5.19)	1.03 (0.72–1.49)	0.95 (0.64–1.40)
Supplement dose[2]				
Non-User	237 (42.63)	31,802 (46.58)	1.00 (reference)	1.00 (reference)
6.4–600 μg/d	200 (35.97)	22,933 (33.59)	1.20 (0.99–1.44)	1.16 (0.95–1.41)
>600 μg/d[d]	119 (21.40)	13,542 (19.83)	1.19 (0.95–1.48)	1.08 (0.86–1.36)
P-trend			0.08	0.36
Diet[3]				
≤2,138.8 μg/d	103 (19.54)	15,967 (25.05)	1.00 (reference)	1.00 (reference)
2,138.9–3,504.9 μg/d	136 (25.81)	15,933 (24.99)	1.22 (0.95–1.58)	1.15 (0.87–1.51)
3,505–5,648.5 μg/d	137 (26.00)	15,934 (24.99)	1.16 (0.90–1.50)	1.07 (0.81–1.42)

Carotenoid	Cases (n = 566), n (%)	Non-Cases (n = 69,069), n (%)	Age & Gender-Adjusted HR (95% CI)	Multivariable-Adjusted HR (95% CI)[1]
>5,648.5 μg/d	151 (28.65)	15,918 (24.97)	1.25 (0.97–1.61)	1.15 (0.87–1.53)
P-trend			0.15	0.46
Total[2,3]				
≤3,515.0 μg/d	101 (19.46)	15,277 (24.23)	1.00 (reference)	1.00 (reference)
3,515.1–6,117.7 μg/d	134 (25.82)	16,276 (25.81)	1.19 (0.92–1.54)	1.17 (0.89–1.53)
6,117.8–9,358.2 μg/d	144 (27.75)	15,750 (24.98)	1.27 (0.98–1.64)	1.16 (0.89–1.53)
>9,358.2 μg/d	140 (26.97)	15,754 (24.98)	1.22 (0.94–1.57)	1.13 (0.86–1.49)
P-trend			0.13	0.47
Total Vitamin A				
Supplement dose[2]				
Non-User	211 (38.22)	26,934 (39.82)	1.00 (reference)	1.00 (reference)
19.3–1,500 RAE/d	273 (49.46)	31,387 (46.41)	1.15 (0.96–1.37)	1.06 (0.88–1.28)
>1,500 RAE /d[4]	68 (12.32)	9,310 (13.77)	0.97 (0.74–1.28)	0.88 (0.66–1.18)
P-trend			0.69	0.66
Diet[3]				
≤574.4 RAE/d	105 (19.92)	15,965 (25.04)	1.00 (reference)	1.00 (reference)
574.5–822.3 RAE/d	140 (26.57)	15,930 (24.99)	1.22 (0.94–1.57)	1.25 (0.94–1.65)
822.4–1,176.6 RAE/d	135 (25.62)	15,935 (25.00)	1.09 (0.84–1.41)	1.07 (0.79–1.45)
>1,176.6 RAE/d	147 (27.89)	15,922 (24.97)	1.12 (0.87–1.46)	1.16 (0.84–1.59)
P-trend			0.64	0.67
Total[2,3]				
≤992.3 RAE/d	125 (24.27)	15,621 (25.01)	1.00 (reference)	1.00 (reference)
992.4–1,984.4 RAE/d	114 (22.14)	15,632 (25.02)	0.88 (0.68–1.13)	0.91 (0.70–1.19)
1,984.5–2,679.6 RAE/d	151 (29.32)	15,595 (24.96)	1.16 (0.91–1.47)	1.10 (0.85–1.41)
>2,679.6 RAE/d	125 (24.27)	15,621 (25.01)	0.92 (0.72–1.18)	0.87 (0.66–1.13)
P-trend			0.94	0.60
Lutein				
Individual supplement use				
Non-User	557 (98.58)	67,399 (97.69)	1.00 (reference)	1.00 (reference)
User	8 (1.42)	1,595 (2.31)	0.64 (0.32–1.28)	0.58 (0.27–1.23)
Diet (lutein + zeaxanthin)[3]				
≤1,449.2 μg/d	94 (17.8)	15,975 (25.1)	1.00 (reference)	1.00 (reference)
1,449.3–2,295.8 μg/d	123 (23.3)	15,948 (25.0)	1.20 (0.91–1.57)	1.07 (0.80–1.42)
2,295.9–3,683.8 μg/d	149 (28.3)	15,920 (25.0)	1.35 (1.04–1.75)	1.25 (0.94–1.66)
>3,683.8 μg/d	161 (30.6)	15,909 (25.0)	1.41 (1.09–1.83)	1.27 (0.95–1.70)
P-trend			<0.01	0.07
Lycopene				
Individual supplement use				
Non-User	563 (99.47)	68,585 (99.36)	1.00 (reference)	1.00 (reference)
User	3 (0.53)	442 (0.64)	0.76 (0.25–2.37)	0.76 (0.24–2.37)

Carotenoid	Cases (*n* = 566), *n* (%)	Non-Cases (*n* = 69,069), *n* (%)	Age & Gender-Adjusted HR (95% CI)	Multivariable-Adjusted HR (95% CI)[1]
Diet[c]				
≤3,163.6 μg/d	113 (21.4)	15,957 (25.0)	1.00 (reference)	1.00 (reference)
3,163.7–5,257.6 μg/d	126 (23.9)	15,944 (25.0)	1.07 (0.83–1.38)	1.01 (0.77–1.33)
5,257.7–8,680.9 μg/d	135 (25.6)	15,934 (25.0)	1.06 (0.82–1.37)	1.07 (0.81–1.42)
>8,680.9 μg/d	153 (29.0)	15,917 (25.0)	1.13 (0.87–1.46)	1.15 (0.86–1.53)
P-trend			0.38	0.31

Abbreviations: CI, Confidence Interval; HR, Hazard Ratio; RAE, Retinol Activity Equivalents (1 RAE=1 μg all-trans-retinol)

[1] Adjusted for age, gender, education, body mass index, alcohol, freckles between the ages of 10 and 20 years, ≥3 severe sunburns between the ages of 10 and 20 years, red or blond hair between the ages of 10 and 20 years, reaction to 1 hour in strong sunlight, family history of melanoma, history of non-melanoma skin cancer, mole removed, and macular degeneration

[2] Includes multivitamin sources

[3] Multivariable models additionally adjusted for energy intake

[4] Greater than amount of that nutrient that could be obtained from daily use of one pill of the multivitamin Centrum Silver (Wyeth, Madison, NJ)

Table 3

Interaction between retinol supplement use and gender in relation to melanoma risk among VITAL participants, (*n* = 69,635)

	Males			Females		
Supplement	**Cases (*n* = 354), *n* (%)**	**Non-Cases (*n* = 33,185), *n* (%)**	**HR (95% CI)[a]**	**Cases (*n* = 212), *n* (%)**	**Non-Cases (*n* = 35,884), *n* (%)**	**HR (95% CI)[1]**
Retinol						
Individual supplement use						
Non-User	318 (90.86)	29,249 (89.29)	1.00 (reference)	188 (92.16)	30,308 (86.03)	1.00 (reference)
Former	10 (2.86)	1,014 (3.10)	0.79 (0.41–1.53)	10 (4.90)	1,641 (4.55)	1.02 (0.54–1.94)
Current	22 (6.29)	2,494 (7.61)	0.83 (0.54–1.27)	6 (2.94)	3,282 (9.32)	0.27 (0.11–0.66)
Supplement dose[2]						
Non-User	143 (40.86)	14,855 (45.36)	1.00 (reference)	70 (34.31)	12,579 (35.70)	1.00 (reference)
19.3–1,200 μg/d	171 (48.86)	13,480 (41.16)	1.17 (0.93–1.48)	108 (52.94)	16,823 (47.75)	1.05 (0.76–1.44)
>1,200 μg/d[3]	36 (10.29)	4,417 (13.49)	0.77 (0.53–1.12)	26 (12.75)	5,829 (16.55)	0.71 (0.43–1.16)
P-trend			0.60			0.29

Abbreviations: CI, Confidence Interval; HR, Hazard Ratio; RAE, Retinol Activity Equivalents (1 RAE=1 μg all-trans-retinol)

[1] Adjusted for age, education, body mass index, alcohol, freckles between the ages of 10 and 20 years, ≥3 severe sunburns between the ages of 10 and 20 years, red or blond hair between the ages of 10 and 20 years, reaction to 1 hour in strong sunlight, family history of melanoma, history of non-melanoma skin cancer, mole removed, and macular degeneration

[2] Includes multivitamin sources

[3] Greater than amount of that nutrient that could be obtained from daily use of one pill of the multivitamin Centrum Silver (Wyeth, Madison, NJ)

Table 4

Association of retinol supplement use with melanoma by anatomic site, among VITAL participants, (*n* = 69,635).

	Cases *n* (%)	HR (95% CI)[a]
Head (*n* = 154)		
Supplement use		
Non-User	141 (94.00)	1.00 (reference)
Former	3 (2.00)	0.54 (0.17–1.71)
Current	6 (4.00)	0.49 (0.21–1.10)
Supplement dose[b]		
Non-User	55 (36.67)	1.00 (reference)
19.3–1200 μg/d	80 (53.33)	1.25 (0.88–1.79)
>1,200 μg/d[c]	15 (10.00)	0.78 (0.44–1.39)
P-trend		0.85
Trunk (*n* = 164)		
Supplement use		
Non-User	143 (88.82)	1.00 (reference)
Former	6 (3.73)	1.03 (0.45–2.33)
Current	12 (7.45)	0.94 (0.52–1.70)
Supplement dose[b]		
Non-User	69 (42.86)	1.00 (reference)
19.3–1200 μg/d	74 (45.96)	1.01 (0.72–1.41)
>1,200 μg/d[c]	18 (11.18)	0.73 (0.43–1.25)
P-trend		0.36
Limbs (*n* = 228)		
Supplement use		
Non-User	205 (91.93)	1.00 (reference)
Former	10 (4.48)	1.01 (0.51–1.97)
Current	8 (3.59)	0.44 (0.22–0.89)
Supplement dose[b]		
Non-User	82 (36.77)	1.00 (reference)
19.3–1200 μg/d	116 (52.02)	1.18 (0.87–1.59)
>1,200 μg/d[c]	25 (11.21)	0.71 (0.44–1.16)
P-trend		0.47

Abbreviations: CI, Confidence Interval; HR, Hazard Ratio

[a] Adjusted for age, gender, education, body mass index, alcohol, freckles between the ages of 10 and 20 years, ≥3 severe sunburns between the ages of 10 and 20 years, red or blond hair between the ages of 10 and 20 years, reaction to 1 hour in strong sunlight, family history of melanoma, history of non-melanoma skin cancer, mole removed, and macular degeneration

[b] Includes multivitamin sources

[c] Greater than amount of that nutrient that could be obtained from daily use of one pill of the multivitamin Centrum Silver (Wyeth, Madison, NJ)

Table 5

Association of retinol supplement use with melanoma aggressiveness, among VITAL participants, (*n* = 69,635).

	In Situ		**Invasive**	
	Cases (*n* = 257), *n* (%)	**HR (95% CI)[a]**	**Cases (*n* = 309), *n* (%)**	**HR (95% CI)[1]**
Supplement use				
Non-User	230 (92.00)	1.00 (reference)	276 (90.79)	1.00 (reference)
Former	8 (3.20)	0.81 (0.40–1.65)	12 (4.00)	0.99 (0.54–1.80)
Current	12 (4.80)	0.57 (0.32–1.02)	16 (5.26)	0.63 (0.37–1.06)
Supplement dose[2]				
Non-User	103 (41.20)	1.00 (reference)	110 (36.18)	1.00 (reference)
19.3–1200 μg/d	121 (48.40)	1.00 (0.76–1.31)	158 (51.97)	1.25 (0.97–1.62)
>1,200 μg/d[3]	26 (10.40)	0.66 (0.42–1.02)	36 (11.84)	0.83 (0.55–1.25)
P-trend		0.13		0.94
	Breslow Depth <1.0mm		**Breslow Depth ≥1.0mm**	
	Invasive Cases (*n* = 162), *n* (%)	**HR (95% CI)[a]**		**Invasive Cases (*n* = 162), *n* (%)**
Supplement use			*Supplement use*	
Non-User	166 (89.73)	1.00 (reference)	Non-User	166 (89.73)
Former	9 (4.86)	1.14 (0.56–2.32)	Former	9 (4.86)
Current	10 (5.41)	0.68 (0.36–1.29)	Current	10 (5.41)
Supplement dose[b]			*Supplement dose*[b]	
Non-User	64 (34.59)	1.00 (reference)	Non-User	64 (34.59)
19.3–1200 μg/d	101 (54.59)	1.44 (1.04–2.00)	19.3–1200 μg/d	101 (54.59)
>1,200 μg/d[c]	20 (10.81)	0.83 (0.49–1.41)	>1,200 μg/d[c]	20 (10.81)
P-trend		0.77	*P*-trend	

Abbreviations: CI, Confidence Interval; HR, Hazard Ratio

[1] Adjusted for age, gender, education, body mass index, alcohol, freckles between the ages of 10 and 20 years, ≥3 severe sunburns between the ages of 10 and 20 years, red or blond hair between the ages of 10 and 20 years, reaction to 1 hour in strong sunlight, family history of melanoma, history of non-melanoma skin cancer, mole removed, and macular degeneration

[2] Includes multivitamin sources

[3] Greater than amount of that nutrient that could be obtained from daily use of one pill of the multivitamin Centrum Silver (Wyeth, Madison, NJ)