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A protective effect of the Mediterranean diet for cutaneous melanoma

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Background Many studies have investigated the Mediterranean diet as a risk factor for cancer, none of which has included cutaneous melanoma. The latter is usually fatal, rendering knowledge about prevention extremely important. We assessed the role of some food components of the Mediterranean diet and cutaneous melanoma.

Methods A hospital-based case–control study was conducted in the inpatient wards of IDI-San Carlo Rome, Italy including 304 incident cases of cutaneous melanoma and 305 controls, frequency matched to cases. Information on socio-demographic characteristics, medical history, smoking, sun exposure, pigmentary characteristics and diet was collected. Logistic regression was the method used to estimated odds ratio and 95% CIs.

Results After careful control for several sun exposure and pigmentary characteristics, we found a protective effect for weekly consumption of fish (OR, 0.65, 95%CI = 0.43–0.97), shellfish (OR, 0.53, 95%CI = 0.31–0.89), fish rich in n-3 fatty acids (OR, 0.52, 95%CI = 0.34–0.78), daily tea drinking (OR, 0.42, 95%CI, 0.18–0.95; $P_{trend} = 0.025$) and high consumption of vegetables (OR, 0.50, 95%CI = 0.31–0.80, $P_{trend} = 0.005$) in particular carrots, cruciferous and leafy vegetables and fruits (OR, 0.54, 95%CI = 0.33–0.86, $P_{trend} = 0.013$), in particular citrus fruits. No association was found for alcohol consumption and any other food items.

Conclusion Overall, our findings suggest that some dietary factors present in the Mediterranean diet might protect from cutaneous melanoma.

Keywords Epidemiology, cutaneous melanoma, Mediterranean diet

Introduction

Skin melanoma has been one of the most rapidly increasing cancers in Caucasian populations over the past several decades.[1] Ultraviolet (UV) exposure is widely accepted as having a predominant role in the genesis of skin melanoma, however, there are others little explored factors such as diet, which could act as promoters or inhibitors of melanoma initiation and/or promotion.[2–3] There is also a striking variation in the cutaneous melanoma risk according to geographic location. For example the United States (20 cases per 100 000 inhabitants) and Australia (50 cases per 100 000 inhabitants) have the highest reported incidence rates, while in Europe the highest rates are found in Scandinavia (about 9–22 cases per 100 000 inhabitants) and the lowest in Mediterranean countries (about 3–11 cases per 100 000 inhabitants).[1] This variation could be explained by differences in latitude, altitude, pigmentation of the population,[3] sun exposure behaviour[2] and by other factors such as different dietary patterns.

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Over the last 20 years there has been growing interest in a potential role in cancer prevention for the Mediterranean diet in the development of cancer. Ancel Keys established that the key explanatory factor for survival differences in the regions bordering the Mediterranean sea was the local diet and in other studies it has been shown to be protective for many cancers.[4] In view of these latter studies, however, no study has yet evaluated the association between Mediterranean diet and cutaneous melanoma.

The aim of this study was to assess the role of food components in the Mediterranean diet on cutaneous melanoma.

Methods

Study design and subjects

A hospital-based case–control study on cutaneous melanoma was conducted at a referral hospital for skin diseases (IDI-San Carlo) in the Lazio Region of Italy. Eligible cases were Caucasian subjects aged 18 years or more, resident in Lazio and admitted to the hospital between May 2001 to May 2003. All cases had a new histologically confirmed diagnosis of primary malignant cutaneous melanoma. Selection was confined to Caucasians since there is still a limited number of other racial and ethnic groups in this area. The study was approved by IDI-IRCCS ethical committee, and written consent was obtained from all participants.

Controls were selected from patients in the same hospital (IDI-San Carlo) during the study period, from the same geographical area and who do not have a personal history of skin diseases or cancer. The control subjects were frequency matched to cases by gender (1 : 1) and age (in 5-year age strata) to yield a sex and an age distribution similar to that of cases. The participants proportions i.e. the percentage of participants in the study who actually completed the interview and had a dermatological visit for nevi count, was 94.7% for case patients and 92.1% for controls.

Exposure assessment

After obtaining informed consent, the participants were interviewed by two trained researchers with a structured questionnaire and then clinically examined for pigmented lesions.

The questionnaire included information on socio-demographic characteristics, personal medical history, smoking habits, phenotypic traits (skin type, skin, hair and eye colour) and family history of skin cancer, life time sunlight exposure, sunburn history, sun bed and/or lamp exposure and diet.

The pigmented lesions were identified and recorded according to the IARC protocol.[5] Acquired melanocytic nevi were defined as brown to black pigmented macules or papules of 2 mm or more in diameter, darker in colour than the surrounding skin and clinically different from freckles, lentigines, cafe-au-lait spots, seborrheic keratoses and pigmented basal cell carcinomas. The number of nevi (>2 mm) over the entire skin surface (except for the scalp, pubic region and perineum) were recorded and then classified as none, few (1–24), moderate (25–59) or many ($\geq$60).

An ‘atypical naevus’ was defined as a melanocytic lesion ($\geq$5 mm) with at least two of the following features: irregularity or ill defined borders, variegated or with an irregular pigment distribution, background erythema or accentuated skin markings. The atypical naevi found were recorded systematically and classified into two groups: none, $\geq$1. Other skin and individual characteristics such as freckles, solar lentigines, actinic keratoses and a past history of skin cancer were also recorded. Solar lentigines were classified as: none, few (limited to a single body part), moderate (two body areas) or many (more than two body areas).

The Fitzpatrick system was used to classify skin phototype (burning and tanning tendency).[6] Hair colour at 20-years-old was classified as red and blonde, light brown, dark brown and black. Eye colour was divided into three categories: blue, grey and green, light brown and dark brown and black. Two categories were used for skin colour (dark and fair). A skin, eye and hair colour chart was used to help define skin and hair colour during the interview.

Sun exposure history included: the average daily hours outdoors in three different life periods: under 12 years, 12–18 years and 19 years and more. Indicators of intermittent exposure were: average daily hours outdoors during vacation, sunburn episodes and sun bed or lamp use. Chronic exposure indicators were: average daily hours outdoors in recreational activities, occupational sun exposure and lifetime sun exposure. Lifetime sun exposure was the sum of the average hours outdoors during lifetime. Average daily hours outdoors was divided into two categories ($\leq$5 and $\geq$6 h). Lifetime sun exposure was classified into terciles (low: <26; medium: 27–36; high: $\geq$37 h) based on the controls distribution. Occupational sun exposure was classified as only indoors or outdoors, or both.

Sunburn episodes (pain and erythema and/or blisters for more than 24 h) were classified into four categories (none; 1; 2–5; $\geq$6). Information on sun protection behaviour such as the habitual use of sunscreens (SPF $\geq$15) and/or a hat and/or T-shirt was also collected and categorized as never/rarely and often/always. The latter information was taken for each lifetime period.

To investigate the relationship between cutaneous melanoma and dietary components of the Mediterranean diet, subjects were requested to complete a food frequency questionnaire (a self-administered questionnaire with 36 food items).[7] To avoid bias caused by recent illness among subjects, questions were specifically asked about frequency consumption in the year before the interview. The frequency intake of all food groups were defined on a seven point scale as following: (i) never, (ii) less than monthly, (iii) less than weekly, (iv) one to two times per week, (v) three to four times per week, (vi) five to seven times per week and (vii) daily.

Food items were subdivided into related groups and subgroups based on the type of phytochemical content such as carrots for β-carotene; tomatoes for lycopene; dark leafy green vegetables (spinach, chicory, beet leaves) for phenols, lutein and zeaxanthin; cruciferous vegetables (broccoli, cauliflower, cabbage) for phenols, isothiocyanates and indoles; citrus fruit (oranges, tangerines) for β-cryptoxanthin. For each individual food or food group, the seven point categorical scale was combined to form three categories representing low, medium and high consumption. Combination of categories was based on the overall distribution among controls. Therefore, for some items such as fish consumption, olive oil and the use of fresh herbs, only two categories were used.

Statistical analysis

Unconditional logistic regression model was the method chosen for the statistical analysis. Using the low consumption group as a baseline, the odds ratios (ORs) and 95% CIs were calculated for the middle and high consumption groups. Sex, age, education, hair colour, skin phototypes, number of nevi, presence of freckles in childhood and sunburns in childhood were all considered in the regression models as potential confounders.

The likelihood ratio test was used to decide whether to keep or eliminate each covariate in the model. The frequency of dietary variables was included as ordinal variables in the logistic regression to test for trend (Wald test). We also evaluated effect modification by sex, age, education, skin phototype and sun exposure variables for each dietary variable. Additional analyses were conducted for only invasive cases and stratified for gender.

To test the robustness of the results we ran all the models excluding cardiovascular and digestive diseases from the control series since they could be associated with dietary changes.

All analyses were performed using the statistical software package PC-STATA (Stata 9.0; StataCorp LP, College Station, TX 77845, USA).

Results

A total of 652 subjects were approached (321 cases and 331 controls). A total of 304 cases (47.0% males; 53.0% females) and 305 controls (47.2% males; 52.8% females) gave written consent, were interviewed and had a full skin examination. The mean age of the cases and controls were 53.0 years (SD = 15.3) and 51.1 years (SD = 16.1), respectively.

Table 1 shows their main demographic characteristics, the diagnosis of the hospital controls, the anatomic site and the frequency distribution of histological types of cutaneous melanoma. Cases were more highly educated than controls. The superficial spreading cutaneous melanoma was the most frequently seen (76%) and the trunk was the most common site (48%). No association was found for smoking.

Table 2 shows that ~60% of melanoma cases had fair hair and 83% fair skin, whereas the controls were 32 and 58%, respectively. An increased cutaneous melanoma risk was found for subjects with light brown hair (OR, 2.93; 95% CI = 2.01–4.27) and for blonds and red heads (OR, 4.40; 95% CI = 2.58–7.52) vs subjects with dark brown and black hair. Fair skin vs dark complexion had an approximately 4-fold risk of cutaneous melanoma (OR, 3.81; 95% CI = 2.59–5.61). Subjects with skin phototypes I and II had an increased risk (OR, 2.77; 95% CI = 1.97–3.90) when compared with subjects with skin phototypes III and IV.

The presence of freckles (OR, 3.38; 95% CI = 2.29–4.99), light colour eyes (blue, green, grey) (OR, 1.99; 95% CI = 1.37–2.89) and many solar lentigines (OR, 3.59; 95% CI = 1.78–7.24) were all associated with an increased cutaneous melanoma risk, as was an elevated number of common nevi (25–59 nevi, OR, 3.33; 95% CI = 2.09–5.30; ⩾60 nevi, OR, 8.27; 95% CI = 5.16–13.2) and one atypical nevi or more (OR, 3.50; 95% CI = 2.27–5.40). The presence of actinic keratosis lesions and/or a past history of non-melanocytic skin cancer and familial history of skin cancer were associated with an increased risk, although CIs were wide.

Table 3 shows that sunburn at any time in life was associated with an increased risk of melanoma. Subjects who reported six or more sunburn episodes in childhood had circa a 4-fold risk of cutaneous melanoma (OR, 3.89; 95%CI = 2.05–7.38). Increased risk, were found for subjects spending 6 h or more each day outdoors while on vacation during adult life (OR, 1.53; 95%CI = 1.04–2.25) and for the use of sun lamp or sun bed (OR, 1.30; 95%CI = 0.83–2.04), although CIs were wide. Lifetime sun exposure, occupational UV job exposure and the number of hours spent outdoors in recreational activities were not associated with an increased risk for melanoma.

The association between consumption of foods of plant origin and melanoma is presented in Table 4, after adjustment for sex, age, education, hair colour, skin phototypes, number of nevi, presence of freckles and sunburns in childhood. We found protective effects for high consumption of vegetables (⩾5 times weekly) and fruits in general (more than once daily) (OR, 0.50, 95% CI = 0.31–0.80; $P_{trend} = 0.005$ and OR, 0.54, 95% CI = 0.33–0.86; $P_{trend} = 0.013$, respectively).

Table 1 Socio-demographic, clinical and histological characteristics of the subjects participating in the study and diagnosis of the controls

	Cases[a] (%) N = 304	Controls[a] (%) N = 305
Sex		
Males	143 (*47.0*)	144 (*47.2*)
Females	161 (*53.0*)	161 (*52.8*)
Age (year)		
<25	8 (*2.6*)	21 (*6.9*)
25–34	37 (*12.2*)	40 (*13.1*)
35–44	54 (*17.8*)	52 (*17.0*)
45–54	61 (*20.1*)	56 (*18.4*)
55–64	70 (*23.0*)	64 (*21.0*)
65–74	53 (*17.4*)	57 (*18.7*)
>75	21 (*6.9*)	15 (*4.9*)
Education (year)		
<8	49 (*16.2*)	64 (*21.0*)
8–13	187 (*61.7*)	209 (*68.5*)
⩾13	67 (*22.1*)	32 (*10.5*)
Anatomic site		
Head/neck	24 (*7.9*)	...
Trunk	145 (*47.7*)	...
Upper limb	46 (*15.1*)	...
Lower limb	88 (*28.9*	...
Other specified sites	1 (*0.3*)	...
Types of melanoma		
Superficial spreading	231 (*76.0*)	...
Nodular	31 (*10.2*)	...
Acral lentiginous	2 (*0.7*)	...
Mixed	14 (*4.6*)	...
In situ	18 (*5.9*)	...
Unclassified	8 (*2.6*)	...
Cell typef[b]		
Epithelioid	201 (*73.1*)	...
Naevocytic	5 (*1.8*)	...
Spindle	14 (*5.1*)	...
Clear	1 (*0.4*)	...
Mixed	26 (*9.5*)	...
Unclassified	28 (*10.2*)	...
Diagnosis		
Benign neoplasms	...	31 (*10.2*)
Endocrine system and disease at the immune system	...	4 (*1.3*)
Diseases of the nervous system and sense organs	...	11 (*3.6*)
Diseases of the circulatory system	...	84 (*27.5*)
Diseases of the respiratory system	...	15 (*4.9*)
Diseases of the digestive system	...	25 (*8.2*)
Diseases of the genitourinary system	...	36 (*11.8*)
Complications of pregnancy, child birth and the puerperium	...	1 (*0.3*)
Diseases of the skin and subcutaneous tissue	...	32 (*10.5*)
Diseases of the musculoskeletal system and connective tissue	...	43 (*14.1*)
Congenital abnormalities	...	10 (*3.3*)
Symptoms, signs and ill defined conditions	...	4 (*1.3*)
Injury	...	9 (*3.0*)
Smoking status		
Never smokers	139 (*45.9*)	140 (*45.9*)
Current smokers	107 (*35.3*)	115 (*37.7*)
Ex smokers	57 (*18.8*)	50 (*16.4*)

[a]Totals may vary because of missing value.
[b]Only for invasive melanoma (Clark > II).

High consumption of cruciferous vegetables (OR, 0.42, 95% CI = 0.26–0.69; $P_{trend} < 0.0001$), leafy green vegetables (OR, 0.40, 95% CI = 0.25–0.65; $P_{trend} < 0.0001$), carrots (OR, 0.57, 95% CI = 0.38–0.84) and citrus fruit (OR, 0.51, 95% CI = 0.32–0.80; $P_{trend} = 0.003$) were also found to be protective. A protective effect for melanoma was found among those who had high intake of fresh herbs (four or more regularly) ($P_{trend} = 0.018$) and especially for rosemary (OR, 0.40 95% CI = 0.22–0.74). Protective effects were also observed for nuts, salad and an exclusive use of olive oil for dressing although these were associated with wide CIs. Tomatoes were not associated with a decreased risk for melanoma.

Table 5 shows the risk estimates of consumption of foods of animal origin and melanoma after adjustment for sex, age, education, hair colour, skin phototypes, number of nevi, presence of freckles and sunburns in childhood. A protective effect for a high consumption (weekly and more) of fish (OR, 0.65, 95%CI = 0.43–0.97), fish rich in n-3 fatty acids (sardines, anchovies, tuna and salmon) (OR, 0.52, 95%CI = 0.34–0.78) and shellfish (OR, 0.53, 95% CI = 0.31–0.89) was observed. No increased risk was found for high intake of meat, liver, offals, cheese, butter, eggs and milk consumption.

Table 2 Association between subjects pigmentary characteristics and cutaneous melanoma

	Cases[a] (%) N = 304	Controls[a] (%) N = 305	OR[b] (95%CI)[b]
Hair colour			
Black/dark brown	123 (*40.5*)	207 (*67.9*)	1
Ligth brown	122 (*40.1*)	74 (*24.3*)	2.93 (2.01–4.27)
Fair/blond/red	59 (*19.4*)	24 (*7.9*)	4.40 (2.58–7.52)
Eye colour			
Black/dark brown	103 (*33.9*)	142 (*46.6*)	1
Ligth brown	65 (*21.4*)	64 (*21.0*)	1.44 (0.93–2.22)
Blue/grey/green	136 (*44.7*)	99 (*32.5*)	1.99 (1.37–2.89)
Skin colour			
Dark	51 (*16.8*)	128 (*42.4*)	1
Fair	253 (*83.2*)	174 (*57.6*)	3.81 (2.59–5.61)
Skin phototype[c]			
III–IV	103 (*34.0*)	176 (*57.9*)	1
I–II	200 (*66.0*)	128 (*42.1*)	2.77 (1.97–3.90)
Presence of freckles			
No	168 (*58.1*)	241 (*81.4*)	1
Yes	121 (*41.9*)	55 (*18.6*)	3.38 (2.29–4.99)
Solar lentigines			
None	13 (*4.3*)	32 (*10.6*)	1
Few/moderate	40 (*13.3*)	93 (*30.7*)	1.07 (0.50–2.26)
Many	248 (*82.4*)	178 (*58.7*)	3.59 (1.78–7.24)
Common nevi (*n*)			
0–24	109 (*35.9*)	210 (*68.9*)	1
25–59	70 (*23.0*)	53 (*17.4*)	3.33 (2.09–5.30)
⩾60	125 (*41.1*)	42 (*13.8*)	8.27 (5.16–13.2)
Atypical nevi (*n*)			
0	208 (*68.4*)	264 (*86.8*)	1
⩾1	96 (*31.6*)	40 (*13.2*)	3.50 (2.27–5.40)
Actinic keratosis/non-melanoma skin cancer			
No	250 (*84.7*)	263 (*89.5*)	1
Yes	45 (*15.3*)	31 (*10.5*)	1.44 (0.84–2.46)
Family history of skin cancer			
No	284 (*95.0*)	290 (*96.3*)	1
Yes	15 (*5.0*)	11 (*3.7*)	1.39 (0.62–3.11)

[a]Totals may vary because of missing value.
[b]OR adjusted for age and sex.
[c]I: always burns, never tans; II: often burns, tans minimally; III: rarely burns, tans well; IV: never burns, tans profusely.

Table 6 reports the results of beverages consumption and melanoma. High tea consumption (daily or more) was associated with a protective effect for melanoma (OR, 0.42, 95%CI = 0.18–0.95). A dose–response relationship was observed for tea drinking ($P_{trend} = 0.025$). Alcohol consumption was not associated with an increased risk for melanoma.

The analysis was also repeated after stratifying for gender. No clear patterns emerged to indicate that these protective effects were restricted to either men or women. The protective effects for fish and carrots was slightly stronger for males, whereas the protective effects of cruciferous vegetables, fresh herbs and fruits was slightly stronger for females (data not shown).

Table 3 Association between sun exposure and cutaneous melanoma

	Cases[a] (%) N = 304	Controls[a] (%) N = 305	OR[b] (95%CI)
Intermittent sun exposure			
Time spent outdoors during vacation in childhood (h)			
<5	33 (*11.3*)	24 (*8.2*)	1
>6	259 (*88.7*)	270 (*91.8*)	0.69 (0.39–1.21)
Time spent outdoors during vacation in adolescence (h)			
<5	42 (*14.4*)	39 (*13.2*)	1
>6	250 (*85.6*)	257 (*86.8*)	0.92 (0.57–1.49)
Time spent outdoors during vacation in adulthood (h)			
<5	67 (*22.3*)	87 (*29.2*)	1
>6	233 (*77 7*)	211 (*70.8*)	1.53 (1.04–2.25)
Sunburns in childhood			
None	131 (*55.3*)	200 (*75.8*)	1
1	17 (*7.2*)	17 (*6.4*)	1.66 (0.80–3.43)
2–5	51 (*21.5*)	31 (*11.7*)	2.72 (1.63–4.53)
>6	38 (*16.0*)	16 (*6.1*)	3.89 (2.05–7.38)
Sunburns in adolescence			
None	135 (*53.4*)	189 (*69.7*)	1
1	26 (*10.3*)	25 (*9.2*)	1.58 (0.86–2.88)
2–5	60 (*23.7*)	41 (*15.1*)	2.17 (1.35–3.48)
>6	32 (*12.6*)	16 (*5.9*)	2.82 (1.47–5.41)
Sunburns in adulthood			
None	128 (*47.6*)	179 (*63.0*)	1
1	35 (*13.0*)	34 (*12.0*)	1.43 (0.84–2.44)
2–5	62 (*23.0*)	48 (*16.9*)	1.80 (1.15–2.81)
>6	44 (*16.4*)	23 (*8.1*)	2.57 (1.46–4.51)
Use of artificial sunbed and/or sunlamp in adulthood (times/yr)			
Never	240 (*78.9*)	244 (*80.0*)	1
>1	64 (*21.1*)	61 (*20.0*)	1.30 (0.83–2.04)
Chronic sun exposure			
Time spent outdoors during recreational activities in childhood (h)			
<5	116 (*39.9*)	112 (*38.1*)	1
⩾6	175 (*60.1*)	182 (*61.9*)	0.87 (0.61–1.23)
Time spent outdoors during recreational activities in adolescence (h)			
<5	142 (*49.3*)	155 (*52.2*)	1
⩾6	146 (*50.7*)	142 (*47.8*)	1.10 (0.78–1.55)
Time spent outdoors during recreational activities in adulthood (h)			
<5	204 (*68.0*)	205 (*68.6*)	1
⩾6	96 (*32.0*)	94 (*31.4*)	1.08 (0.75–1.54)
Lifetime sun exposure (h)			
Low	105 (*37.0*)	96 (*33.0*)	1
Medium	79 (*27.8*)	104 (*35.7*)	0.68 (0.45–1.03)
High	100 (*35.2*)	91 (*31.3*)	0.98 (0.64–1.50)
Occupational exposure			
Indoor	215 (*71.0*)	210 (*69.3*)	1
Indoor/ outdoor	45 (*14.9*)	54 (*17.8*)	0.81 (0.51–1.27)
Outdoor	43 (*14.2*)	39 (*12.9*)	1.03 (0.63–1.69)

[a]Totals may vary because of missing value.
[b]OR adjusted for age and sex.

In males, but not in females, high intake of butter (⩾1 weekly) was associated with an increased risk for melanoma (OR, 4.37, 95%CI = 1.09–17.4).

When we restricted the analysis to only invasive cutaneous melanoma the protective effect of these foods and tea drinking remained. Further analyses showed that the association between melanoma and these foods items and tea drinking was not altered by adjustment for BMI and the regular use of non-steroid anti-inflammatory drugs (NSAIDs) (data not shown).

To confirm the findings, the analyses were conducted excluding cardiovascular and digestive diseases from the controls series. The protective effect of food items remained but with wider CIs (data not shown).

In all multivariable models common nevi, hair colour, skin phototype, presence of freckles and sunburns in childhood remained all associated with melanoma. There was no evidence of confounding by other sun exposure variables. We also controlled, one at a time in the model, for other potential melanoma risk factors, such as eye and skin colour, solar lentigines, presence of actinic keratosis, family history of skin cancer including melanoma, the use of sun protective measures (e.g. sunscreen, hat and T-shirt) and smoking. None of these variables had a confounding role.

No effect modification was seen between sex, age, education, skin type and dietary variables, except for butter consumption and sex ($P = 0.04$).

In a further multivariate model, considering food items simultaneously (vegetables, fruits, fish, fresh herbs and tea), the protective effects remained apparent after adjustment although with wider CIs. For example, weekly intake of fish rich in n-3 fatty acids had OR of 0.62 (95%CI = 0.39–0.98) (data of other adjustments are not shown).

Discussion

The term Mediterranean diet refers to a dietary pattern of societies in countries surrounded by the Mediterranean Sea. It is a plant-based diet rich in

Table 4 Association between cutaneous melanoma and weekly consumption of plant origin foods

	Cases[a] (%) N = 304	Controls[a] (%) N = 305	OR[b] (95%CI)	OR[c] (95%CI)	*P*-value[d]
Cooked vegetables					
Low (up to 2 times/week)	99 (*32.6*)	84 (*27.6*)	1	1	
Medium (3–4 times/week)	93 (*30.6*)	93 (*30.6*)	0.84 (0.55–1.27)	0.62 (0.38–1.02)	
High (>5times/week)	112 (*36.8*)	127 (*41.8*)	0.68 (0.46–1.02)	0.50 (0.31–0.80)	*0.005*
Salad					
Low (up to 2 times/week)	74 (*24.3*)	69 (*22.8*)	1	1	
High (>3 times/week)	230 (*75.7*)	234 (*77.2*)	0.87 (0.59–1.37)	0.86 (0.54–1.35)	
Cruciferous vegetables					
Low (less than weekly)	138 (*45.5*)	107 (*35.2*)	1	1	
Medium (1–2 times/week)	93 (*30.7*)	96 (*31.6*)	0.72 (0.49–1.07)	0.63 (0.40–1.01)	
High (>3 times/week)	72 (*23.8*)	101 (*33.2*)	0.51 (0.34–0.76)	0.42 (0.26–0.69)	*<0.0001*
Leafy green vegetables					
Low (less than weekly)	125 (*41.1*)	105 (*34.5*)	1	1	
Medium (1–2 times/week)	103 (*33.9*)	85 (*28.0*)	1.01 (0.68–1.50)	0.81 (0.51–1.30)	
High (> 3 times/week)	76 (*25.0*)	114 (*37.5*)	0.55 (0.37–0.82)	0.40 (0.25–0.65)	*<0.0001*
Tomatoes					
Low (up to 2 times/week)	76 (*25.0*)	92 (*30.4*)	1	1	
Medium (3–4 times/week)	93 (*30.6*)	79 (*26.1*)	1.45 (0.94–2.24)	1.08 (0.65–1.80)	
High (>5 times/week)	135 (*44.4*)	132 (*43.6*)	1.27 (0.86–1.90)	1.15 (0.71–1.84)	*0.57*
Carrots					
Low (less than weekly)	176 (*57.9*)	145 (*47.5*)	1	1	
High (weekly and more)	128 (*42.1*)	160 (*52.5*)	0.62 (0.45–0.86)	0.57 (0.38–0.84)	
Use of fresh herbs (*n*)					
Low (<1)	45 (*14.8*)	43 (*14.1*)	1	1	
Medium (2–3)	98 (*32.2*)	74 (*24.3*)	1.20 (0.70–2.05)	0.88 (0.46–1.66)	
High (4)	161 (*53.0*)	188 (*61.6*)	0.73 (0.45–1.20)	0.56 (0.31–1.00)	*0.018*
Type of fresh herbs:					
Parsley					
No	28 (*9.9*)	22 (*7.9*)	1	1	
Yes	254 (*90.1*)	257 (*92.1*)	0.75 (0.41–1.36)	0.94 (0.46–1.95)	
Sage					
No	110 (*39.0*)	85 (*30.5*)	1	1	
Yes	172 (*61.0*)	194 (*69.5*)	0.65 (0.46–0.94)	0.68 (0.44–1.05)	
Basil					
No	19 (*6.7*)	16 (*5.7*)	1	1	
Yes	263 (*93.3*)	263 (*94.3*)	0.80 (0.40–1.61)	0.75 (0.33–1.69)	
Rosemary					
No	52 (*18.4*)	25 (*9.0*)	1	1	
Yes	230 (*81.6*)	254 (*91.0*)	0.43 (0.25–0.71)	0.40 (0.22–0.74)	
Fruits					
Low (up to 4 times/week)	110 (*36.3*)	95 (*31.1*)	1	1	
Medium (5–7 times/week)	64 (*21.1*)	84 (*27.5*)	0.55 (0.35–0.86)	0.57 (0.34–0.96)	
High (daily and more)	129 (*42.6*)	126 (*41.3*)	0.75 (0.51–1.12)	0.54 (0.33–0.86)	*0.013*

(continued)

Table 4 Continued

	Cases[a] (%) N = 304	Controls[a] (%) N = 305	OR[b] (95%CI)	OR[c] (95%CI)	*P*-value[d]
Citrus fruits					
Low (up to 2 times/week)	115 (*38.2*)	100 (*32.9*)	1	1	
Medium (3–4 times/week)	73 (*24.3*)	72 (*23.7*)	0.89 (0.58–1.36)	0.79 (0.47–1.32)	
High (>5 times/week)	113 (*37.5*)	132 (*43.4*)	0.70 (0.48–1.02)	0.51 (0.32–0.80)	*0.003*
Nuts					
Low (less than weekly)	267 (*88.1*)	251 (*82.8*)	1	1	
High (weekly and more)	36 (*11.9*)	52 (*17.2*)	0.66 (0.42–1.06)	0.61 (0.35–1.05)	
Exclusive use of olive oil					
No	22 (*7.2*)	21 (*6.9*)	1	1	
Yes	282 (*92.8*)	282 (*93.1*)	0.95 (0.50–1.78)	0.88 (0.42–1.86)	

[a]Totals may vary because of missing value.
[b]OR adjusted for age and sex.
[c]OR adjusted for sex, age, education, hair colour, skin phototypes, number of nevi, presence of freckles in childhood and sunburns in childhood.
[d]Test for trend (Wald test).

bioactive molecules with powerful antioxidant and anti-inflammatory potential, their high concentration in characteristics foods such as cruciferous vegetables, tomatoes, green leafy vegetables, citrus fruit, fresh herbs, wine and olive oil.[8]

An inverse association between consumption of dark green and yellow vegetables and citrus fruit and melanoma was observed in some studies[9,10] but not in others.[11–13] One study suggests that fish consumption may be also protective for melanoma[14] while another does not support it.[9]

After a careful control for individual characteristics and sun exposure, the results of our study show that the Mediterranean dietary profile, characterized by regular use of fresh herbs, high intake of citrus fruits, carrots, cruciferous and dark green vegetables and high consumption of fish rich in n-3 fatty acids and shellfish give protection against cutaneous melanoma decreasing by about half, the risk of cutaneous melanoma.

The biological rationale for the protective effect of some food items[15–26] found in this study are the following: citrus fruits are main sources of β-cryptoxanthin, carrots are rich in β-carotene and rosemary and sage, cruciferous and dark green vegetables and tea are all rich in polyphenols, for which are known to have many anticarcinogenic properties including: photoprotection by scavenging of reactive oxygen species generated in photooxidative processes and reducing UV radiation induced erythema,[18,24] stimulation of the immune system,[16] cell proliferation inhibition and induction of apoptosis.[16,19,20,22] Cruciferous vegetables are also rich in glucosinolates that are known to modulate Phase I and Phase II enzymes that detoxify carcinogens.[17]

Overexpression of cyclooxygenase (COX-2) and deregulation of prostaglandin (PG) synthesis has been reported in many cancers including melanoma.[25] Both polyphenols and n-3 fatty acids, especially the long chain polyunsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) present in fatty fish, have been shown to inhibit carcinogenesis by inhibiting COX-2.[21,23] n-3 fatty acids have also been shown to inhibit photocarcinogenesis by reducing erythemal sensitivity to UV radiation, probably by PG modulation.[26] In fact, a case–control study on melanoma showed a protective effect (RR = 0.45, 95% CI = 0.22–0.92) for the regular intake of NSAIDs.[27] NSAIDs has been shown to be effective in reducing the risk of cancer development by COX-2 activity inhibition and then blocking cell progression and angiogenesis and inducing apoptosis.[28]

It has been suggested in some studies that alcohol may have a harmful role in the development of melanoma[11,10] but not in others.[9,29] In our study, alcohol consumption did not increase cutaneous melanoma risk, which is in agreement with two other Italian studies.[9,29] The lack of a harmful effect of alcohol on melanoma seen in our study may be explained by the fact that half of the subjects drank wine exclusively that is rich in polyphenols, which might neutralize the alcohol-induced oxidative stress. With regard to other beverages and melanoma no relationship was found, with the exception of tea drinking, which was associated with a more than 2-fold decrease in risk.

Other food items such as different types of fat sources, liver, red and white meat, eggs and dairy products were not associated with high risk of melanoma that is in agreement with other studies published elsewhere.[9,11,29]

This study has some strengths and limitations. A strength of the study is the high response rate of both cases and controls. Another strength is the dose response effects observed for some dietary variables. Limitations of our study include the possibility

Table 5 Association between cutaneous melanoma and weekly consumption of animal origin foods

	Cases[a] (%) N = 304	Controls[a] (%) N = 305	OR[b] (95%CI)	OR[c] (95%CI)	*P*-value[d]
Milk					
Low (less than weekly)	76 (*25.0*)	79 (*25.9*)	1	1	
Medium (weekly)	125 (*41.1*)	107 (*35.1*)	1.26 (0.83–1.90)	1.02 (0.62–1.67	
High (daily and more)	103 (*33.9*)	119 (*39.0*)	0.88 (0.58–1.33)	0.69 (0.42–1.15)	*0.12*
Butter					
Low (never)	179 (*60.1*)	184 (*60.7*)	1	1	
Medium (less than weekly)	88 (*29.5*)	93 (*30.7*)	0.99 (0.69–1.42)	0.98 (0.63–1.51)	
High (weekly and more)	31 (*10.4*)	26 (*8.6*)	1.24 (0.70–2.20)	1.08 (0.54–2.17)	*0.91*
Eggs					
Low (never/rarely)	67 (*22.1*)	52 (*17.0*)	1	1	
Medium (less than weekly)	75 (*24.8*)	67 (*22.0*)	0.88 (0.53–1.44)	1.00 (0.55–1.82)	
High (weekly and more)	161 (*53.1*)	186 (*61.0*)	0.68 (0.44–1.05)	0.73 (0.44–1.22)	*0.15*
Cheese					
Low (less than weekly)	53 (*17.5*)	69 (*22.6*)	1	1	
Medium (1–2 times/week)	83 (*27.4*)	80 (*26.2*)	1.33 (0.82–2.15)	1.33 (0.75–2.35)	
High (>3 times/week)	167 (*55.1*)	156 (*51.1*)	1.33 (0.87–2.04)	1.06 (0.64–1.75)	*0.96*
Fish					
Low (less than weekly)	125 (*41.3*)	101 (*33.1*)	1	1	
High (weekly and more)	178 (*58.7*)	204 (*66.9*)	0.72 (0.52–1.01)	0.65 (0.43–0.97)	
Fish rich in n-3 fatty acids[e]					
Low (less than weekly)	199 (*65.9*)	177 (*58.2*)	1	1	
High (weekly and more)	103 (*34.1*)	127 (*41.8*)	0.71 (0.51–1.00)	0.52 (0.34–0.78)	
Shellfish					
Low (less than weekly)	259 (*85.8*)	240 (*78.9*)	1	1	
High (weekly and more)	43 (*14.2*)	64 (*21.1*)	0.65 (0.42–1.01)	0.53 (0.31–0.89)	
Meat					
Low (less than weekly)	38 (*12.5*)	41 (*13.4*)	1	1	
Medium (1–2 times/week)	85 (*28.0*)	92 (*30.2*)	0.98 (0.57–1.68)	1.03 (0.54–1.95)	
High (>3 times/week)	181 (*59.5*)	172 (*56.4*)	1.16 (0.70–1.91)	1.25 (0.69–2.27)	*0.34*
Liver and offals					
No	188 (*62.3*)	193 (*63.5*)	1	1	
Yes	114 (*37.7*)	111 (*36.5*)	1.07 (0.77–1.51)	1.24 (0.83–1.85)	

[a]Totals may vary because of missing value.
[b]OR adjusted for age and sex.
[c]OR adjusted for sex, age, education, hair colour, skin phototypes, number of nevi, presence of freckles in childhood and sunburns in childhood.
[d]Test for trend (Wald test).
[e]Sardines, anchovies, tuna and salmon.

of information bias. Differential misclassification may occur if cases, aware of the hypothesis, tend to report more fully than controls, with resultant overestimation of the odds ratio. In our study cases were not aware of the study hypothesis, not even the study collaborators responsible for collecting the data. Moreover, there is no awareness in the general population of a potential relationship between diet and melanoma. The influence of current diet on recall of diet may also lead to bias when the eating habits of cases have changed as a result of diagnosis. However, the use of incident cases and the recall of diet about consumption levels 1 year before the interview decreased the possibility of this sort of bias. Another potential limitation of our study is the use of hospital controls. A balance between diagnoses was kept when sampling controls in order to minimize bias

Table 6 Association between cutaneous melanoma and weekly consumption of beverages

	Cases[a] (%) N = 304	Controls[a] (%) N = 305	OR[b] (95%CI)	OR[c] (95%CI)	P-value[d]
Wine					
Low (less than weekly)	149 (*49.0*)	158 (*52.1*)	1	1	
Medium (weekly)	105 (*34.5*)	71 (*23.4*)	1.49 (1.00–2.21)	1.28 (0.80–2.04)	
High (daily and more)	50 (*16.4*)	74 (*24.4*)	0.66 (0.42–1.03)	0.83 (0.49–1.42)	*0.73*
Exclusive wine consumption					
Low (less than weekly)	82 (*68.9*)	92 (*68.1*)	1	1	
Medium (weekly)	25 (*21.0*)	24 (*17.8*)	1.03 (0.51–2.05)	0.79 (0.34–1.84)	
High (daily and more)	12 (*10.1*)	19 (*14.1*)	0.68 (0.30–1.53)	0.64 (0.22–1.88)	*0.36*
Liquorous wine					
Non-drinkers	208 (*68.9*)	232 (*76.1*)	1	1	
Drinkers	94 (*31.1*)	73 (*23.9*)	1.45 (1.00–2.11)	1.35 (0.87–2.10)	
Beer					
Never	149 (*49.2*)	154 (*50.5*)	1	1	
Low (less than weekly)	113 (*37.3*)	107 (*35.1*)	1.12 (0.77–1.63)	1.05 (0.67–1.64)	
High (more than weekly)	41 (*13.5*)	44 (*14.4*)	0.99 (0.59–1.66)	0.98 (0.53–1.79)	*0.99*
Spirits					
Non-drinkers	220 (*72.8*)	232 (*76.3*)	1	1	
Drinkers	82 (*27.2*)	72 (*23.7*)	1.29 (0.87–1.90)	1.15 (0.72–1.83)	
Tea					
Low (less than weekly)	230 (*76.7*)	214 (*70.4*)	1	1	
Medium (weekly)	52 (*17.3*)	63 (*20.7*)	0.75 (0.49–1.14)	0.73 (0.44–1.21)	
High (daily and more)	18 (*6.0*)	27 (*8.9*)	0.59 (0.31–1.21)	0.42 (0.18–0.95)	*0.025*
Coffee[e]					
Low (<l)	105 (*35.1*)	110 (*36.4*)	1	1	
Medium (2–3)	158 (*52.8*)	146 (*48.3*)	1.1 (0.75–1.53)	0.95 (0.62–1.45)	
High (>4)	36 (*12.0*)	46 (*15.2*)	0.8 (0.44–1.28)	0.78 (0.41–1.46)	*0.48*

[a]Totals may vary because of missing value.
[b]OR adjusted for age and sex.
[c]OR adjusted for sex, age, education, hair colour, skin phototypes, number of nevi, presence of freckles in childhood and sunburns in childhood.
[d]Test for trend (Wald test).
[e]Number of cups.

and the analyses were repeated to confirm the findings after excluding illness, which could be associated with dietary changes such as cardiovascular and/or digestive diseases. Misclassification of dietary exposure could be also a problem. Part of this misclassification is a result of food-frequency questionnaire being an imperfect measure of dietary history, and the error can be assumed to be similar for both cases and controls. Similarly, the absence of information on portion size may also to lead to further non-differential misclassification. It has been previously shown that, in the presence of moderate to substantial non-differential misclassification error, ORs are biases towards the null.[30] However, portion size data have been shown to be positive correlated with frequency of use.[31] We evaluated the reproducibility of the food frequency questionnaire used in this case–control study on 276 subjects. Overall, there was a fair to good reproducibility between answers in two different periods (12 months apart). For example, agreement for frequency of use of fish, tea, vegetables and fruits were as following: 74% (weighted κ: 0.42), 90% (weighted κ: 0.55), 82% (weighted κ: 0.49) and 84% (weighted κ: 0.58), respectively, and it did not vary by case–control status.

It is clear that dietary profiles are associated with many factors, such as socioeconomic status and cigarette smoking. However, we considered these variables. Another important aspect is the residual confounding of sun exposure. However, we considered in details these variables.

Our findings support evidence linking some foods rich in polyphenols and n-3 fatty acids to decrease cutaneous melanoma risk and suggest that these foods may be indicators of the protective effect of the Mediterranean diet.

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KEY MESSAGES

- Cutaneous melanoma is an increasingly common malignancy of the melanocytes, which has steadily increased over the past decades.
- Cutaneous melanoma is usually fatal, rendering knowledge about prevention extremely important.
- It cannot be denied that sun exposure is the best identified environmental risk factor for melanoma; however, there are other, little explored, potential risk factors, such as diet.
- Many studies have investigated the Mediterranean diet as a risk factor for cancer, none of which has included cutaneous melanoma.
- Our findings support evidence linking some foods rich in polyphenols and n-3 fatty acids to decrease cutaneous melanoma risk and suggest that these foods may be indicators of the protective effect of the Mediterranean diet.

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