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Diet Quality and Risk of Melanoma in an Italian Population[1–3]

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Abstract

Background: Some results from laboratory and epidemiologic studies suggest that diet may influence the risk of melanoma, but convincing evidence for a role of single nutrients or food items is lacking. Diet quality, which considers the combined effect of multiple food items, may be superior for examining this relation.

Objective: We sought to assess whether diet quality, evaluated with the use of 4 different dietary indexes, is associated with melanoma risk.

Methods: In this population-based case-control study, we analyzed the relation between 4 diet quality indexes, the Healthy Eating Index 2010 (HEI-2010), Dietary Approaches to Stop Hypertension (DASH) index, Greek Mediterranean Index (GMI), and Italian Mediterranean Index (IMI), and melanoma risk in a northern Italian community, with the use of data from 380 cases and 719 matched controls who completed a semiquantitative food frequency questionnaire.

Results: In the overall sample, we found an inverse association between disease risk and the HEI-2010 and DASH index, but not the Mediterranean indexes, adjusting for potential confounders (skin phototype, body mass index, energy intake, sunburn history, skin sun reaction, and education). However, in sex stratified analyses, the association appeared only in women (*P*-trend: 0.10 and 0.04 for the HEI-2010 and DASH index, respectively). The inverse relations were stronger in women younger than age 50 y than in older women, for whom the GMI and IMI scores also showed an inverse association with disease risk (*P*-trend: 0.05 and 0.02, respectively).

Conclusions: These results suggest that diet quality may play a role in cutaneous melanoma etiology among women. *J Nutr* 2015;145:1800–7.

Keywords: diet, diet quality, dietary patterns, melanoma, case-control study, epidemiology

Introduction

Cutaneous melanoma accounts for ~4% of skin cancers in the United States but is responsible for nearly 80% of skin cancer deaths and 1–2% of all cancer deaths (1). Its incidence has increased in recent years and this upward trend is expected to continue in many countries, despite primary prevention efforts (2–5). It has been postulated that the trend is due to increased exposure to environmental factors acting together with increased genetic susceptibility (6). Among environmental and lifestyle factors such as sun exposure, diet has recently received considerable attention (7–9). The biological plausibility of an association between diet and melanoma etiology is supported in laboratory models by the antioxidant activity of several dietary factors; considerations include the potential involvement of reactive oxygen species and free radicals in skin carcinogenesis,

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[3] Supplemental Table 1 is available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://jn.nutrition.org.

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and the ability of some nutrients to inhibit melanoma cell proliferation (7, 8).

Epidemiologic studies examining the possible relation between dietary habits and risk of cutaneous melanoma, however, have been few and have not yielded consistent results. Recent studies variously report an inverse association of melanoma risk with intake of vitamins C, D, and E, soluble carbohydrates, alcohol, and specific foods and beverages such as fish, vegetables, fruit, tea, and coffee (9–16). Conversely, direct associations have been found with PUFAs, linoleic acid (18:2n–6), and selenium (10–12, 14, 15, 17–20). These inconsistencies may be due to a lack of true association between diet and melanoma risk, biases such as inadequate dietary assessment or uncontrolled confounding, or the methodologic inadequacy of an approach based on single nutrients or foods. Concerning the latter hypothesis, it is possible that an approach based on dietary pattern, which considers the cumulative effects and interactions of multiple food items, may be superior for identifying a relation between diet and melanoma risk (21). Diet quality represents a departure from the traditional focus on single nutrients, providing a better understanding of disease etiology and prevention in nutritional epidemiology, and this explains its growing use in epidemiologic studies (22–28). Two alternative approaches are commonly used in epidemiologic research when dealing with dietary patterns and health risks: an a priori one, based on already-established patterns that have been demonstrated to correlate with the risk of several chronic diseases (including cancer), and an "exploratory," a posteriori approach newly defined on the basis of the specific data collected within a study. Both approaches have advantages and limitations. Here, we take the a priori approach, which some authors consider a stronger approach (29).

To our knowledge, to date, no epidemiologic studies have assessed the association of a priori–defined dietary patterns on melanoma risk despite the growing awareness of a potential role of diet in its etiology, and only one randomized trial has addressed the effect of complex dietary changes on melanoma risk (30). In that trial, carried out in the United States, a low-fat diet was associated with increased melanoma risk among those with higher baseline fat intake and decreased risk among those with lower baseline fat intake (30). In the present population-based case-control study, we investigated the risk of cutaneous melanoma in association with 3 well-established a priori diet-quality indexes, the Healthy Eating Index 2010 (HEI-2010)[13] (31), the Dietary Approaches to Stop Hypertension (DASH) diet (32), and the Greek Mediterranean Index (GMI) (33), and with another pattern we recently defined, the Italian Mediterranean Index (IMI) (34, 35). All of these dietary patterns have been related to a decreased risk of several chronic diseases, such as cardiovascular disease and cancer (36–38). The potential etiologic role of a Mediterranean diet is also of special interest for melanoma, considering that its incidence in the southern Italian population is about one-half that observed in northern Italy (39), and that Greece and Albania show the lowest melanoma incidence in Europe (40).

Methods

Details of our case-control study on dietary risk factors of cutaneous melanoma in the population (~3 million people) of 5 provinces of the Emilia Romagna region in northern Italy have been provided elsewhere (13, 15). Briefly, in the years 2005–2006, we attempted to recruit all patients with newly diagnosed cutaneous malignant melanoma residing in the provinces of Bologna, Ferrara, Modena, Parma, and Reggio Emilia and being seen at local dermatology clinics. Inclusion criteria were a histologically based diagnosis of cutaneous malignant melanoma without clinical evidence of metastasis. Five hundred seventy-two eligible patients were contacted by their dermatologists to participate in the study immediately after diagnosis, and 394 (69%) agreed to participate. Each subject was administered lifestyle questionnaires and FFQs (see below) when attending a routine visit at the beginning of follow-up care for their disease, in all cases within 1 mo of the date of melanoma excision and usually at the time of communication of the diagnosis. The FFQ questionnaire could be returned at the following visit or sent back to the Center for Environmental, Genetic, and Nutritional Epidemiology at Modena and Reggio Emilia University. Six referents matched to each case for gender, year of birth (±5 y), and province of residence were randomly selected from the database of the Emilia-Romagna region National Health Service directory (mandatory for all Italian residents) after enrollment of cases. An envelope containing a lifestyle questionnaire and FFQ, a description of the study, and a prepaid return envelope were mailed to these 2825 potential controls. Family doctors of these potential controls, also retrieved through the Emilia-Romagna region National Health Service directory, were informed by mail about the study and its purpose to encourage involvement of the potential participants. Seven hundred forty-seven (26%) potential controls agreed to participate in the study and returned the questionnaires. Fourteen cases and 28 controls were excluded from subsequent analysis because of incompleteness of data or extreme values (ratio of total energy intake to calculated basal metabolic rate lower than the 0.5th percentile or higher than the 99.5th percentile) derived from the FFQ. All participants gave their written informed consent before enrollment.

Dietary assessment. Habitual diet during the previous 12 mo was investigated with the use of a validated semiquantitative FFQ designed to capture eating behaviors in Italy, specifically developed as part of the EPIC (European Prospective Investigation into Cancer and Nutrition) study for the northern Italian population (41–43). The EPIC questionnaire was designed to be self-administered and was checked by trained personnel after compilation. Participants were asked to respond to 248 questions about 188 different food items, including seasonal foodstuffs, and to indicate the number of times a given item was consumed (per day, week, month, or year), from which the absolute frequency of consumption of each item was calculated.

The quantity of food consumed was assessed by selecting an image of a food portion or selection of a predefined standard portion when no image was available. The food items were then linked with the use of specially designed software (42, 43) to the Italian Food Tables (44) to obtain estimates of daily intake of macro- and micronutrients plus energy.

Diet quality indexes. For each study participant, we computed scores for 4 a priori–defined diet quality indexes. Components and standard portions for the scoring of each index are provided in **Supplemental Table 1**.

Two of the diet quality indexes were originally developed in the United States and have been shown to be inversely associated with cancer risk on the basis of sound epidemiologic evidence (36, 38, 45). The HEI-2010 was originally designed to monitor the diet quality of the US population and compliance with the 2010 Dietary Guidelines for Americans and can be applied to any defined set of foods and menu (31, 46). It has been used for epidemiologic research to examine relations between diet and health-related outcomes and the effectiveness of nutrition intervention programs (46). We adjusted the food quantities in our database to the HEI-2010 quantities with the use of the MyPyramid Equivalents Database, Version 2.0 (USDA). The HEI-2010 has 12 components, each assessed as servings per 4.18 MJ (1000 kilocalories): total fruit, whole fruit, total vegetables, dark green vegetables and beans, whole grains, refined grains, dairy, total protein foods, seafood and plant proteins, FAs (ratio of PUFAs and MUFAs to SFAs), sodium, and empty

[13] Abbreviations used: DASH, Dietary Approaches to Stop Hypertension; EPIC, European Prospective Investigation into Cancer and Nutrition; GMI, Greek Mediterranean Index; HEI-2010, Healthy Eating Index 2010; IMI, Italian Mediterranean Index.

calories (calories from solid fats, alcohol, and added sugars). The intake of components is scored such that a maximum score indicates optimal consumption. For most components, a higher score indicates higher consumption, whereas for refined grains, sodium, and empty calories, a higher score indicates lower consumption. For total fruit, whole fruit, total vegetables, dark green vegetables and beans, total protein foods, and seafood and plant proteins, the scores were 0–5. For whole grains, dairy, refined grains, and sodium, the scores were 0–10. For empty calories, the score was 0–20. The range of possible total scores was 0–100.

The DASH diet was originally designed to reduce blood pressure and has been demonstrated to be effective in this regard (32, 47). It is considered to be an effective healthy eating pattern according to several studies (36, 45, 48, 49). We scored adherence to the DASH diet as suggested by Fung et al. (50). The score is based on 8 components: fruits, vegetables, nuts and legumes, low-fat dairy products, and whole grains, with high intake yielding high DASH scores, and sodium, sweetened beverages, and red and processed meats, with low intake yielding high scores. Participants were classified into quintiles according to intake of each component and the component scores were summed to obtain the DASH score (overall possible range 8–40).

The third and fourth patterns, the GMI and IMI, were formulated as Mediterranean diet scales (33, 35), taking into account the large body of evidence supporting the beneficial effect of a Mediterranean diet in preventing cancer and other chronic disease (37, 51). For the GMI, scoring is based on intake of 9 items: vegetables, legumes, fruit and nuts, dairy products, cereals, meat and meat products, fish, alcohol, and the ratio of MUFAs to SFAs. For most items, consumption above the study median received 1 point; all other intake received 0 points. For dairy products and meat and meat products, consumption below the median received 1 point. Medians were gender specific. For ethanol, men who consumed 10–50 g/d and women who consumed 5–25 g/d received 1 point; otherwise, the score was 0. The range of possible scores was 0–9.

The IMI pattern was recently developed by the Epidemiology and Prevention Unit of the Milan National Cancer Institute (35) by adapting the GMI to typical Italian eating behavior. The score is based on intake of 11 items: 6 typical Mediterranean foods or food groups (pasta; typical Mediterranean vegetables such as raw tomatoes, leafy vegetables, onion and garlic, salad, and fruiting vegetables; fruit; legumes; olive oil; and fish), 4 non-Mediterranean foods (soft drinks, butter, red meat, and potatoes), and alcohol. One point is received for consumption of each typical Mediterranean food in the upper tertile of the distribution, and for consumption of each non-Mediterranean food in the bottom tertile; all other intake received 0 points. Ethanol received 1 point for intake up to 12 g/d; abstainers and persons who consumed >12 g/d received a 0 score. The range of possible scores was 0–11.

Additional variables. In addition to the EPIC FFQ, each participant completed a questionnaire collecting additional information. The questionnaire included items on demographic characteristics (place and date of birth, province of residence, marital status, and education), self-reported weight and height, phenotypic characteristics (eye, hair, and skin color), sunburn history (never, only before, or only after 18 y of age) and skin sun reaction (speed of tan and tendency to burn). Eye color was classified into light (blue/green), light brown, and dark (brown/black) categories. Hair color was classified as blond, red, light brown, or dark brown/black at 20 y, and skin color was classified as white, light brown, brown/olive, or dark brown/ebony. Each subject was assigned to the corresponding skin phototype with the use of the Fitzpatrick phototyping scale (52).

Statistical analysis. All melanoma cases were matched to one or more controls on province of residence, sex, and age (± 5 y). We compared the frequency of categorical variables between cases and controls with the use of chi-square tests, and we assessed the correlations among the 4 diet

TABLE 1 Characteristics of study subjects[1]

	Cases	Controls
Gender		
Men	175 (46.1)	319 (44.4)
Women	205 (53.9)	400 (55.6)
Age, y		
<40	108 (15.0)	64 (13.0)
40–59	306 (42.5)	170 (34.4)
60–79	278 (38.7)	235 (47.6)
≥80	27 (3.8)	25 (5.6)
Education		
Elementary or less	91 (23.9)	170 (23.6)
Middle school	95 (25.0)	176 (24.5)
High school	136 (35.8)	266 (37.0)
College or more	54 (15.3)	107 (14.9)
Marital status		
Married	257 (67.6)	493 (68.7)
Unmarried/single	68 (17.9)	103 (14.3)
Divorced	23 (6.0)	48 (6.6)
Widowed	31 (8.2)	74 (10.3)
Unknown	1 (0.3)	1 (0.1)
BMI, kg/m^2		
<20	31 (8.2)	45 (6.3)
≥20 to <25	164 (43.2)	306 (42.7)
≥25 to <30	133 (35.0)	287(39.9)
≥30	52 (13.6)	81 (11.3)
Phototype		
I	105 (27.6)	109 (15.2)
II	136 (35.8)	238 (33.1)
III	122 (32.1)	312 (43.4)
IV	17 (4.5)	60 (8.3)
Sunburn history		
Never	182 (47.9)	452 (62.9)
Before 18 y	108 (28.4)	164 (22.8)
After 18 y	90 (23.7)	103 (14.3)
Skin sun reaction (speed to tan and tendency to burn)		
High tendency to burn and never tan	21 (5.5)	22 (3.1)
High tendency to burn and moderate tan	117 (30.8)	131 (18.2)
Moderate tendency to burn and gradual tan	160 (42.1)	357 (49.7)
No tendency to burn and golden tan	65 (17.1)	149 (20.7)
No tendency to burn and intense tan	17 (4.5)	60 (8.3)
Dietary pattern score, median (range)		
HEI-2010	57 (22–92)	59 (22–95)
DASH	23 (8–36)	24 (11–36)
GMI	4 (1–9)	5 (0–9)
IMI	4 (0–10)	4 (0–9)

[1] Values are *n* (%) unless otherwise indicated; overall *n* = 380 (34.6%) for cases and *n* = 719 (65.4%) for controls. DASH, Dietary Approaches to Stop Hypertension; GMI, Greek Mediterranean Index; HEI-2010, Healthy Eating Index 2010; IMI, Italian Mediterranean Index; Phototype I, eyes/hair/skin light, high tendency to burn and never/moderate tan; Phototype II, eyes/hair/skin light, moderate tendency to burn and gradual tan or eyes/hair/skin brown, high tendency to burn and moderate tan; Phototype III, eyes/hair/skin brown, moderate/no tendency to burn and gradual/golden tan; Phototype IV, no tendency to burn and intense tan.

TABLE 2 Pearson correlation coefficients (95% CIs) among the scores of the dietary indexes in the men and women studied[1]

	DASH	GMI	IMI
HEI-2010	0.73 (0.71, 0.76)	0.52 (0.47, 0.56)	0.54 (0.49, 0.58)
DASH		0.53 (0.49, 0.57)	0.60 (0.56, 0.64)
GMI			0.54 (0.50, 0.58)

[1] $P < 0.001$ for all values. DASH, Dietary Approaches to Stop Hypertension; GMI, Greek Mediterranean Index; HEI-2010, Healthy Eating Index 2010; IMI, Italian Mediterranean Index.

TABLE 3 Overall and sex-stratified adjusted ORs (95% CIs) for cutaneous melanoma by level of adherence to dietary pattern scores from a case-control study of diet and melanoma in the Emilia-Romagna region, Italy[1]

	Score categories					
Dietary patterns	1	2	3	4	OR (95% CI)[2]	*P*-trend[3]
All subjects (380 cases and 719 controls)						
HEI-2010						0.03
Score	<40	40–59	60–79	≥80		
Cases/controls	37/71	178/295	145/307	20/46		
OR (95% CI)	1.00	1.19 (0.74, 1.92)	0.87 (0.54, 1.41)	0.85 (0.42, 1.74)	0.91 (0.83, 1.01)	
DASH						0.03
Score	<20	20–24	25–29	≥30		
Cases/controls	89/152	154/249	93/233	44/85		
OR (95% CI)	1.00	1.01 (0.71, 1.45)	0.68 (0.46, 1.00)	0.70 (0.42, 1.16)	0.90 (0.83, 0.98)	
GMI						0.34
Score	0–2	3–4	5–6	7–9		
Cases/controls	61/102	140/250	128/282	51/85		
OR (95% CI)	1.00	0.82 (0.54, 1.23)	0.66 (0.43, 1.01)	0.86 (0.52, 1.45)	0.96 (0.89, 1.04)	
IMI						0.38
Score	0–2	3–4	5–6	7–10		
Cases/controls	76/159	157/263	117/222	30/75		
OR (95% CI)	1.00	1.26 (0.88, 1.80)	1.13 (0.77, 1.65)	0.76 (0.44, 1.32)	0.97 (0.90, 1.04)	
Men (175 cases and 319 controls)						
HEI-2010						0.31
Score	<40	40–59	60–79	≥80		
Cases/controls	22/40	86/142	60/126	7/11		
OR (95% CI)	1.00	1.09 (0.57, 2.08)	0.81 (0.41, 1.59)	1.26 (0.39, 4.03)	0.95 (0.82, 1.11)	
DASH						0.42
Score	<20	20–24	25–29	≥30		
Cases/controls	42/85	79/116	35/85	19/33		
OR (95% CI)	1.00	1.38 (0.80, 2.38)	0.86 (0.46, 1.62)	0.88 (0.40, 1.93)	0.95 (0.83, 1.07)	
GMI						0.81
Score	0–2	3–4	5–6	7–9		
Cases/controls	20/42	63/110	67/119	25/48		
OR (95% CI)	1.00	0.99 (0.49, 1.98)	0.99 (0.49, 1.98)	0.93 (0.41, 2.10)	0.98 (0.87, 1.12)	
IMI						0.43
Score	0–2	3–4	5–6	7–10		
Cases/controls	38/79	66/106	58/99	13/35		
OR (95% CI)	1.00	1.38 (0.79, 2.40)	1.16 (0.66, 2.05)	0.65 (0.28, 1.50)	0.96 (0.86, 1.07)	
Women (205 cases and 400 controls)						
HEI-2010						0.10
Score	<40	40–59	60–79	≥80		
Cases/controls	15/31	92/153	85/181	13/35		
OR (95% CI)	1.00	1.49 (0.70, 3.17)	1.08 (0.51, 2.26)	0.90 (0.34, 2.39)	0.90 (0.79, 1.02)	
DASH						0.04
Score	<20	20–24	25–29	≥30		
Cases/controls	47/67	75/133	58/148	25/52		
OR (95% CI)	1.00	0.75 (0.46, 1.25)	0.57 (0.35, 0.95)	0.58 (0.30, 1.13)	0.88 (0.79, 0.88)	
GMI						0.23
Score	0–2	3–4	5–6	7–9		
Cases/controls	41/60	77/140	61/163	26/37		
OR (95% CI)	1.00	0.74 (0.44, 1.25)	0.49 (0.28, 0.86)	0.93 (0.46, 1.86)	0.94 (0.985, 1.05)	
IMI						0.73
Score	0–2	3–4	5–6	7–10		
Cases/controls	38/80	91/157	59/123	17/40		
OR (95% CI)	1.00	1.25 (0.77, 2.03)	1.14 (0.67, 1.93)	0.92 (0.44, 1.93)	0.98 (0.89, 1.09)	

[1] ORs adjusted for phototype, BMI, nonalcoholic energy intake, sunburn history, skin sun reaction, and education. DASH, Dietary Approaches to Stop Hypertension; GMI, Greek Mediterranean Index; HEI-2010, Healthy Eating Index 2010; IMI, Italian Mediterranean Index.

[2] Adjusted OR for melanoma for 10-point increase in HEI-2010, 3-point increase in DASH, and 1-point increase GMI and IMI pattern scores.

[3] *P* value for linear trend with the use of continuous values of dietary index score in conditional logistic regression models.

quality indexes with the use of Pearson correlation coefficients. We defined exposure categories by setting a priori cutoffs of diet quality scores (53). We used conditional logistic regression to obtain ORs and 95% CIs of cutaneous melanoma associated with diet quality score, both crude and with adjustment for BMI (continuous), education (4 categories), nonalcoholic energy intake (continuous), skin phototype (4 categories), sunburn history (3 categories) and skin sun reaction (5 categories). Because unadjusted and adjusted ORs were similar, only adjusted results are presented. We also tested for linear trend by entering diet quality scores as continuous variables in conditional logistic regression models (54). In these analyses, a 1-unit increase was defined as a 10-point increase in HEI-2010, a 3-point increase in DASH index, and a 1-point increase in the GMI or IMI; these increments each correspond to ~10% of the total score range.

We also investigated age, gender, and skin phototype as potential effect modifiers by conducting analyses stratified on these factors (4, 55–57). Because these analyses involved smaller sample sizes, rather than use cutoffs, which requires more df, we tested for linear trend by entering the diet quality scores as continuous variables in conditional logistic regression models.

Results

Three hundred eighty patients, 175 men and 205 women with mean age 58 ± 16 and 53 ± 15, respectively, and 719 age-, sex-, and province of residence–matched referents were included in the analysis. Demographic and clinical characteristics of cases and controls are reported in **Table 1**. Educational attainment and marital status were similar in the 2 groups (chi-square P = 0.97 and 0.46, respectively). Cases tended to have more fair skin types and were more likely to report a history of sunburns and difficulty tanning (all comparisons, $P < 0.01$). The overall distribution of diet quality scores in the participants, reported in Table 1, was similar to that observed in other Italian populations (35). The 4 dietary index scores were moderately correlated, with the highest correlation between the HEI-2010 and DASH index (**Table 2**).

Adjusted ORs for melanoma for each dietary index are shown in **Table 3**, both in the whole sample and by sex. In the overall sample, ORs for the highest score category compared with the lowest were consistent with decreased risk for all 4 indexes. Analysis for linear trend on continuous values, however, suggested decreasing risk with higher diet quality only for the HEI-2010 and DASH index. In sex-stratified analyses, among men, there was no evidence of decreasing risk with increasing scores, aside from a low OR in the highest category of the DASH index (OR: 0.88; 95% CI: 0.40, 1.93) and IMI (OR: 0.65; 95% CI: 0.28, 1.50). Among women, trend analyses suggested possible inverse associations with disease risk for the HEI-2010

TABLE 4 Adjusted ORs (95% CIs) for melanoma according to adherence to dietary pattern in age- and phototype-stratified analysis[1]

	All cases (380 cases/719 controls)		Men (175 cases/319 controls)		Women (205 cases/400 controls)	
	OR (95% CI)	*P*-trend	OR (95% CI)	*P*-trend	OR (95% CI)	*P*-trend
Age stratification						
HEI-2010						
<50 y	0.89 (0.76, 1.04)	0.08	0.90 (0.67, 1.21)	0.37	0.85 (0.70, 1.04)	0.06
≥50 y	0.93 (0.82, 1.06)	0.22	0.97 (0.80, 1.17)	0.47	0.93 (0.78, 1.01)	0.48
DASH						
<50 y	0.86 (0.76, 0.98)	0.03	0.93 (0.71, 1.20)	0.74	0.80 (0.70, 0.93)	0.01
≥50 y	0.93 (0.83, 1.04)	0.25	0.94 (0.80, 1.10)	0.36	0.94 (0.80, 1.11)	0.65
GMI						
<50 y	0.87 (0.76, 0.99)	0.04	0.82 (0.62, 1.09)	0.17	0.85 (0.73, 1.00)	0.05
≥50 y	1.03 (0.93, 1.14)	0.58	1.02 (0.88, 1.19)	0.78	1.02 (0.88, 1.18)	0.84
IMI						
<50 y	0.93 (0.83, 1.06)	0.27	1.04 (0.84, 1.30)	0.71	0.83 (0.70, 0.97)	0.02
≥50 y	0.98 (0.89, 1.08)	0.74	0.90 (0.78, 1.04)	0.14	1.08 (0.94, 1.24)	0.29
Phototype stratification						
HEI-2010						
Phototype I-II	0.90 (0.78, 1.05)	0.14	1.00 (0.78, 1.28)	0.78	0.86 (0.70, 1.06)	0.16
Phototype III-IV	0.90 (0.73, 1.11)	0.33	0.83 (0.57, 1.20)	0.37	0.98 (0.75, 1.28)	0.74
DASH						
Phototype I-II	0.89 (0.78, 1.01)	0.09	0.89 (0.72, 1.08)	0.27	0.90 (0.76, 1.06)	0.26
Phototype III-IV	0.93 (0.79, 1.10)	0.48	1.13 (0.85, 1.49)	0.50	0.84 (0.67, 1.06)	0.20
GMI						
Phototype I-II	0.96 (0.85, 1.09)	0.53	1.00 (0.82, 1.22)	0.99	0.94 (0.80, 1.11)	0.47
Phototype III-IV	0.98 (0.83, 1.15)	0.77	0.97 (0.75, 1.25)	0.79	0.97 (0.78, 1.22)	0.80
IMI						
Phototype I-II	0.90 (0.79, 1.02)	0.10	1.00 (0.83, 1.20)	1.00	0.82 (0.68, 0.98)	0.03
Phototype III-IV	1.03 (0.89, 1.20)	0.68	1.02 (0.80, 1.30)	0.88	1.08 (0.88, 1.34)	0.44

[1] Adjusted for age, phototype, BMI, nonalcoholic energy intake, sunburn history, skin sun reaction, and education. OR for melanoma for 10-point increase in HEI-2010, 3-point increase in DASH, and 1-point increase in GMI and IMI pattern scores. DASH, Dietary Approaches to Stop Hypertension; GMI, Greek Mediterranean Index; HEI-2010, Healthy Eating Index 2010; IMI, Italian Mediterranean Index; Phototype I, eyes/hair/skin light, high tendency to burn and never/moderate tan; Phototype II, eyes/hair/skin light, moderate tendency to burn and gradual tan or eyes/hair/skin brown, high tendency to burn and moderate tan; Phototype III, eyes/hair/skin brown, moderate/no tendency to burn and gradual/golden tan; Phototype IV, no tendency to burn and intense tan.

(OR: 0.90; 95 CI%: 0.34, 2.39; P = 0.10) and DASH index (OR: 0.58; 95% CI: 0.30, 1.13; P = 0.04), whereas a consistent association across all categories of exposure emerged only for the DASH diet.

In age-stratified analysis (cutoff 50 y), there was indication of an inverse association only among the younger subjects (**Table 4**). When further stratifying for sex, an inverse association was much more evident among younger women than younger men. When stratifying for phototype (I and II vs. III and IV), trend analysis yielded some suggestion of stronger inverse associations between dietary pattern and disease risk among individuals with lighter phototypes compared with darker phototypes (Table 4), although both category-based and continuous ORs had wide CIs.

Discussion

Diet is considered a major risk factor for several cancers, but melanoma generally has not been regarded as a disease influenced by dietary habits. Rather, etiologic importance is attributed to dysplastic nevi, history of sunburns, UV light exposure, phototype, and genetic factors. A few studies have investigated the possible relation between diet and melanoma etiology, most of them in the United States and Italy, and they provided inconsistent evidence of a relation between dietary factors and disease risk (7, 8).

The results of the present study give some support to an inverse association between disease risk and indicators of diet quality, particularly as assessed through the HEI-2010 and DASH index. However, this inverse association was almost entirely due to an association in women, and particularly younger women, suggesting effect modification of gender and age. In fact, all 4 indexes showed an inverse association with disease risk for women under 50 y old. There was a weaker suggestion of effect modification by phototype. The reasons for a gender-specific association between diet quality and melanoma prevention cannot be inferred from the current study. However, our finding of a stronger relation among women younger than 50 y, a premenopausal age group, suggests that hormonal factors could play a role (55, 57). Regardless, our results clearly need to be confirmed by further studies before this conclusion can be reached. Another possible explanation for our findings might be differential diet reporting by sex.

Contrary to our expectations, in our southern European population, the dietary patterns more strongly associated with disease risk in the overall sample were not the scores related to the Mediterranean diet but those assessing diet quality of the US population; that is, the HEI-2010 and DASH index. The Mediterranean diet indexes have shown associations with risk of other diseases: the Italian index was recently shown to be associated with decreased risk of colorectal cancer and stroke (34, 35), and the Greek index has been associated with decreased mortality from various diseases (58–60). Although the 4 dietary patterns we examined share common characteristics, including an emphasis on high intake of fruit and vegetables, moderate consumption of dairy products, and low intake of animal protein such as red and processed meat, there are important differences. The Mediterranean diet puts emphasis on pasta and fish intake and on moderate consumption of alcohol (with different quantities for the IMI and GMI) (34, 60), whereas the DASH diet and HEI-2010 favor a low consumption of refined grains, sugar-sweetened beverages, and sodium and a high intake of low-fat dairy, with alcohol intake ignored in the DASH diet and penalized in the HEI-2010 (31, 46).

A limitation of our study was the lack of information about type and number of dysplastic nevi or details about occupational history, long-term exposure to UV light, physical activity (a potential marker of vitamin D and UV light exposure), and family history of melanoma; these factors were not assessed because of the risk of recall bias among cases. However, these factors are unlikely to explain the gender-specific associations we detected. Furthermore, we adjusted our ORs for a number of potential confounders, including phototype, BMI, education, nonalcoholic energy intake, history of sunburn, and skin sun reaction, and this adjustment had limited effects on the point estimates, suggesting that major confounding was unlikely. Information about smoking was not collected in the study, but it should not play a major role in melanoma etiology (61–63); therefore, lack of consideration of smoking should not have substantially biased our estimates. Weight and height were self-reported by study participants, which may have introduced some misclassification of BMI.

Diet is not widely regarded as a risk factor for melanoma by the general population, making recall bias in long-term dietary habits unlikely. Moreover, the melanoma cases were recruited at clinical diagnosis of the disease and in the absence of metastases; hence, it is unlikely that the disease itself or its diagnosis induced substantial metabolic abnormalities or change in dietary habits. However, general beliefs about associations between healthy diets and chronic disease may have biased reporting of diet, and thus the occurrence of differential misclassification in women cannot be entirely ruled out. Results from cohort investigations are clearly needed to confirm our findings.

Another limitation of the present study is the dependence on a single assessment—the FFQ—to estimate antecedent dietary habits, with the potential for measurement error because of difficulties in recalling usual dietary habits and insensitivity to long-term dietary changes. However, the FFQ used in this study is a validated tool specifically designed to assess long-term (1 y) usual consumption of as many as 188 different food items. In addition, the sample sizes may have been inadequate to detect some associations.

Although our findings are not sufficiently strong to support recommendations on specific dietary guidelines for melanoma prevention, as has been put forth for other cancers and cardiovascular disease (37, 38, 51, 63), they suggest that an approach focused on indicators of diet quality, rather than on single nutrients or food items, can identify important areas of future research.

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CM, MM, CMC, CA, SS, VK, GP, and MV designed the study, were responsible for the development of the overall research plan and study oversight, wrote the paper, and had primary responsibility for the final content. CM, CF, FF, CL, CR, GA, AL, LV, AV, CP, MS, PAF, ED, GP, and MV conducted the research by recruiting patients and controls and collecting the data. CM, MM, CA, CMC, SS, VK, and MV performed the statistical analysis. CM, MM, CMC, and MV wrote the paper. All authors read and approved the final manuscript.

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