Mediterranean dietary pattern and skin cancer risk: A prospective cohort study in French women

Yahya Mahamat-Saleh,[1,2] Iris Cervenka,[1,2] Marie Al Rahmoun,[1,2] Isabelle Savoye,[3] Francesca Romana Mancini,[1,2] Antonia Trichopoulou,[4,5] Marie-Christine Boutron-Ruault,[1,2] and Marina Kvaskoff[1,2]

[1]Centre for Research in Epidemiology and Population Health (CESP) - School of Medicine, Université Paris Sud - School of Medicine,Université Versailles Saint-Quentin-en-Yvelines (UVSQ); INSERM (French National Institute for Health and Medical Research), Université Paris Saclay, Villejuif, France; [2]Gustave Roussy, Villejuif, France; [3]Belgian Health Care Knowledge Centre (KCE), Brussels, Belgium; [4]Hellenic Health Foundation, Athens, Greece; and [5]WHO Collaborating Center for Nutrition and Health, Unit of Nutritional Epidemiology and Nutrition in Public Health, Department of Hygiene, Epidemiology and Medical Statistics, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece

ABSTRACT

Background: The Mediterranean diet (MD) has been reported to be associated with lower cancer risk. However, while previous studies explored major single components of the MD, only 1 previous study has investigated adherence to the MD in relation to melanoma risk.

Objective: The aim of this study was to explore the relations between adherence to the MD and the risk of skin cancer, including melanomas, basal cell carcinomas (BCCs), and squamous cell carcinomas (SCCs).

Design: Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale (E3N) is a prospective cohort of 98,995 French women aged 40–65 y in 1990. Dietary data were collected via a validated food questionnaire in 1993. Adherence to the MD was assessed using a 9-unit dietary score that incorporates intakes of fruit, vegetables, legumes, cereal products, olive oil, fish, dairy products, meat products, and alcohol. We used Cox proportional hazards regression models to compute HRs and 95% CIs adjusted for age and main known skin cancer risk factors.

Results: From 1993 to 2008, a total of 2003 skin cancer cases were ascertained among 67,332 women, including 404 melanomas, 1367 BCCs, and 232 SCCs. Score of adherence to the MD was associated with lower risk of skin cancer (HR: 0.83; 95% CI: 0.73, 0.93 for high compared with low score, $P_{trend} = 0.001$). MD score was also inversely and linearly associated with risks of melanoma (HR: 0.72; 95% CI: 0.54, 0.96; $P_{trend} = 0.02$) and BCC (HR: 0.77; 95% CI: 0.66, 0.90; $P_{trend} = 0.0006$) but not SCC (HR: 1.08; 95% CI: 0.75, 1.55; $P_{trend} = 0.68$), although with no heterogeneity across skin cancer types ($P_{heterogeneity} = 0.23$).

Conclusion: These findings suggest that adherence to the MD is associated with a lower skin cancer risk in women, particularly melanoma and BCC. If confirmed in future research, these findings may have important implications in skin cancer prevention. *Am J Clin Nutr* 2019;110:993–1002.

Keywords: cohort studies, epidemiology, keratinocyte cancers, Mediterranean diet, melanoma

Introduction

Skin cancers are the most common cancers worldwide (1), and their incidence has been rising over the past decades (2–4). These cancers include cutaneous malignant melanoma, the most lethal type, resulting in 55,000 skin cancer–related deaths globally in 2012 (1, 5), and keratinocyte cancers, namely, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), which are associated with dramatic impacts on quality of life and health care costs (6, 7). Exposure to UV radiation is the major environmental risk factor for skin cancers (8) and currently the sole factor on which prevention can be based. Other risk

The E3N cohort from the French National Institute of Health and Medical Research (Inserm) was supported by the Mutuelle Générale de l'Education Nationale, the Gustave Roussy Institute, and the French League against Cancer (LNCC). YM-S, IC, and MAR were supported by research scholarships from the Paris Ile-de-France region, the French Ministry of Research, and the French National Cancer Institute, respectively.

This study is listed at clinicaltrials.gov as NCT03285230.

Supplemental Tables 1–4 and Supplemental Figure 1 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

Address correspondence to MK (e-mail: marina.kvaskoff@gustaveroussy.fr).

Abbreviations used: BCC, basal cell carcinoma; E3N, Etude Epidemiologique auprès de femmes de l'Education Nationale; MD, Mediterranean diet; SCC, squamous cell carcinoma; SPF, sun protection factor.

Received February 26, 2019. Accepted for publication July 9, 2019.

First published online August 6, 2019; doi: https://doi.org/10.1093/ajcn/nqz173.

factors include pigmentary traits and family history of skin cancer (9).

An antioxidant-rich diet has been proposed to prevent skin cancer (10, 11). UV radiation was shown to generate free radicals that can induce premature skin aging and cutaneous carcinogenesis (12, 13), and experimental studies suggested that antioxidants, such as β-carotene and vitamins A, C, and E, could alleviate the UV-induced oxidative damage to the skin and act as chemopreventive agents for skin cancer (10, 13–16). Unfortunately, epidemiologic studies yielded inconsistent findings: while some investigations reported a lower skin cancer risk associated with intakes of fruit and vegetables (17, 18), which are known to be the main sources of dietary antioxidants, other studies reported no association (19, 20).

However, foods and nutrients are not consumed alone but as part of an overall diet, and exploring overall dietary patterns has been suggested to improve assessment of the diet–disease association compared with the single-nutrient approach, especially as components of these patterns may interact synergistically. In this context, the Mediterranean dietary pattern has been particularly investigated over recent years in relation to common chronic diseases (21), including cancer (22). The Mediterranean diet (MD) is characterized by a high consumption of plant foods, such as fruit, vegetables, cereals, and legumes, and of wine and olive oil, which are rich in polyphenols and other bioactive molecules with powerful antioxidant and anti-inflammatory properties (23). To date, only 1 study has explored the association between adherence to the MD and melanoma risk and highlighted an inverse association restricted to women with a moderate MD score (5, 6) and to those aged <50 y (24). However, this study was retrospective with a limited sample size, and associations with other skin cancer types could not be investigated. Therefore, we sought to examine the relations between adherence to the MD and the risk of skin cancer, including melanoma, BCC, and SCC, in a prospective cohort of 67,322 women with 15 y of follow-up.

Subjects and Methods

E3N cohort

E3N (Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale) is an ongoing prospective cohort involving 98,995 women born in 1925–1950 and affiliated with a national health plan covering workers from the French National Education System (25). Women were enrolled in 1990 after returning a baseline self-administered questionnaire on lifestyle and medical history along with informed and signed consent. Participants then completed biennial follow-up questionnaires. The average response rate for each follow-up questionnaire was 83%. The E3N cohort received ethical approval from the French National Commission for Data Protection and Privacy (Commission Nationale Informatique et Libertés).

Identification of incident skin cancer cases

In each follow-up questionnaire, women were invited to report skin cancer events, which were then investigated and validated by requesting the contact details of the participants' physicians and permission to contact them to retrieve histologic records. Skin cancer events were mostly confirmed through pathology reports for 95% of cases (melanoma: 95%; BCC: 94%; SCC: 95%). A small proportion of cancer events was obtained from insurance files and death certificates. In the absence of a pathology report, 4% of cases were ascertained through confirmation from the women's physicians; 1% was self-reported. In the present study, we considered both invasive and *in situ* skin cancer cases, which represent 87% and 13% of cases, respectively.

Data collection

Diet.

In 1993, dietary data were collected via a self-administered food questionnaire assessing consumption of 208 food items. The questionnaire included quantitative questions with a booklet of photographs to facilitate estimation of portion sizes and frequency of consumption, as well as qualitative questions on food groups. Estimated individual nutrient intakes were obtained using a food-composition table derived from the updated French national database (26). The questionnaire was validated using twelve 24-h recalls carried out monthly as the reference, and its reproducibility was tested after 1 y (27). For the food groups included in this study, the correlation coefficients ranged from 0.40 to 0.75 for reproducibility and from 0.25 to 0.67 for validity (27).

MD.

A score of adherence to the MD was measured using 9 key components of the MD as proposed by Trichopoulou et al. (21) in 1995, which includes intakes of fruit, vegetables, legumes, cereal products, lipids (ratio of monounsaturated to saturated lipids), fish, dairy products, meat products, and alcohol. Because olive oil is the main source of monounsaturated fat in the Greek diet, the original MD score used the monounsaturated-to-saturated lipid ratio (23). However, because in the French diet the main sources of monounsaturated fatty acids are pork and poultry, we used a revised version of the score in which the lipid ratio was replaced by olive oil intake (28). Values of 0 or 1 were assigned to each of 9 components, using the medians of intake among participants (except for olive oil and alcohol) as cut-off values: for components frequently consumed in the MD (fruit, vegetables, legumes, cereal products, and fish), participants were assigned a value of 1 for intakes above the median and a value of 0 otherwise. For components traditionally less consumed in the MD (dairy and meat products), a value of 0 was assigned for intakes above the median and a value of 1 otherwise. For alcohol, a value of 1 was given to women consuming a moderate amount of alcohol (5–25 g/d) and a value of 0 otherwise. The scoring for olive oil was modified because of the large proportion of nonconsumers in our population (~60%): a value of 1 was assigned to consumers and of 0 to nonconsumers. Therefore, the sum of values for each component could take values from 0 (no adherence) to 9 points (maximum adherence). The MD score was further classified into approximate tertiles to reflect low (0–3), medium (4, 5), or high (6–9) adherence to the MD to achieve 3 categories with a similar number of participants in each group, as reported previously (22).

Skin cancer risk factors.

Data on pigmentary traits, such as skin sensitivity to the sun (high, moderate, low), number of nevi and of freckles (very many, many, few/none), skin (very fair, fair, medium, dark, very dark) and hair color (red, blond, light brown, dark brown, black), and education (<12, 12–15, ≥15 y), were collected through questionnaire at inclusion. Family history of skin cancer was collected in 2000. To estimate average levels of residential sun exposure during childhood and adulthood, we linked data on county of birth and of residence at baseline to a database containing mean daily UV radiation doses in French counties provided by the Joint Research Center of the European Commission (29).

Other factors.

Height was collected at baseline and in the 1994, 2000, 2002, and 2005 questionnaires, and self-reported weight and smoking status (nonsmoker, former, or current smoker) were available in each questionnaire. BMI was calculated at each time point by dividing weight (kilograms) by height (squared meters) (<18.5, 18.5–24.9, 25–30, >30 kg/m^2). In this study, because mean BMI was stable across questionnaires, we only considered BMI at baseline in the adjustment models. Baseline physical activity was assessed in metabolic equivalents of task (hours per week, assessed in tertiles) using data on time spent walking, biking, swimming, playing tennis, or fitness exercising in a typical week over the past year. Each questionnaire inquired about history of health screening tests, and we have used number of screening tests since the last questionnaire (mammography, Pap smear, and colonoscopy) as a proxy for frequency of health screening.

Study population

Women contributed person-time from the return date of the dietary questionnaire until the date of skin cancer or any other cancer diagnosis, date of last completed questionnaire, or date of end of follow-up (June 2008), whichever occurred first. From the population of 98,995 women, we excluded women who did not return the dietary questionnaire sent in 1993 (n = 29,891), those with a prevalent cancer at baseline in 1993 (n = 421), and those with extreme energy intake values (<1st and >99th percentiles of the distribution) (n = 1351), leaving a final sample of 67,322 women.

Statistical analysis

Statistical analyses were performed using the SAS package (version 9.4; SAS Institute). As previously published in this study population (30–32), the primary outcome of this research was the overall risk of skin cancer, and the secondary outcome variables were the risks of cutaneous melanoma, BCC, and SCC. We estimated HRs and 95% CIs for the association between MD score and skin cancer risk using Cox proportional hazards regression models with age as the time scale. The proportional hazards assumption was tested using Schoenfeld residuals (33) and was satisfied. We first assessed MD score in a categorical approach (i.e., low, medium, and high), then through a continuous approach (1-point increments in score). The lowest MD score (0–3) was used as the reference category in the models. Tests for linear trend were performed using an ordinal variable across MD score tertiles. Primary models were adjusted for age and stratified by birth cohort (in 5-y categories) to consider a possible cohort effect (model 1) (34–36), then also adjusted for pigmentary traits, family history of skin cancer (yes, no), levels of residential sun exposure in childhood and at baseline (tertiles), and energy intake (g/d, continuous) (model 2). Model 3 was further adjusted for BMI, physical activity, smoking status (nonsmoker, former, or current smoker), education (<12, 12–15, ≥15 y), and coffee intake (g/d, tertiles). BMI, smoking status, education, physical activity, and coffee intake are several lifestyle factors that may be associated with a healthy diet, particularly with the MD, and thereby may act as confounders of the association between MD score and skin cancer risk. Previous studies have shown an association between these factors and melanoma risk (37–40). In particular, we showed that coffee, but not tea, was associated with a reduced melanoma risk in the European Prospective Investigation into Cancer and nutrition (EPIC) cohort study (41). To exclude potential residual confounding by these lifestyle factors, we thus took these variables into account in the analyses (37–40). We analyzed melanoma risk according to anatomic site and histologic subtype using competing-risk models with the cause-specific hazards approach. For these analyses, we excluded cases with missing information on anatomic site (n = 22) or histologic subtype (n = 22). Tests for heterogeneity were performed to compare estimates over strata using Wald χ^2 tests (42). We also assessed associations between single dietary components of the MD and skin cancer risk. We performed sensitivity analyses by replacing olive oil in the MD score by the ratio of mono/polyunsaturated to saturated lipids to compare our revised version of the MD score with previous versions (22, 43). Because alcohol intake has been positively associated with skin cancer risk in recent meta-analyses (44, 45), and as wine is likely the most consumed alcoholic beverage in the Mediterranean region, we performed sensitivity analyses by *1*) excluding the alcohol component from the MD score, and *2*) replacing alcohol with wine in the MD score.

To explore the hypothesis that the association between MD score and skin cancer risk is explained by sun exposure behaviors, we examined the associations between behavioral sun exposure and MD score in the controls of E3N-SunExp, a case-control study nested in E3N including 1558 skin cancer cases and 3647 matched controls (matched on age, county of birth, education, and length of follow-up in the cohort) in whom we collected detailed information on the participants' residential and recreational UV exposure over lifetime (31). We used age-adjusted logistic regression models, excluding 352 participants with missing data on diet. We evaluated potential effect modification by relevant factors using Wald tests. Values were missing in <5% of observations for all adjustment variables and were imputed to the median or modal categories in our population. All statistical tests were 2-sided, and significance was set at the 0.05 level.

Results

From 1993 to 2008, 404 melanoma, 1367 BCC, and 232 SCC cases were ascertained among the 67,332 included women. The MD score distribution was as follows: low (31%), medium (46%), and high (23%). Participants with a high MD score were slightly

older and more likely to have medium/dark skin, as well as higher levels of residential sun exposure, education, and physical activity than those with a low MD score (**Table 1**). However, they were less likely to be overweight/obese or smokers. As expected, participants with a high MD score were more likely to have high intakes of fruit, vegetables, legumes, cereal products, fish, and olive oil; a higher ratio of unsaturated to saturated lipids; and lower intakes of dairy and meat products (**Supplementary Table 1**).

Score of adherence to the MD was associated with lower skin cancer risk in the fully adjusted model (HR: 0.83; 95% CI: 0.73, 0.93 for high compared with low, $P_{trend} = 0.001$; HR: 0.97; 95% CI: 0.94, 0.99 per unit increase in MD score) (**Table 2**). When considering skin cancer type, adherence to the MD was inversely and linearly associated with risks of melanoma (HR: 0.72; 95% CI: 0.54, 0.96 for high compared with low, $P_{trend} = 0.02$) and BCC (HR: 0.77; 95% CI: 0.66, 0.90, $P_{trend} = 0.0006$; HR: 0.96; 95% CI: 0.93, 0.99 per unit increase). However, we found no association between MD score and SCC risk (HR: 1.08; 95% CI: 0.75, 1.55 for high compared with low, $P_{trend} = 0.68$), although we detected no heterogeneity across skin cancer types ($P_{heterogeneity} = 0.23$). The results did not substantially change throughout the 3 models tested.

When assessing the relations between single dietary components in the MD score and skin cancer risk, we found an inverse association between the score associated with vegetable intake and overall skin cancer risk (HR: 0.90; 95% CI: 0.81, 0.97); however, other components of the MD score were not associated with skin cancer risk (**Table 3**).

In stratified analyses according to body site and histologic type of melanoma, associations seemed stronger for melanoma on the trunk and upper limbs and for superficial spreading melanoma. However, we detected no heterogeneity across subtypes ($P_{heterogeneity} = 0.23$) or sites ($P_{heterogeneity} = 0.60$) (**Table 4**).

Stratified analyses showed no substantial difference in the association between MD score and skin cancer risk across categories of selected factors (**Supplementary Table 2**). Results remained similar when considering the previous version of the MD score that considers the ratio of unsaturated to saturated lipids instead of olive oil (22, 43) (**Supplementary Table 3**). In a sensitivity analysis excluding the alcohol component from the MD score, we observed little changes in the results by 1-unit increment and in the associations between MD score and skin cancer risk overall and BCC risk (data not tabulated). However, the inverse association with melanoma was no longer statistically significant (HR: 0.82; 95% CI: 0.62, 1.09 for high compared with low, $P_{trend} = 0.20$). We had the same observations in another sensitivity analysis in which we replaced alcohol with wine consumption: the results were not substantially modified, except for melanoma, for which the association was no longer statistically significant (HR: 0.89; 95% CI: 0.69, 1.19 for high compared with low, $P_{trend} = 0.51$). Finally, results were unchanged when associations between MD score and skin cancer risk were also adjusted for health screening (data not tabulated).

When investigating the potential associations between behavioral sun exposure and MD score among the controls of E3N-SunExp, we found that sunscreen use after age 25 y was positively associated with a higher score of adherence to the MD [sunscreen use with sun protection factor (SPF) 8: OR: 1.23; 95% CI: 0.87, 1.75; SPF 8–15: OR: 1.22; 95% CI: 0.96, 1.62; SPF 15–30: OR: 1.23; 95% CI: 0.98, 1.56; SPF >30: OR: 1.64; 95% CI: 1.27, 2.12 compared with no sunscreen; $P_{trend} = 0.05$]. However, other UV exposure factors, such as number of sunburns since age 25 y, reapplication of sunscreen, tanning bed use, and lifetime hours of total, residential, or recreational sun exposure, were not associated with the MD score (**Supplementary Table 4**).

Discussion

In this large prospective cohort of women, we found that a high score of adherence to the MD was associated with a lower skin cancer risk, particularly of melanoma and BCC. However, single components of the MD were generally not associated with skin cancer risk, except for vegetable intake, which was inversely associated with overall skin cancer risk. To our knowledge, this study is the first investigation to prospectively examine associations between the MD pattern and skin cancer risk.

Previous studies have suggested a protective effect of the MD on health and longevity (21, 23). A recent meta-analysis including 4 million subjects suggested a beneficial effect of the MD on the occurrence of several chronic diseases, including cancer (28). However, while numerous investigations explored associations between single components of the MD and skin cancer risk (17, 20, 46), few explored the MD pattern: only 1 Italian case-control study is available on melanoma (24). The latter study showed no overall association between MD score and melanoma risk; however, there was an inverse association in women with a moderate score (5, 6) and in those aged <50 y. In contrast, we found no evidence of effect modification by age or birth cohort in our study. Differences compared with our results may be explained by a relatively small population in the Italian study (205 cases/400 controls) and by the difference in the age structure of our study populations: the Italian study included a majority of women aged <60 y (mean: 53 y), whereas E3N women were aged 40–65 y in 1990 and thus 58–83 y at the end of follow-up (mean: 65 y). The authors also mentioned that residual confounding may have occurred because of a lack of information on several factors (nevi/freckling, family history of skin cancer, smoking, physical activity).

Another Italian case-control study explored single components of the MD pattern and has shown a lower melanoma risk associated with the use of fresh herbs and high intakes of fruit, carrots, cruciferous and dark-green vegetables, and fish (47). Two case-control studies also reported associations with single components of the MD: intake of cereal products was inversely associated with BCC risk in Italy (20), and fish, cereal products, fruit, and vegetable intakes were also inversely associated with melanoma risk in the United States (17). These results are consistent with our findings of a lower overall skin cancer risk associated with vegetable intake.

Several potential mechanisms could explain a lower risk of skin cancer in relation to the MD pattern. First, in our study, a high MD score was associated with high intakes of antioxidant nutrients, such as β-carotene, retinol, and vitamins C and E, and with high intakes of folate, vitamin D, and coffee. A high MD score has also been reported to be associated with

TABLE 1 Baseline characteristics of study subjects according to score of adherence to the MD, E3N cohort ($N = 67,332$)[1]

Characteristic	Score of adherence to the MD			P value[2]
	Low (0–3)	Medium (4–5)	High (6–9)	
Total	20,879 (31.0)	30,709 (45.6)	15,744 (23.4)	
Age at baseline, y	52.4 ± 6.6	52.8 ± 6.6	53.2 ± 6.6	<0.0001
Skin sensitivity to the sun				
High	6047 (29.0)	8620 (28.1)	4133 (26.2)	
Moderate	10,268 (49.2)	15,168 (49.4)	8060 (51.2)	
Low	4564 (21.8)	6921 (22.5)	3551 (22.6)	<0.0001
Skin color				
Very fair/fair	12,654 (60.6)	18,210 (59.3)	9140 (58.1)	
Medium/dark/very dark	8225 (39.4)	12,499 (40.7)	6604 (41.9)	<0.0001
Hair color				
Red	344 (1.6)	493 (1.6)	260 (1.6)	
Blond	2095 (10.1)	3043 (9.9)	1588 (10.2)	
Light brown	12,663 (60.6)	18,522 (60.3)	9410 (59.7)	
Dark brown/black	5777 (27.7)	8651 (28.2)	4486 (28.5)	0.67
Number of nevi				
Very many	2275 (10.9)	3302 (10.8)	1674 (10.6)	
Many	9096 (43.6)	13,269 (43.2)	6857 (43.6)	
A few/none	9508 (45.5)	14,138 (46.0)	7213 (45.8)	0.78
Number of freckles				
Very many	1053 (5.0)	1545 (5.0)	818 (5.2)	
Many	5889 (28.3)	8907 (29.0)	4621 (29.4)	
A few	4956 (23.7)	7522 (24.5)	3864 (24.5)	
None	8981 (43.0)	12,735 (41.5)	6441 (40.9)	0.002
Family history of skin cancer				
No	20,664 (98.9)	30,374 (98.9)	15,563 (98.8)	
Yes	215 (1.1)	335 (1.1)	181 (1.2)	0.54
Level of residential sun exposure at birth, kJ/m^2	2.5 ± 0.2	2.5 ± 0.2	2.6 ± 0.2	<0.0001
Level of residential sun exposure at baseline, kJ/m^2	2.5 ± 0.3	2.6 ± 0.3	2.6 ± 0.3	<0.0001
Education level, y				
<12	3201 (15.3)	4168 (13.6)	2034 (12.9)	
12–15	10,665 (51.1)	15,695 (51.1)	7956 (50.6)	
≥15	7013 (33.6)	10,846 (35.3)	5754 (36.5)	<0.0001
BMI, kg/m^2				
<18.5	3030 (14.5)	4472 (14.5)	2299 (14.6)	
18.5–24	13,350 (63.9)	19,773 (64.4)	10,398 (66.0)	
25–29	3632 (17.4)	5223 (17.0)	2567 (16.3)	
≥30	867 (4.2)	1241 (4.0)	480 (3.1)	<0.0001
Smoking status				
Nonsmoker	12,457 (59.6)	17,885 (58.2)	8989 (57.1)	
Former smoker	6209 (29.8)	9727 (31.7)	5297 (33.6)	
Current smoker	2213 (10.60)	3097 (10.1)	1458 (9.3)	<0.0001
Physical activity level, METs-h/wk				
Tertile 1 (≤27.3)	7886 (37.7)	9883 (32.2)	4307 (27.4)	
Tertile 2 (27.4–50.8)	6677 (32.0)	10,156 (33.1)	5231 (33.2)	
Tertile 3 (>50.8)	6316 (30.3)	10,670 (34.7)	6206 (39.4)	<0.0001

[1] Values are presented as n (%) or mean ± SD. E3N, Etude Epidémiologique auprès de femmes de l'Education Nationale; MD, Mediterranean diet; METs, metabolic equivalents of task.

[2] Values were estimated using χ^2 tests for categorical variables and ANOVA tests for continuous variables.

higher total antioxidant capacity from diet (48) and higher circulating levels of antioxidants (49). Experimental studies have shown that dietary intakes of antioxidants reduce oxidative DNA damage and increase the skin's ability to neutralize free radicals, thereby contributing to alleviate skin photodamage (50, 51). Epidemiological studies have shown that diets rich in carotenoids; vitamins A, C, and E; polyphenols; and flavones may lower melanoma risk (45–48). Furthermore, we observed that a higher MD score was associated with low intakes of saturated fat (known as proinflammatory) and high intakes of mono- and polyunsaturated fats, and omega-3 polyunsaturated fatty acids are known to be associated with lower inflammation levels (52, 53). Results from observational studies indeed suggested that a greater adherence to the MD was associated with a reduction in various inflammatory factors such as C-reactive protein and IL-6 (54) and that the MD has anti-inflammatory effects (55). Chronic inflammation is linked to the development and progression of multiple cancers, including of the skin (56), and anti-inflammatory nutrients may have a beneficial influence on skin cancer risk (57–59).

TABLE 2 HRs and 95% CIs for score of adherence to the MD in relation to incident skin cancer risk, E3N cohort ($N = 67,332$)[1]

	Score of adherence to the MD				
	Low (0–3) HR (95% CI)	Medium (4–5) HR (95% CI)	High (6–9) HR (95% CI)	*P*-trend	Per 1-unit increment in MD score HR (95% CI)
Skin cancer ($n = 2174$)[2]					
Number of cases	716	970	488		
Model 1[3]	1 [Reference]	0.91 (0.82, 1.00)	0.87 (0.77, 0.97)	0.01	0.98 (0.95, 1.01)
Model 2[4]	1 [Reference]	0.90 (0.81, 0.99)	0.84 (0.75, 0.95)	0.004	0.97 (0.95, 1.00)
Model 3[5]	1 [Reference]	0.89 (0.81, 0.98)	0.83 (0.73, 0.93)	0.001	0.97 (0.94, 0.99)
Melanoma ($n = 404$)					
Number of cases	141	185	78		
Model 1[3]	1 [Reference]	0.89 (0.71, 1.10)	0.72 (0.55, 0.95)	0.02	0.95 (0.89, 1.01)
Model 2[4]	1 [Reference]	0.90 (0.72, 1.13)	0.74 (0.56, 0.98)	0.04	0.95 (0.89, 1.02)
Model 3[5]	1 [Reference]	0.89 (0.71, 1.11)	0.72 (0.54, 0.96)	0.02	0.95 (0.89, 1.01)
BCC ($n = 1367$)					
Number of cases	460	608	299		
Model 1[3]	1 [Reference]	0.89 (0.79, 1.00)	0.83 (0.72, 0.96)	0.009	0.97 (0.94, 1.01)
Model 2[4]	1 [Reference]	0.87 (0.77, 0.98)	0.79 (0.68, 0.92)	0.001	0.96 (0.93, 1.00)
Model 3[5]	1 [Reference]	0.86 (0.76, 0.97)	0.77 (0.66, 0.90)	0.0006	0.96 (0.93, 0.99)
SCC ($n = 232$)					
Number of cases	68	104	60		
Model 1[3]	1 [Reference]	1.01 (0.74, 1.37)	1.09 (0.77, 1.54)	0.63	1.05 (0.96, 1.13)
Model 2[4]	1 [Reference]	1.02 (0.75, 1.39)	1.12 (0.78, 1.60)	0.55	1.05 (0.97, 1.15)
Model 3[5]	1 [Reference]	1.01 (0.74, 1.37)	1.08 (0.75, 1.55)	0.68	1.05 (0.96, 1.14)

[1] Values were estimated with the use of Cox proportional hazards models. BCC, basal cell carcinoma; E3N, Etude Epidémiologique auprès de femmes de l'Education Nationale; MD, Mediterranean diet; METs, metabolic equivalent of task; SCC, squamous cell carcinoma.

[2] A total of 171 participants with unknown skin cancer types.

[3] Adjusted for age (timescale) and stratified by birth cohort (1925–1930, 1930–1935, 1935–1940, 1940–1945, 1945–1950).

[4] Also adjusted for skin sensitivity to sun exposure (high, moderate, low), number of nevi (very many, many, few/none), number of freckles (very many, many, few, none), skin color (very fair/fair, medium/dark/very dark), hair color (red, blond, light brown, dark brown, black), family history of skin cancer (yes, no), levels of residential sun exposure at birth and at baseline (tertiles), and energy intake (continuous).

[5] Also adjusted for BMI (<18.5, 18.5–24, 25–30, >30 kg/m^2), physical activity (METs-h per week, assessed in tertiles), smoking status (nonsmoker, former, or current smoker), education level (<12, 12–15, ≥15 y), and coffee intake (tertiles). Tests for heterogeneity using the *Q* test were performed to compare estimates over strata. $P_{heterogeneity}$ across skin cancer types was 0.23.

While we found inverse linear associations between the MD score and melanoma and BCC risks, there was no association with SCC risk in our study. However, given the absence of heterogeneity in estimates across skin cancer types, this may be explained by the lower number of SCC cases in our population. It is also possible that SCC develops through different pathways than other skin cancer types. Generally, melanoma and BCC have similar associations with regard to potential risk factors, and SCC seems to be sensitive to a different risk factor profile. For example, melanoma and BCC are known to be associated with childhood and intermittent sun exposure (60), while SCC is more determined by cumulative chronic sun exposure (61, 62). Number of nevi is associated with melanoma and BCC but not with SCC (63), and while smoking is inversely associated with melanoma and BCC, it is positively associated with SCC risk (64). It is thus plausible that the MD affects melanoma and BCC but not SCC. Further studies are needed to investigate this hypothesis.

We also found no association between single components of the MD score and skin cancer risk, except for vegetable intake and skin cancer, which could be because food items may have small individual effects that are visible only as part of an overall dietary pattern, when cumulative and synergistic effects of multiple foods are being considered. Indeed, it has been suggested that biological interactions between different dietary components may be difficult to detect when studying single food items (65). When we excluded the alcohol component from the MD score or replaced alcohol with wine consumption in the score, we observed that the association with melanoma had lost statistical significance. This can be explained by the fact that alcohol consumption is inversely associated with melanoma risk in our study population (66), which is likely due to the fact that women in the cohort are moderate drinkers (median alcohol intake: 7.9 g/d) and mostly consume wine, 2 characteristics associated with the MD and considered a healthy pattern in the score.

Our study has several limitations that should be considered in the interpretation of our findings. Dietary intakes and potential confounding factors were self-reported, and some degree of misclassification cannot be excluded. However, such misclassification is likely to be nondifferential because dietary factors were collected prior to skin cancer diagnosis and thus to only reduce the study power. We estimated the MD score through a single baseline dietary assessment, which could not consider dietary changes during follow-up. In addition, it could be hypothesized that participants with a higher adherence to the MD use the medical care system or perform health screening tests more frequently and thus are more likely to be health-conscious and have their pigmented lesions removed. However, our results were similar after adjustment for health screening tests, suggesting that our findings are not mainly explained by

TABLE 3 Adjusted HRs and 95% CIs for intake of dietary components of the MD score in relation to incident skin cancer risk, E3N cohort ($N = 67,332$)[1]

MD score component	Skin cancer HR (95% CI)[2]	Melanoma HR (95% CI)[2]	BCC HR (95% CI)[2]	SCC HR (95% CI)[2]
Fruit				
0	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
1	1.02 (0.94, 1.12)	1.12 (0.91, 1.37)	1.00 (0.90, 1.12)	1.06 (0.81, 1.38)
Vegetables				
0	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
1	0.90 (0.81, 0.97)	0.87 (0.71, 1.06)	0.91 (0.82, 1.02)	0.82 (0.62, 1.07)
Legumes				
0	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
1	0.93 (0.85, 1.01)	0.93 (0.76, 1.15)	0.89 (0.80, 1.00)	1.04 (0.79, 1.37)
Cereals				
0	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
1	0.96 (0.87, 1.06)	0.88 (0.70, 1.11)	1.01 (0.90, 1.15)	0.90 (0.67, 1.20)
Fish products				
0	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
1	1.02 (0.93, 1.11)	1.12 (0.91, 1.37)	0.98 (0.88, 1.10)	1.09 (0.83, 1.42)
Dairy products				
0	1.05 (0.97, 1.15)	1.11 (0.91, 1.35)	1.09 (0.97, 1.21)	0.93 (0.72, 1.21)
1	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Meat products				
0	1.05 (0.96, 1.15)[1]	1.07 (0.87, 1.31)	1.07 (0.96, 1.20)	0.77 (0.59, 1.02)
1	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Olive oil				
0	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
1	1.04 (0.95, 1.13)	0.91 (0.74, 1.11)	1.03 (0.92, 1.15)	1.29 (0.98, 1.67)
Alcohol				
0	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
1	0.98 (0.90, 1.06)	0.89 (0.73, 1.09)	0.99 (0.88, 1.10)	0.99 (0.76, 1.28)
Wine				
0	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
1	1.05 (0.96, 1.15)	1.06 (0.86, 1.30)	1.03 (0.92, 1.16)	1.03 (0.78, 1.35)

[1]Values were estimated with the use of Cox proportional hazards models. BCC, basal cell carcinoma; E3N, Etude Epidémiologique auprès de femmes de l'Education Nationale; MD, Mediterranean diet; METs, metabolic equivalents of task; SCC, squamous cell carcinoma.

[2]Stratified by birth cohort (1925–1930, 1930–1935, 1935–1940, 1940–1945, 1945–1950) and adjusted for age, skin sensitivity to sun exposure (high, moderate, low), number of nevi (very many, many, few/none), number of freckles (very many, many, few, none), skin color (very fair/fair, medium/dark/very dark), hair color (red, blond, light brown, dark brown, black), family history of skin cancer (yes, no), levels of residential sun exposure at birth and at baseline (tertiles), BMI (<18.5, 18.5–24, 25–30, >30 kg/m^2), physical activity (METs-h per week, assessed in tertiles), smoking status (nonsmoker, former, or current smoker), education level (<12, 12–15, ≥15 y), and energy intake (g/d, continuous), coffee intake (g/d, tertiles), and also adjusted for other dietary components of the MD score listed in the table.

better health screening in women with a higher MD score. Future studies should investigate more specifically if skin examinations have an impact on these associations. Also, participants with a high MD score were more likely to be educated and physically active and less likely to be overweight/obese or smokers than those with a low MD score, which could suggest a bias related to socioeconomic factors. However, it should be noted that we found no effect modification by education level, smoking status, or physical activity on the relation between MD score and skin cancer risk. Finally, we cannot rule out residual confounding because data on confounding factors such as eye color and UV exposure were unavailable or incomplete in the cohort. Regarding UV exposure in particular, we had data only on UV exposure based on residence, which is an incomplete evaluation of total UV exposure. It could be hypothesized that our findings are explained by an association between the MD pattern and sun-protective behaviors. However, while our sensitivity analysis showed that women with a higher MD score were more likely to use sunscreen with a high SPF, it should be noted that sunscreen use was previously associated with a higher skin cancer risk in this population (31)—which has been observed in other populations around the world and has been explained by the "sunscreen abuse" hypothesis (use of sunscreen with the intention to tan). Therefore, these results do not support the hypothesis that the inverse association between MD score and skin cancer risk is explained by healthier sun exposure behaviors in participants with a higher MD score. Ideally, future studies should investigate the potential impact of UV exposure on these associations using prospectively collected data on sun exposure to deepen our understanding of these associations. Despite these limitations, the present study has several strengths, including its prospective design, large sample size, long duration of follow-up, and use of a validated dietary score. Skin cancer cases were confirmed through pathology reports, and dietary intakes were assessed from a validated questionnaire.

In conclusion, in this large prospective cohort of French women, adherence to the MD was linearly associated with a decreased risk of skin cancer, particularly of melanoma and

TABLE 4 HRs and 95% CIs for the associations between score of adherence to the MD and melanoma risk according to body site and histologic type of melanoma, E3N cohort ($N = 67,332$)[1]

Characteristic	Number of cases	Score of adherence to the MD			*P*-trend
		Low (0–3) HR (95% CI)	Medium (4–5) HR (95% CI)	High (6–9) HR (95% CI)	
Melanoma body site					
Head and neck	44	1 [Reference]	0.79 (0.41, 1.52)	0.52 (0.21, 1.29)	0.15
Trunk	60	1 [Reference]	0.88 (0.51, 1.51)	0.27 (0.10, 0.71)	0.01
Upper limbs	84	1 [Reference]	0.69 (0.43, 1.11)	0.48 (0.25, 0.92)	0.02
Lower limbs	194	1 [Reference]	0.98 (0.70, 1.37)	1.00 (0.67, 1.49)	0.93
Melanoma histologic type					
SSM	256	1 [Reference]	0.94 (0.71, 1.24)	0.71 (0.50, 1.02)	0.07
NM	12	1 [Reference]	0.12 (0.02, 1.06)	1.70 (0.47, 6.08)	0.65
LM	37	1 [Reference]	0.72 (0.35, 1.48)	0.52 (0.19, 1.37)	0.16
ALM	17	1 [Reference]	1.52 (0.46, 5.01)	1.24 (0.30, 5.22)	0.75
Other	60	1 [Reference]	0.76 (0.43, 1.33)	0.69 (0.33, 1.45)	0.28

[1]Competing-risk models were adjusted for age (time scale) and stratified by birth cohort (1925–1930, 1930–1935, 1935–1940, 1940–1945, 1945–1950) and also adjusted for skin sensitivity to sun exposure (high, moderate, low), number of nevi (very many, many, few/none), number of freckles (very many, many, few, none), skin color (very fair/fair, medium/dark/very dark), hair color (red, blond, light brown, dark brown, black), family history of skin cancer (yes, no), levels of residential sun exposure at birth and at baseline (tertiles), BMI (<18.5, 18.5–24, 25–30, >30 kg/m^2), physical activity (METs-h per week, assessed in tertiles), smoking status (nonsmoker, former, or current smoker), education level (<12, 12–15, ≥ 15 y), energy intake (g/d, continuous), and coffee intake (g/d, tertiles). $n = 22$ Melanoma cases with missing histologic type were excluded for subtype-specific analyses, and $n = 22$ melanoma cases with missing location were excluded for site-specific analyses. Tests for heterogeneity using the *Q* test were performed to compare estimates over strata. $P_{\text{heterogeneity}}$ across melanoma subtypes and sites were 0.23 and 0.60, respectively. ALM, acro-lentiginous melanoma; E3N, Etude Epidémiologique auprès de femmes de l'Education Nationale; LMM, lentigo maligna melanoma; MD, Mediterranean diet; METs, metabolic equivalents of task; NM, nodular melanoma; SSM, superficial spreading melanoma.

BCC. Although these findings cannot be extrapolated to men or the general population, they support the hypothesis that a high level of adherence to the MD may confer protection against skin cancer. If confirmed in future research, these findings may have important public health implications in primary prevention of skin cancer.

We are thank all members of the E3N study group, particularly Rafika Chaït, Marie Fangon, Pascale Gerbouin-Rérolle, Sofiane Harizi, Lyan Hoang, Anita Kowal, Camille Laplanche, and Maxime Valdenaire, for their technical assistance.

The authors' contributions were as follows—MK conceived and designed the study; YM-S performed the statistical analysis and drafted the manuscript; YM-S, IC, MAR, IS, FRM, AT, M-CB-R, and MK: contributed to the interpretation of data discussed in the manuscript, critically revised the manuscript, and approved its final version. MK is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript. None of the authors declared a conflict of interest.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359–386.
2. de Vries E, Bray FI, Coebergh JWW, Parkin DM. Changing epidemiology of malignant cutaneous melanoma in Europe 1953–1997: rising trends in incidence and mortality but recent stabilizations in western Europe and decreases in Scandinavia. Int J Cancer 2003;107:119–26.
3. Urbach F. Incidence of nonmelanoma skin cancer. Dermatol Clin 1991;9:751–5.
4. Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. Br J Dermatol 2012;166:1069–80.
5. Miller AJ, Mihm MC. Melanoma. N Engl J Med 2006;355:51–65.
6. Guy GP, Ekwueme DU. Years of potential life lost and indirect costs of melanoma and non-melanoma skin cancer. PharmacoEconomics 2011;29:863–74.
7. Joseph AK, Mark TL, Mueller C. The period prevalence and costs of treating nonmelanoma skin cancers in patients over 65 years of age covered by medicare. Dermatol Surg 2001;27:955–9.
8. Gandini S, Sera F, Cattaruzza MS, Pasquini P, Picconi O, Boyle P, Melchi CF. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. Eur J Cancer 2005;41:45–60.
9. Gandini S, Sera F, Cattaruzza MS, Pasquini P, Zanetti R, Masini C, Boyle P, Melchi CF. Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors. Eur J Cancer 2005;41:2040–59.
10. Payette MJ, Whalen J, Grant-Kels JM. Nutrition and nonmelanoma skin cancers. Clin Dermatol 2010;28:650–62.
11. Jensen JD, Wing GJ, Dellavalle RP. Nutrition and melanoma prevention. Clin Dermatol 2010;28:644–9.
12. Halliwell B. Free radicals, antioxidants, and human disease: curiosity, cause, or consequence? Lancet 1994;344:721–4.
13. Sander CS, Chang H, Hamm F, Elsner P, Thiele JJ. Role of oxidative stress and the antioxidant network in cutaneous carcinogenesis. Int J Dermatol 2004;43:326–35.
14. Werninghaus K, Meydani M, Bhawan J, Margolis R, Blumberg JB, Gilchrest BA. Evaluation of the photoprotective effect of oral vitamin E supplementation. Arch Dermatol 1994;130:1257–61.
15. Katiyar SK, Bergamo BM, Vyalil PK, Elmets CA. Green tea polyphenols: DNA photodamage and photoimmunology. J Photochem Photobiol B 2001;65:109–14.
16. Gupta S, Mukhtar H. Chemoprevention of skin cancer: current status and future prospects. Cancer Metastasis Rev 2002;21:363–80.
17. Millen AE, Tucker MA, Hartge P, Halpern A, Elder DE, Guerry D, Holly EA, Sagebiel RW, Potischman N. Diet and melanoma in a case-control study. Cancer Epidemiol Biomark Prev 2004;13:1042–51.

18. Naldi L, Gallus S, Tavani A, Imberti GL, La Vecchia C; Oncology Study Group of the Italian Group for Epidemiologic Research in Dermatology. Risk of melanoma and vitamin A, coffee and alcohol: a case-control study from Italy. Eur J Cancer Prev 2004;13:503–8.
19. George SM, Park Y, Leitzmann MF, Freedman ND, Dowling EC, Reedy J, Schatzkin A, Hollenbeck A, Subar AF. Fruit and vegetable intake and risk of cancer: a prospective cohort study. Am J Clin Nutr 2009;89:347–53.
20. Davies TW, Treasure FP, Welch AA, Day NE. Diet and basal cell skin cancer: results from the EPIC-Norfolk cohort. Br J Dermatol 2002;146:1017–22.
21. Trichopoulou A, Kouris-Blazos A, Wahlqvist ML, Gnardellis C, Lagiou P, Polychronopoulos E, Vassilakou T, Lipworth L, Trichopoulos D. Diet and overall survival in elderly people. BMJ 1995;311:1457–60.
22. Couto E, Boffetta P, Lagiou P, Ferrari P, Buckland G, Overvad K, Dahm CC, Tjønneland A, Olsen A, Clavel-Chapelon F, et al. Mediterranean dietary pattern and cancer risk in the EPIC cohort. Br J Cancer 2011;104:1493–9.
23. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. N Engl J Med 2003;348:2599–608.
24. Malagoli C, Malavolti M, Agnoli C, Crespi CM, Fiorentini C, Farnetani F, Longo C, Ricci C, Albertini G, Lanzoni A, et al. Diet quality and risk of melanoma in an Italian population. J Nutr 2015;145:1800–7.
25. Clavel-Chapelon F; E3N Study Group. Cohort profile: the French E3N Cohort Study. Int J Epidemiol 2015;44:801–9.
26. Favier J, Ireland-Ripert J, Toque C, Feinberg M. Répertoire Général des Aliments. Table de composition (General repertory of foods. Composition tables), Paris. INRA. 1995.
27. van Liere MJ, Lucas F, Clavel F, Slimani N, Villeminot S. Relative validity and reproducibility of a French dietary history questionnaire. Int J Epidemiol 1997;26 Suppl 1:S128–136.
28. Sofi F, Macchi C, Abbate R, Gensini GF, Casini A. Mediterranean diet and health status: an updated meta-analysis and a proposal for a literature-based adherence score. Public Health Nutr 2014;17:2769–82.
29. Verdebout J. A European satellite-derived UV climatology available for impact studies. Radiat Prot Dosimetry 2004;111:407–11.
30. Farland LV, Lorrain S, Missmer SA, Dartois L, Cervenka I, Savoye I, Mesrine S, Boutron-Ruault M-C, Kvaskoff M. Endometriosis and the risk of skin cancer: a prospective cohort study. Cancer Causes Control 2017;28:1011–9.
31. Savoye I, Olsen CM, Whiteman DC, Bijon A, Wald L, Dartois L, Clavel-Chapelon F, Boutron-Ruault M-C, Kvaskoff M. Patterns of ultraviolet radiation exposure and skin cancer risk: the E3N-SunExp Study. J Epidemiol 2018;28:27–33.
32. Kvaskoff M, Mesrine S, Fournier A, Boutron-Ruault M-C, Clavel-Chapelon F. Personal history of endometriosis and risk of cutaneous melanoma in a large prospective cohort of French women. Arch Intern Med 2007;167:2061–5.
33. Schoenfeld D. Partial residuals for the proportional hazards regression model. Biometrika 1982;69:239–41.
34. Leiter U, Eigentler T, Garbe C. Epidemiology of skin cancer. Adv Exp Med Biol 2014;810:120–40.
35. Boyle P, Day NE, Magnus K. Mathematical modelling of malignant melanoma trends in Norway, 1953–1978. Am J Epidemiol 1983;118:887–96.
36. Thörn M, Bergström R, Adami HO, Ringborg U. Trends in the incidence of malignant melanoma in Sweden, by anatomic site, 1960–1984. Am J Epidemiol 1990;132:1066–77.
37. Pothiawala S, Qureshi AA, Li Y, Han J. Obesity and the incidence of skin cancer in US Caucasians. Cancer Causes Control 2012;23:717–26.
38. Thompson CA, Zhang Z-F, Arah OA. Competing risk bias to explain the inverse relationship between smoking and malignant melanoma. Eur J Epidemiol 2013;28:557–67.
39. Lee TK, MacArthur AC, Gallagher RP, Elwood MJ. Occupational physical activity and risk of malignant melanoma: the Western Canada Melanoma Study. Melanoma Res 2009;19:260–6.
40. Stensvold I, Jacobsen BK. Coffee and cancer: a prospective study of 43,000 Norwegian men and women. Cancer Causes Control 1994;5:401–8.
41. Caini S, Masala G, Saieva C, Kvaskoff M, Savoye I, Sacerdote C, Hemmingsson O, Hammer Bech B, Overvad K, Tjønneland A, et al. Coffee, tea and melanoma risk: findings from the European Prospective Investigation into Cancer and Nutrition. Int J Cancer 2017;140:2246–55.
42. Allison PD. Survival analysis using SAS® system: a practical guide. Cary, NC: SAS Institute; 1995.
43. Trichopoulou A, Orfanos P, Norat T, Bueno-de-Mesquita B, Ocké MC, Peeters PH, Schouw YT van der, Boeing H, Hoffmann K, Boffetta P, et al. Modified Mediterranean diet and survival: EPIC-elderly prospective cohort study. BMJ 2005;330:991.
44. Rota M, Pasquali E, Bellocco R, Bagnardi V, Scotti L, Islami F, Negri E, Boffetta P, Pelucchi C, Corrao G, et al. Alcohol drinking and cutaneous melanoma risk: a systematic review and dose-risk meta-analysis. Br J Dermatol 2014;170:1021–8.
45. Yen H, Dhana A, Okhovat J-P, Qureshi A, Keum N, Cho E. Alcohol intake and risk of nonmelanoma skin cancer: a systematic review and dose-response meta-analysis. Br J Dermatol 2017;177:696–707.
46. Yang K, Fung T, Nan H. An epidemiological review of diet and cutaneous malignant melanoma. Cancer Epidemiol Prev Biomark 2018;27(10):1115–22.
47. Fortes C, Mastroeni S, Melchi F, Pilla MA, Antonelli G, Camaioni D, Alotto M, Pasquini P. A protective effect of the Mediterranean diet for cutaneous melanoma. Int J Epidemiol 2008;37:1018–29.
48. Pitsavos C, Panagiotakos DB, Tzima N, Chrysohoou C, Economou M, Zampelas A, Stefanadis C. Adherence to the Mediterranean diet is associated with total antioxidant capacity in healthy adults: the ATTICA study. Am J Clin Nutr 2005;82:694–9.
49. Ortner Hadžiabdić M, Vitali Čepo D, Rahelić D, Božikov V. The effect of the Mediterranean diet on serum total antioxidant capacity in obese patients: a randomized controlled trial. J Am Coll Nutr 2016;35:224–35.
50. Pauling L. Effect of ascorbic acid on incidence of spontaneous mammary tumors and UV-light–induced skin tumors in mice. Am J Clin Nutr 1991;54:1252S–5S.
51. Godic A, Poljšak B, Adamic M, Dahmane R. The role of antioxidants in skin cancer prevention and treatment. Oxid Med Cell Longev 2014;2014:860479.
52. Giugliano D, Ceriello A, Esposito K. The effects of diet on inflammation: emphasis on the metabolic syndrome. J Am Coll Cardiol 2006;48:677–85.
53. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hébert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. Public Health Nutr 2014;17:1689–96.
54. Chrysohoou C, Panagiotakos DB, Pitsavos C, Das UN, Stefanadis C. Adherence to the Mediterranean diet attenuates inflammation and coagulation process in healthy adults: the ATTICA study. J Am Coll Cardiol 2004;44:152–8.
55. Ahluwalia N, Andreeva VA, Kesse-Guyot E, Hercberg S. Dietary patterns, inflammation and the metabolic syndrome. Diabetes Metab 2013;39:99–110.
56. Tang L, Wang K. Chronic inflammation in skin malignancies. J Mol Signal 2016;11:2.
57. Ulu A, Harris TR, Morisseau C, Miyabe C, Inoue H, Schuster G, Dong H, Iosif A-M, Liu J-Y, Weiss RH, et al. Anti-inflammatory effects of omega-3 polyunsaturated fatty acids and soluble epoxide hydrolase inhibitors in angiotensin-II dependent hypertension. J Cardiovasc Pharmacol 2013;62:285–97.
58. Shahbakhti H, Watson REB, Azurdia RM, Ferreira CZ, Garmyn M, Rhodes LE. Influence of eicosapentaenoic acid, an omega-3 fatty acid, on ultraviolet-B generation of prostaglandin-E2 and proinflammatory cytokines interleukin-1 beta, tumor necrosis factor-alpha, interleukin-6 and interleukin-8 in human skin *in vivo*. Photochem Photobiol 2004;80:231–5.
59. Katiyar SK. Silymarin and skin cancer prevention: anti-inflammatory, antioxidant and immunomodulatory effects. Int J Oncol 2005;26:169–76.
60. Elwood JM, Jopson J. Melanoma and sun exposure: an overview of published studies. Int J Cancer 1997;73:198–203.
61. Armstrong BK, Kricker A. The epidemiology of UV induced skin cancer. J Photochem Photobiol B 2001;63:8–18.
62. Armstrong BK, Kricker A, English DR. Sun exposure and skin cancer. Australas J Dermatol 1997;38 Suppl 1:S1–6.

63. Wei EX, Li X, Nan H. Extremity nevus count is an independent risk factor for basal cell carcinoma and melanoma, but not squamous cell carcinoma. J Am Acad Dermatol 2019;80: 970–8.
64. Pirie K, Beral V, Heath AK, Green J, Reeves GK, Peto R, McBride P, Olsen CM, Green AC. Heterogeneous relationships of squamous and basal cell carcinomas of the skin with smoking: the UK Million Women Study and meta-analysis of prospective studies. Br J Cancer 2018;119:114–20.
65. Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. Curr Opin Lipidol 2002;13:3–9.
66. Kvaskoff M, Clavel-Chapelon F, Boutron-Ruault M. Cutaneous malignant melanoma and alcoholic beverages intake: a French prospective study. Nouv Dermatol 2007;26:241–2.