Diet and Melanoma in a Case-Control Study

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Abstract

Background: Malignant melanoma has been one of the most rapidly increasing cancers within the United States with few modifiable risk factors. This study investigates risk related to dietary factors, which are potentially modifiable. Methods: Newly diagnosed patients with melanoma (n = 502) were recruited from pigment lesion clinics and controls (n = 565) were recruited from outpatient clinics. To investigate the relationship between melanoma and dietary factors in this case-control study, study subjects were requested to complete a food frequency questionnaire, which assessed diet over the previous year. Using logistic regression, odds ratios (ORs) for melanoma were computed for nutrient and alcohol intake. Results: Persons in high versus low quintiles of energy-adjusted vitamin D, α-carotene, β-carotene, cryptoxanthin, lutein, and lycopene had significantly reduced risk for melanoma (ORs ≤ 0.67), which remained after adjustment for presence of dysplastic nevi, education, and skin response to repeated sun exposure. Addition of micronutrients from supplements did not add an additional reduction in risk. High alcohol consumption was associated with an increased risk for melanoma, which remained after adjustment for confounders [OR (95% confidence interval) in highest versus lowest quintiles, 1.65 (1.09-2.49)]. Conclusions: Diets consisting of foods rich in vitamin D and carotenoids and low in alcohol may be associated with a reduction in risk for melanoma. These analyses should be repeated in large, prospective studies. (Cancer Epidemiol Biomarkers Prev 2004;13(6):1042–51)

Introduction

Malignant melanoma has been one of the most rapidly increasing cancers in the United States, with an estimated annual percentage increase in incidence of 3% from 1975 to 2000 (1). For this reason, it was termed an ''epidemic cancer'' and a major public health concern (2). It was estimated that, in 2003, 54,200 persons would be diagnosed with melanoma and 7,600 persons would die from this disease (3).

Increased risk for melanoma is associated with the presence of several known host risk factors such as light complexions and skin reactivity to sun exposure (burning versus tanning; ref. 4). Other host risk factors include presence of dysplastic nevi, prior history of cancer, family history of melanoma, and immunosuppression (5). Other than sun exposure, there are few known exposures that increase the risk for melanoma (5-8). Diet has been hypothesized to be a possible modifiable risk factor for melanoma, and previous research suggests that certain nutrients may protect against development of melanoma, whereas other nutrients may promote its development (9-22). Therefore, further investigation of dietary factors may ultimately provide a means to alter risk for susceptible individuals as well as provide information on biological mechanisms of the disease process.

Intake of carotenoids and vitamins C, E, D, and A are hypothesized to reduce risk of developing melanoma. Carotenoids, vitamin C, and vitamin E, because of their photoprotective and antioxidant properties, are hypothesized to protect against the photooxidative damaging effects of solar radiation on skin (9-12). Some human supplementation trials have shown that intake of these antioxidants suppresses the sunburn reaction/light–induced erythema of human skin (13-16). Vitamins D and A, the receptors of which are found in human malignant melanoma cancer cell lines (17, 18), are thought to prevent proliferation of malignant melanoma cells or promote their differentiation and apoptosis, as supported by studies in human melanoma cells (17-22).

Linoleic acid and alcohol are hypothesized to promote development of melanoma (23, 24). Intake of linoleic acid has been shown to increase the linoleic acid content of human epidermal membranes (25) and the biosynthesis of prostaglandins throughout the body (26), thus possibly intensifying the prostaglandin-induced erythema of skin after sun exposure (27). Additionally, increased consumption of alcohol has been hypothesized to increase risk for melanoma (24), although the exact mechanism through which alcohol may act remains speculative.

The purpose of this study was to investigate the relationship between intake of selected nutrients and risk for melanoma in a case-control study. We hypothesized that intake of carotenoids and vitamins C, E, D, and A would be associated with a decreased risk for

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melanoma and that intake of linoleic acid and alcohol would be associated with an increased risk of this skin cancer. Exploratory analyses of the relationship between melanoma and other nutrients were also conducted. This study provided the opportunity to investigate the relationship between diet and risk for melanoma, in men and women, in one of the largest case-control studies of melanoma containing dietary data and highly specific sun exposure and skin damage variables.

Materials and Methods

Participants. As described previously (28), individuals ages 20 to 79 with newly diagnosed, histologically confirmed invasive cutaneous melanoma were recruited between January 1, 1991 and December 31, 1992 at the Pigmented Lesion Clinic of the Hospital of the University of Pennsylvania in Philadelphia and the Melanoma Clinic of the University of California in San Francisco. Of the 768 eligible cases, 738 (96%) agreed to participate. Controls were from outpatient clinics with catchment areas similar to the melanoma clinics. A stratified random sampling scheme was used to enroll control patients of the same gender, age, race, and geographic distribution as the cases. Of the 1,228 randomly selected controls, 1,030 (84%) agreed to participate. Any potential control with dermatologic or psychiatric reason for clinic visit was excluded. The majority of participants (99%) were white.

Data Collection. After obtaining informed consent, study staff interviewed participants at the clinics (6, 28**).** Participants were queried regarding their history of sun exposure, occupation, residence, personal medical history, and family history of melanoma and other cancers. All cases and controls underwent full skin examination for phenotyping. Counts of nevi that were >2 mm or dysplastic were recorded. Expert senior examiners confirmed dysplastic nevi status for each study participant (29).

Variable Definitions. A value of either absent, mild, moderate, or extensive was assigned for degree of freckling on four body areas (face, arms/hands/legs, upper back, and lower back) and summed for an overall score from 0 to 12. Based on this scale, ''freckles'' was created by grouping subjects according to score, either none to few or moderate to many. ''Skin response after repeated sun exposure'' consisted of tanning response (deep, moderate, light, or no tanning), and ''blistering sunburn at any age'' was defined as either yes or no. Two categories were created for ''dysplastic nevi'' (none and ''≥ 1'') based on the total number of dysplastic nevi over the entire body minus the scalp, pubic region, and perineum (28). Persons with no or indeterminate dysplastic nevi were categorized as ''none.'' Persons with histologic evidence but no clinical evidence of dysplastic nevi and those with one or more clinically verified dysplastic nevi were categorized as ''≥ 1'' (28).

Dietary Data. A reduced, 60-item version of the Block Food Frequency Questionnaire (FFQ), described elsewhere and validated previously (30), was used to assess usual dietary intake over the previous year. Participants were given the FFQ at the clinic to complete. If they did not complete the FFQ at the clinic, they were asked to mail back the completed questionnaire. Follow-up telephone calls were conducted if the FFQ was not returned within 1 week. Cases diagnosed with melanoma between January 1, 1991 and June 30, 1992 and controls enrolled between the same dates were considered eligible for the dietary study. Participants were told that they would receive a dietary assessment report from the FFQ as an incentive to finish the questionnaire. DIETSYS analysis software (version 4.01, ''NCI Dietary Analysis System'') was used to compute usual daily intake estimates from questionnaire responses (31**).** All nutrient estimates from foods, except for vitamin D, were based on the dietary composition database developed for the DIETSYS analysis software. Estimates of the vitamin D content of foods were based on a provisional table from the U.S. Department of Agriculture (32).

Additionally, the FFQ queried vitamins and mineral supplement usage in the past year. Participants who reported use of supplements were asked about the number of tablets and frequency of use of multivitamins; vitamins A, C, and E; and calcium/dolomite. If a participant reported use of a multivitamin, vitamin A, or vitamin E, they were assigned standard doses for specific nutrients contained in the multivitamin, a standard dose for single supplement vitamin A use, or a standard dose for single supplement vitamin E use, respectively. The standard doses for nutrients in the multivitamins and the standard dose values for single supplement vitamin A or E are stored in the DIETSYS Food Database (31). Participants who used calcium or vitamin C supplements were asked to report the milligrams of calcium or vitamin C per tablet that they consumed and were assigned that corresponding dose for vitamin C and calcium single supplement use.

There were 1,127 participants (532 cases and 595 controls) who provided dietary data out of 610 cases and 753 controls asked to fill out the FFQs. The response rate for interview and dietary components was 84% for cases and 66% for controls. Individuals who reported too few foods per day (males < 3, females < 2) on the FFQ ($n = 37$) were excluded from the analyses. Additional participants were excluded for the following missing data: skin exam or the main study questionnaire ($n = 23$), level of education ($n = 1$), and skin response after repeated/prolonged sun exposure ($n = 8$). This provided a final sample of 497 cases and 561 controls.

Statistical Analysis. Demographic and clinical characteristics among cases and controls were compared using χ^2 tests for categorical variables, directly standardized for age, and analysis of covariance for continuous variables, adjusted for age.

Nutrients and alcohol were energy adjusted using the nutrient density method to account for differences due to body size, metabolic efficiency, and activity level (33). Energy-adjusted nutrient intakes (from foods alone and from foods and supplements combined) and alcohol consumption (% kcal) were divided into quintile ranks based on the distribution of the control population. Additionally, food groups that were rich sources of our hypothesized nutrients were classified into four levels by inspection of the frequencies of intake with emphasis on creating levels of approximately equal size. Odds ratios (ORs) and 95% confidence intervals (95% CIs) for melanoma were calculated using logistic regression

models for each quintile of nutrient or alcohol intake or level of food group relative to the lowest quintile or food group level, respectively. ORs for key nutrients were tested for the influence of potential confounders including education, smoking status, freckles, blistering sunburn at any age, skin response after repeated sun exposure, family history of melanoma, body mass index (BMI), body surface area (BSA), and ''ever pregnant'' (among females). Exogenous estrogen exposure, as determined by use of oral contraceptives or hormone replacement therapy, was not a risk factor for melanoma in this data set. Final models were adjusted for age, sex, study site, presence of dysplastic nevi, education, and skin response to repeated sun exposure. Trend analyses using quintile medians were conducted for adjusted analyses.

Relationships of nutrient and alcohol intake were evaluated for interactions. The consistencies of the relationships of nutrient intake to melanoma were evaluated after stratification by hypothesized potential effect modifiers: gender, education, total calorie intake, BMI, BSA, smoking, and skin response to repeated sun exposure. A Wald χ^2 test $P < 0.05$ for the overall interaction term was considered significant.

All analyses were conducted using SAS version 8.2 software (SAS Institute, Inc., Cary, NC). All tests were two sided.

Results

Table 1 shows baseline characteristics of cases and controls. Cases were less educated, less likely to use supplements, more likely to have had a pregnancy, and more likely to have had a family history of melanoma compared with controls. Cases were also more likely than controls to have more freckles, to have had a blistering sunburn, to tan lightly or not at all, and to have a dysplastic nevi, blue/gray/green eyes, and reddish or blonde hair. Cases and controls did not differ in age, gender, study site, BMI, BSA, and smoking status.

Macronutrient Intake from Foods and Alcohol Consumption. Table 2 presents the ORs for risk for melanoma by level of total energy and by level of intake of macronutrients from foods and alcohol consumption. There was no association between melanoma and

Table 1. Age-adjusted means and age-standardized percentages of demographic and clinical characteristics among cases and controls (*n* = 1,058)

Characteristic	Cases (n = 497)	Controls (n = 561)	P value
Age, y, mean (SE)	50 (0.7)	50 (0.6)	0.55
Gender, % females	46	43	0.25
Study site, %			0.26
Philadelphia	50	53	
San Francisco	50	47	
BMI, kg/m^2, mean (SE)	25 (0.2)	25 (0.2)	0.15
BSA,* mean (SE)	1.9 (0.01)	1.9 (0.01)	0.17
Education, %			<0.0001
Before high school	26	16	
Post high school	29	25	
College graduate	45	59	
Current smoking status, %			0.81
Yes	14	14	
No	84	83	
Use vitamins in past year, %			0.005
No	32	23	
Yes, fairly regularly	33	33	
Yes, but not regularly	23	25	
Ever pregnant, % yes (among women)	85	74	0.001
Family history of melanoma, % any relative	8	4	0.005
Freckles, %			<0.0001
None to few	43	65	
Moderate to many	57	35	
Blistering sunburn at any age, % yes	77	66	<0.0001
Skin response after repeated/prolonged exposure, %			<0.0001
Deep tan	16	27	
Moderate tan	49	49	
Light tan	28	19	
Do not tan	7	4	
Confirmed dysplastic nevi status, grouped, %			<0.0001
None	51	89	
≥ 1	49	11	
Natural eye color, %			<0.0001
Blue/gray/green	79	66	
Brown	21	34	
Natural hair color, %			0.01
Red/blonde	27	19	
Brown/red-brown/black	73	81	

NOTE: Some percentages do not add up to 100% due to missing data.
*BSA calculated by $\sqrt{height(inches) * weight(pounds)/3131}$.

Table 2. ORs and 95% CIs for malignant melanoma among participants in quintiles 2 to 5 compared with quintile 1 of energy, macronutrients, and alcohol intake (n = 1,058)

Energy, macronutrient, alcohol (quintile range)	Cases	Controls	Crude OR*	Adjusted OR[c]	95% CI	P for trend[b]
Total calories (kcal)						
≤1,063	106	112	1.00	1.00	—	0.59
1,068-1,331	97	112	0.95	0.85	0.55-1.31	
1,333-1,647	99	113	0.97	0.97	0.63-1.49	
1,648-2,020	92	112	0.94	0.96	0.61-1.50	
≥ 2,021	103	112	1.06	1.07	0.68-1.69	
Carbohydrate (% kcal)						
≤39	116	111	1.00	1.00	—	0.006
39-44	121	113	1.04	0.99	0.65-1.49	
44-48	98	114	0.83	0.75	0.49-1.15	
48-53	97	111	0.83	0.78	0.51-1.19	
≥ 53	65	112	0.53[§]	0.55[§]	0.35-0.87	
Protein (% kcal)						
≤13	120	112	1.00	1.00	—	0.004
13-15	105	112	0.88	0.79	0.52-1.19	
15-16	85	113	0.71	0.62[§]	0.40-0.96	
16-19	111	112	0.94	0.76	0.50-1.16	
≥ 19	76	112	0.63[§]	0.50[§]	0.33-0.78	
Total fat (% kcal)						
≤28	83	112	1.00	1.00	—	0.06
28-33	85	112	1.07	1.03	0.66-1.63	
33-37	100	113	1.24	1.19	0.76-1.84	
37-41	108	112	1.36	1.20	0.77-1.86	
≥ 41	121	112	1.51[§]	1.47	0.95-2.27	
Saturated fat (% kcal)						
≤9	87	112	1.00	1.00	—	0.01
9-11	75	112	0.91	0.84	0.53-1.32	
11-12	85	113	1.02	0.85	0.54-1.33	
12-14	119	112	1.46	1.31	0.85-2.01	
≥ 14	131	112	1.62[§]	1.53	0.99-2.36	
Oleic acid (% kcal)						
≤10	88	112	1.00	1.00	—	0.28
10-12	87	112	1.01	0.96	0.62-1.50	
12-13	98	113	1.16	1.18	0.76-1.82	
13-15	117	112	1.39	1.28	0.83-1.96	
≥ 15	107	112	1.25	1.16	0.75-1.79	
Linoleic acid (% kcal)						
≤4	80	112	1.00	1.00	—	0.04
4-6	91	112	1.16	1.05	0.67-1.65	
6-7	87	113	1.09	1.04	0.67-1.64	
7-9	115	112	1.45	1.40	0.91-2.16	
≥ 9	124	112	1.56[§]	1.45	0.94-2.23	
Alcohol (% kcal)						
0	154	198	1.00	1.00	—	0.003
0.2-1	63	90	0.92	0.97	0.62-1.50	
1-4	76	91	1.12	1.16	0.76-1.77	
4-10	108	91	1.59[§]	1.86[§]	1.24-2.78	
≥ 10	96	91	1.41	1.65[§]	1.09-2.49	

*Crude OR adjusted for age, sex, and study site.
[c]Adjusted OR adjusted for age, sex, study site, confirmed dysplastic nevi status, education, and skin response after repeated/prolonged sun exposure.
[b]P for trend across quintile medians in the adjusted model.
[§]$P \leq 0.05$.

energy or oleic acid. In the crude model, there was a statistically significant decreased risk for melanoma for high compared with low intake of carbohydrate and protein and a statistically significant increased risk for intake of total fat, saturated fat, and linoleic acid. After adjustment for dysplastic nevi, education, and skin response to repeated sun exposure, the observed associations remained significant for carbohydrate and protein and the OR became stronger and statistically significant for increased risk for melanoma with high alcohol consumption. Further adjustment for total energy did not alter the significance or direction of the estimates.

Micronutrient Intake from Foods. Table 3 presents the ORs for risk for melanoma by level of intake of micronutrients from foods. We observed a statistically significant decreased risk for melanoma in high compared with low intake of the following micronutrients: vitamin C, vitamin D, retinol, α-carotene, β-carotene, cryptoxanthin, lutein, and lycopene. After adjustment for confounders, the ORs remained statistically significant for all micronutrients, except vitamin C. Further adjustment of these micronutrients for total energy did not alter the significance or direction of the estimates.

Supplement users may have been misclassified with regard to micronutrient intake from foods. Therefore, we

Table 3. ORs and 95% CIs for malignant melanoma among participants in quintiles 2 to 5 compared with quintile 1 of micronutrient intake (n = 1,058)

Micronutrient (quintile range)	Cases	Controls	Crude OR*	Adjusted OR[c]	95% CI	P for trend[b]
Micronutrients from foods						
Vitamin C (mg/1000 kcal)						
≤49	136	112	1.00	1.00	—	0.05
50-67	102	112	0.76	0.71	0.47-1.09	
67-89	90	113	0.65[§]	0.61[§]	0.40-0.94	
89-117	73	112	0.52[§]	0.54[§]	0.35-0.84	
≥ 117	96	112	0.67[§]	0.66	0.43-1.01	
Vitamin D (IU/1000 kcal)						
≤58	120	112	1.00	1.00	—	0.03
58-85	106	112	0.88	0.80	0.53-1.22	
85-115	94	113	0.78	0.70	0.46-1.07	
115-158	93	112	0.76	0.71	0.46-1.09	
≥ 158	84	112	0.67[§]	0.61[§]	0.40-0.95	
Vitamin E (mg α-Te[#]/1000 kcal)						
≤4	104	112	1.00	1.00	—	0.02
4-5	114	112	1.09	1.12	0.73-1.71	
5-6	115	113	1.05	1.06	0.69-1.62	
6-8	91	112	0.84	0.97	0.62-1.51	
≥ 8	73	112	0.68	0.64	0.41-1.01	
Retinol (μg/1000 kcal)						
≤223	111	112	1.00	1.00	—	0.13
224-289	95	112	0.85	0.82	0.54-1.27	
290-364	112	113	1.00	1.07	0.70-1.62	
364-481	106	112	0.93	1.06	0.69-1.62	
≥ 482	73	112	0.63[§]	0.63[§]	0.40-0.99	
α-Carotene (μg/1000 kcal)						
≤82	112	112	1.00	1.00	—	0.02
82-158	137	112	1.18	0.98	0.64-1.48	
158-257	82	113	0.70	0.64	0.41-1.00	
258-447	89	112	0.75	0.74	0.48-1.16	
≥ 452	77	112	0.64[§]	0.59[§]	0.38-0.94	
β-Carotene (μg/1000 kcal)						
≤942	151	112	1.00	1.00	—	<0.0001
947-1,383	101	112	0.64[§]	0.56[§]	0.37-0.85	
1,384-1,981	100	113	0.61[§]	0.54[§]	0.36-0.83	
1,986-3,041	87	112	0.53[§]	0.54[§]	0.35-0.83	
≥ 3,048	58	112	0.35[§]	0.36[§]	0.22-0.56	
Cryptoxanthin (μg/1000 kcal)						
≤13	123	112	1.00	1.00	—	0.05
13-27	99	112	0.80	0.75	0.49-1.15	
28-47	102	113	0.83	0.83	0.55-1.26	
47-77	101	112	0.82	0.81	0.53-1.23	
≥ 77	72	112	0.57[§]	0.60[§]	0.38-0.92	
Lutein (μg/1000 kcal)						
≤494	130	112	1.00	1.00	—	0.003
494-838	109	112	0.83	1.00	0.66-1.52	
840-1,297	98	113	0.73	0.82	0.54-1.26	
1,305-2,236	89	112	0.64[§]	0.68	0.44-1.05	
≥ 2,242	71	112	0.51[§]	0.56[§]	0.36-0.88	
Lycopene (μg/1000 kcal)						
≤448	103	112	1.00	1.00	—	0.005
450-785	126	112	1.22	1.13	0.75-1.71	
789-1,187	121	113	1.16	1.02	0.67-1.55	
1,197-1,705	82	112	0.77	0.82	0.53-1.27	
≥ 1,708	63	112	0.59[§]	0.58[§]	0.37-0.92	
Micronutrients from foods and supplements						
Vitamin C (mg/1000 kcal)						
≤55	133	112	1.00	1.00	—	0.65
55-80	91	112	0.69	0.70	0.46-1.07	
80-113	77	113	0.56[§]	0.55[§]	0.35-0.85	
113-206	90	112	0.65[§]	0.65	0.42-1.00	
≥ 210	106	112	0.76	0.83	0.55-1.26	
Vitamin D (IU/1000 kcal)						
≤63	115	112	1.00	1.00	—	0.04
63-99	115	112	0.99	1.03	0.68-1.56	
99-146	89	113	0.76	0.75	0.49-1.16	
147-261	96	112	0.82	0.82	0.54-1.26	
≥ 262	82	112	0.69	0.66	0.42-1.02	

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Table 3. ORs and 95% CIs for malignant melanoma among participants in quintiles 2 to 5 compared with quintile 1 of micronutrient intake (*n* = 1,058) (Cont'd)

Micronutrient (quintile range)	Cases	Controls	Crude OR*	Adjusted OR[c]	95% CI	*P* for trend[b]
Vitamin E (mg α-Te/1000 kcal)						
≤4	89	112	1.00	1.00	—	0.33
4-6	140	112	1.55	1.63	1.07-2.50	
6-7	88	113	0.92	0.99	0.63-1.55	
7-16	92	112	1.02	0.94	0.60-1.47	
≥ 16	88	112	0.94	1.02	0.65-1.60	
β-Carotene (μg/1000 kcal)						
≤1,022	153	112	1.00	1.00	—	0.0004
1,029-1,519	92	112	0.59[§]	0.46[§]	0.30-0.70	
1,520-2,194	102	113	0.63[§]	0.55[§]	0.36-0.83	
2,195-3,424	87	112	0.52[§]	0.50[§]	0.32-0.76	
≥ 3,432	63	112	0.38[§]	0.38[§]	0.24-0.60	

*Crude OR adjusted for age, sex, and study site.
[c]Adjusted OR adjusted for age, sex, study site, confirmed dysplastic nevi status, education, and skin response after repeated/prolonged sun exposure.
[b]*P* for trend across quintile medians in the adjusted model.
[§]$P \leq 0.05$.
‖α-Te, α-tocopherol equivalents.

repeated these analyses after excluding individuals who reported any supplement use, which did not affect the direction of the ORs and strengthened the dietary findings. The adjusted ORs (95% CIs) for highest compared with lowest intake of these nutrients were 0.64 (0.38-1.08) for vitamin C, 0.52 (0.32-0.86) for vitamin D, 0.59 (0.35-1.02) for vitamin E, and 0.27 (0.16-0.45) for β-carotene.

Micronutrient from Foods and Supplements. Table 3 also presents the ORs for risk for melanoma by level of intake of micronutrients from foods and supplements combined. Addition of micronutrients from supplements did not add a reduction in risk. After addition of vitamin D from supplements, the association between intake of vitamin D and risk for melanoma was no longer statistically significant.

Interactions. The possibility of effect modification of the associations between melanoma and dietary constituents by gender, education, total calorie intake, BMI, BSA, smoking, and skin response to repeated sun exposure was investigated. In general, the overall patterns presented in Tables 2 and 3 were seen in all subgroups investigated, with the exception of the associations presented in Table 4. The relationship

Table 4. Adjusted ORs and 95% CIs for malignant melanoma for specific nutrients from foods stratified by factors for which there was a statistically significant interaction (*n* = 1,058)

Nutrient (unit/1000 kcal)	Quintile 2		Quintile 3		Quintile 4		Quintile 5		Interaction*
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	
Stratified by gender									
Vitamin E (α-Te[c] mg/1000 kcal)									0.003
Males	1.32	0.71-2.48	0.76	0.39-1.49	1.16	0.61-2.19	0.81	0.44-1.49	
Females	0.71	0.38-1.34	1.35	0.76-2.38	1.26	0.70-2.25	0.41	0.21-0.81	
Stratified by the median level for BSA[b]									
Vitamin E (α-Te[c] mg/1000 kcal)									0.03
BSA < 1.88	1.20	0.67-2.15	0.80	0.42-1.52	0.78	0.41-1.46	0.81	0.44-1.52	
BSA ≥ 1.88	1.01	0.53-1.95	1.44	0.78-2.64	1.55	0.82-2.92	0.43	0.21-0.89	
Retinol (μg/1000 kcal)									0.02
BSA < 1.88	0.70	0.36-1.35	1.69	0.93-3.08	1.26	0.67-2.36	1.01	0.53-1.91	
BSA ≥ 1.88	0.90	0.50-1.64	0.53	0.28-1.00	0.94	0.52-1.70	0.35	0.18-0.69	
α-Carotene (μg/1000 kcal)									0.01
BSA < 1.88	0.69	0.39-1.24	0.44	0.24-0.83	0.48	0.26-0.90	0.29	0.15-0.58	
BSA ≥ 1.88	1.57	0.84-2.93	0.95	0.48-1.85	1.05	0.53-2.05	1.45	0.75-2.79	
β-Carotene (μg/1000 kcal)									0.02
BSA < 1.88	0.38	0.21-0.68	0.38	0.21-0.70	0.37	0.20-0.67	0.28	0.15-0.54	
BSA ≥ 1.88	0.98	0.53-1.80	0.75	0.40-1.42	1.00	0.54-1.87	0.57	0.29-1.12	

NOTE: Participants with light and no tanning response were combined to get more stable risk estimates. Adjusted OR adjusted for age, sex, study site, confirmed dysplastic nevi status, education, and skin response after repeated/prolonged sun exposure.
*P for interaction test.
[c]α-Te, α-tocopherol equivalents.
[b]BSA calculated by $\sqrt{height(inches) * weight(pounds)/3131}$.

between vitamin E and melanoma varied by gender but not in a consistent manner. The association between α-carotene and β-carotene with melanoma risk was stronger among individuals with smaller BSAs, although the reverse was true with increasing intake of retinol and vitamin E. There was also a statistically significant interaction ($P < 0.05$) by BMI for the association between melanoma risk and α-carotene and β-carotene, with results in the same direction as observed for BSA (data not shown). No other statistically significant interactions were observed for the above potential effect modifiers with respect to the relationships between melanoma and intake of vitamin C, D, E, retinol, carotenoids, or alcohol.

Foods and Alcoholic Beverages. Analyses of the relationship between melanoma and frequency of consumption of food groups are shown in Table 5. There was a significant reduction in risk for melanoma in the highest compared with the lowest frequency category for consumption of vegetables, fruits and vegetables combined, dark green/yellow fruits and vegetables, and fish. There was also a suggestion of reduced risk with cereals and grains, and possibly fruits and fruit juices, although these results were not statistically significant. Food groups were analyzed with stratification by gender and none showed differential relative risk by gender.

Compared with nondrinkers of alcoholic beverages, individuals who consumed alcoholic beverages at a

Table 5. Adjusted ORs and 95% CIs for malignant melanoma by level of intake of specific foods with low intakes as referent (*n* = 1,058)

Food group range of intake (frequency/d)	Cases	Controls	OR	95% CI	*P* for trend*
Fruits and fruit juices					
0-1.0	209	198	1.00	—	0.10
1.1-1.5	86	110	0.71	0.49-1.05	
1.6-2.0	75	93	0.63[c]	0.41-0.95	
2.1-7.0	127	160	0.76	0.54-1.08	
Vegetables					
0-1.0	82	61	1.00	—	0.003
1.1-2.0	190	207	0.60[c]	0.39-0.93	
2.1-3.0	139	162	0.58[c]	0.36-0.91	
3.1-8.7	86	131	0.43[c]	0.26-0.70	
Fruits and vegetables					
0-2.0	101	84	1.00	—	0.008
2.1-3.0	117	134	0.66	0.42-1.01	
3.1-5.0	176	207	0.62[c]	0.41-0.94	
5.1-12.6	103	136	0.61[c]	0.39-0.95	
Citrus fruits and juices					
0-0.1	134	126	1.00	—	0.19
0.2-0.5	159	184	0.75	0.52-1.08	
0.6-1.0	97	134	0.59[c]	0.39-0.89	
1.1-3.0	107	117	0.77	0.51-1.17	
Dark green/yellow fruit and vegetables					
0-0.1	110	98	1.00	—	0.04
0.2	97	99	0.71	0.46-1.12	
0.3-0.4	127	144	0.74	0.49-1.11	
0.5-3.3	163	220	0.62[c]	0.42-0.92	
Dairy					
0-1.0	162	191	1.00	—	0.85
1.1-2.0	132	144	1.09	0.76-1.56	
2.1-3.0	108	108	1.19	0.81-1.75	
3.1-21.2	95	118	0.95	0.64-1.40	
Cereals and grains					
0-0.4	172	177	1.00	—	0.06
0.5-0.9	142	158	0.87	0.61-1.25	
1.0-1.4	115	133	0.85	0.58-1.23	
1.5-4.0	68	93	0.66	0.43-1.01	
Fish					
0	167	158	1.00	—	0.04
0.1	182	215	0.82	0.59-1.15	
0.2	63	51	0.89	0.54-1.46	
0.3-1.0	85	137	0.63[c]	0.43-0.94	
Vegetable fats, oils, and nuts					
0-0.5	137	151	1.00	—	0.16
0.6-1.0	146	140	1.24	0.85-1.80	
1.1-1.5	102	123	0.93	0.62-1.38	
1.6-6.1	112	147	0.83	0.56-1.21	

NOTE: Adjusted OR adjusted for age, sex, study site, confirmed dysplastic nevi status, education, and skin response after repeated/prolonged sun exposure.

*P for trend across quintile medians in the adjusted model.

[c] $P \leq 0.05$.

frequency of $\geq$ 1.4 drinks per week had an increased risk for melanoma (Table 6). Direct associations were also observed for wine, liquor, and beer intake, although these associations were not consistently statistically significant. Further analyses, incorporating portion size along with frequency, showed consistent results with the above; i.e., an increased risk for melanoma was associated with an alcohol consumption of $\geq$ 2 servings of alcoholic beverages per week (data not shown). The magnitude of relative risk for melanoma with increasing alcohol consumption was greater among women than men, but the interaction was not statistically significant (data not shown).

Discussion

Our most consistent results show that greater intake of carotenoids (α-carotene, β-carotene, cryptoxanthin, lutein, and lycopene) are associated with decreased risk for melanoma, while greater alcohol intake may increase risk for the disease. There was some suggestion of decreased risk for melanoma associated with increasing intake of vitamin D and retinol from foods. Because the FFQ asked about usual dietary intake in the past year, these results suggest that recent dietary intake may protect against development of melanoma.

Three nested case-control studies reported on serologic carotenoids and risk for melanoma (34-36). Although one study reported higher baseline plasma β-carotene levels among controls (34), two other studies reported no association (35, 36). These studies were limited with <30 cases each. A larger case-control study, however, found no association between melanoma and plasma α-carotene, β-carotene, or lycopene despite a greater number of cases (n = 204; ref. 37).

Several case-control studies have also investigated the relationship between dietary intake of carotenoids and melanoma (37-40), with mixed results. Stryker et al. (37) observed an inverse but not statistically significant decreasing risk for melanoma with increasing consumption of carotenes [OR (95% CI) in the highest quintile of carotene intake, 0.7 (0.4-1.2)]. Another case-control study of women showed an inverse association between β-carotene intake and risk for melanoma (41 cases; ref. 38). However, other case-control studies observed no associations between risk for melanoma and intake of carotenoids (39, 40).

Only two previous prospective studies have investigated the relationship between diet and melanoma (41, 42). Veierod et al. (41) investigated the association between diet and melanoma among men and women in Norway, but the authors state that their dietary questionnaire was unable to accurately assess for intake of carotenoids, retinoids, vitamin C, or vitamin E. Feskanich et al. (42), in a cohort of women in the United States, observed no association between melanoma and intake of carotenoids, tocopherols, or vitamin A, but they did observe an increased risk for melanoma with increasing intake of vitamin C from food. These investigators did not control for socioeconomic status, which may have confounded their results because socioeconomic status is directly related to risk for melanoma (4, 8) and may also influence an individual's dietary intake. In addition, dietary intake was assessed as the cumulative average of FFQs collected from baseline until diagnosis with melanoma. It is unknown if dietary intake close to other risk factor exposures, such as sunlight, or dietary intake over the lifetime, would be most influential, if at all, on risk for melanoma.

Results of studies investigating the relationship between carotenoids and melanoma have shown either a protective effect of these micronutrients on melanoma development or no association. Most studies, except for the case-control study by Holman et al. (39), which had 511 cases of melanoma, may have been limited by their

Table 6. Adjusted ORs and 95% CIs for malignant melanoma in high compared with low levels of alcohol consumption (n = 1,058)

Alcohol consumption range of intake (frequency/wk)	Cases	Controls	OR	95% CI	P for trend*
Alcoholic beverages					
0	154	198	1.00	—	0.04
0.7	77	102	1.04	0.69-1.57	
1.4-7.0	160	154	1.55[c]	1.09-2.20	
7.7-59	106	107	1.53[c]	1.03-2.29	
Wine					
0	248	265	1.00	—	0.12
0.7	125	171	0.87	0.63-1.21	
2.8	68	72	1.12	0.73-1.72	
5.6-42	56	53	1.38	0.86-2.20	
Liquor					
0	300	371	1.00	—	0.05
0.7	103	133	1.21	0.85-1.73	
2.8	45	65	1.69	1.00-2.87	
5.6-42	49	46	1.51	0.93-2.48	
Beer					
0	274	317	1.00	—	0.11
0.7	122	133	1.25	0.89-1.77	
2.8	43	65	0.94	0.58-1.55	
5.6-30	58	46	1.64	1.00-2.70	

NOTE: Adjusted OR adjusted for age, sex, study site, confirmed dysplastic nevi status, education, and skin response after repeated/prolonged sun exposure.

*P for trend across quintile medians in the adjusted model.

[c] $P \leq 0.05$.

sample sizes. Additionally, carotenoids are hypothesized to prevent melanoma by protecting an individual from damaging UV light exposure. Because serum/plasma values are reflective of recent dietary intake (43), the measured carotenoid values in studies may not reflect an individual's tissue carotenoid status during a period of damaging sun exposure.

In our study, we observed that intake of certain carotenoids was protective against risk for melanoma at levels easily obtained through the diet. No additional benefit seems to be incurred through use of supplements. However, the precision of nutrient intake from foods and supplements combined may have been limited by assigning standard doses for some supplements. The observed protective effect of carotenoid intake on melanoma was also supported by the results of the analyses conducted in whole foods. Intake of foods that are rich sources of carotenoids, such as fruits and vegetables of a dark green/yellow color, was associated with decreased risk for melanoma. However, it must be noted that strong correlations existed between many nutrients in this data set, which are concentrated in fruits and vegetables. For example, β-carotene was highly correlated with magnesium ($r = 0.51$, $P < 0.0001$) and fiber ($r = 0.60$, $P < 0.0001$) and folate was highly correlated with vitamin E ($r = 0.71$, $P < 0.0001$), vitamin C ($r = 0.67$, $P < 0.0001$), fiber ($r = 0.66$, $P < 0.0001$), and β-carotene ($r = 0.34$, $P < 0.0001$). For this reason, it was not surprising that exploratory analyses showed that intake of fiber, B vitamins, folate, magnesium, and zinc were significantly associated with decreased risk for melanoma.

In general, the overall patterns observed for macronutrients and micronutrients were consistent by subgroup analysis. However, in these data, BSA did appear to be interacting with the carotenoids effect. We observed that an individual's BSA might determine the degree to which carotenoids protect against melanoma, but other studies would need to confirm this finding. However, if a similar observation is made in other data sets, then perhaps individuals with greater BSAs need to consume more carotenoids than individuals with smaller BSAs to achieve an equivalent dermal pigment density for protection from UV light exposure.

Several studies have investigated the association between alcohol consumption and melanoma (37-41, 44-46). Holman et al. (39) found over a 2-fold increased risk for melanoma with consumption of >3 kg of alcohol per year in current drinkers, which is equivalent to about 4 drinks per week (15 g of alcohol per drink). Stryker et al. (37) found an OR (95% CI) of 1.8 (1.0-3.3) among individuals who consumed alcohol >10 g per day compared with individuals who did not drink. Some case-control studies have observed nonsignificant, direct relationships only among women (38, 41) or men (44), while other studies have found no associations between alcohol and melanoma (40, 45). One found a significant protective effect of alcohol consumption (41).

Our study showed that consumption of ≥ 1.4 alcoholic beverage per week was associated with increased risk for melanoma. This is a much smaller frequency than the alcohol consumption associated with melanoma in other studies. Perhaps our cases underreported their consumption of alcohol. Previous research has shown that underreporting bias exists among heavier drinkers (47). Interestingly, our results showed a slightly greater risk for melanoma associated with alcohol among women than men, which was also observed in some previous studies (38, 41).

It is important to note that the observed results for alcohol consumption and carotenoid intake were independent of one another. Further analyses showed that the associations between carotenoids and melanoma were not altered by adjustment for alcohol intake and vice versa. The correlations between intake of different carotenoids and alcohol were very weak (between β-carotene and alcohol, $r = -0.06$, $P = 0.36$). It seems unlikely that the observed alcohol effect was due to alcohol-related nutrient deficiencies because the increased risk for melanoma was observed among individuals consuming only a small percentage of their total calories from alcohol.

How alcohol may increase an individual's risk for melanoma is unknown. Williams (24) hypothesized that alcohol stimulates the secretion of hormones from the anterior pituitary, including melanocyte-stimulating hormone, which may induce mitosis of melanocytes. Additional research to support this proposed mechanism, to our knowledge, has not been conducted. We can only speculate that alcohol may be increasing risk for melanoma through mechanisms proposed to increase risk for other cancers: (1) altering carcinogenic metabolism, (2) inducing DNA damage or methylation, or (3) systemic effects on hormones that may promote malignant melanoma (48). However, the observed associations between melanoma and alcohol intake may be partially explained by associations between alcohol and sun-seeking behaviors among cases. However, adjustment for the variable skin response to repeated/prolonged exposure, a marker for both an individuals' ability to tan and for extent of sun exposure in this data set, did not remove this association.

Our results may have been affected by possible study limitations. Cases were likely to have known their diagnosis of melanoma prior to attending the study clinic and may have recalled their dietary intake differently than controls. However, this seems unlikely in a study of diet and melanoma where little knowledge of an association between diet and this cancer exists. In this study, the more highly educated control group, compared with the cases, may have been more likely to overreport socially desirable foods, such as fruits and vegetables, and underreport alcohol consumption. Third, the response rate for the control group was relatively low (66%), but the risk factors in this substudy were similar to what had been observed in the larger study (28) and in other studies (5, 8, 37). For this reason, we make the assumption that the reported dietary intake of controls is representative of individuals without melanoma.

Our study also had several strengths. This was one of the largest case-control studies investigating the association between diet and melanoma. Because this study was designed to investigate risk factors for melanoma, variables such as sun exposure and presence of dysplastic nevi were measured using the most current validated techniques (6, 28, 29). The assessment of exposure in these analyses was conducted using a validated FFQ (30). We were also able to investigate the associations between diet and disease in both genders as well as investigate

potential interactions. The results of this case-control study show that a decreased risk for melanoma may be related to diets high in fruits and vegetables, rich sources of carotenoids, and low in alcohol intake. These results need to be replicated in more prospective studies that can ensure less potential reporting bias among participants. Additionally, evaluation is needed of whether dietary exposure over the lifetime, close in time to diagnosis, or some other critical time periods has the most impact, if any, on risk.

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