Mediterranean diet, Dietary Approaches to Stop Hypertension, and Pro-vegetarian dietary pattern in relation to the risk of basal cell carcinoma: a nested case-control study within the Seguimiento Universidad de Navarra (SUN) cohort

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ABSTRACT

Background: The association of dietary pattern with the risk of basal cell carcinoma (BCC) is little understood and has scarcely been investigated.

Objectives: We assessed the association of several complete dietary patterns [Mediterranean, Dietary Approaches to Stop Hypertension (DASH), and Pro-vegetarian dietary pattern] with the risk of BCC, conducting a nested case-control study (4 controls for each case).

Methods: Cases and controls were selected from the SUN (Seguimiento Universidad de Navarra) cohort using risk set sampling. Cases were identified among subjects free of skin cancer at baseline but who later reported a physician-made BCC diagnosis during the follow-up period. In the cohort we identified 101 incident cases of BCC.

Results: In multivariable-adjusted conditional logistic regression analyses, better adherence to the Mediterranean diet (highest compared with lowest quintile) was associated with a 72% relative reduction in the odds of BCC (OR: 0.28; 95% CI: 0.10, 0.77; $P_{trend} = 0.014$); the DASH diet was associated with a 68% RR reduction (OR: 0.32; 95% CI: 0.14, 0.76; $P_{trend} = 0.013$) for the comparison between extreme quintiles. No association was found between a Pro-vegetarian dietary pattern and BCC. Higher fruit consumption (highest compared with lowest quintile, OR: 0.27; 95% CI: 0.11, 0.64; $P_{trend} < 0.001$) and low-fat dairy products (OR: 0.39; 95% CI: 0.16, 0.92; $P_{trend} = 0.014$) were associated with a lower BCC risk.

Conclusions: Our results suggest that Mediterranean and DASH dietary patterns may be associated with a lower risk of BCC, but confirmatory studies are required. *Am J Clin Nutr* 2020;112:364–372.

Introduction

Basal cell carcinoma (BCC), the most frequent nonmelanoma skin cancer (NMSC) (1), represents 70%–80% of skin cancers (2) and, despite the low metastatic potential and mortality rates (3, 4), it is a cause of great morbidity and an economic burden to health services (2, 5).

Several risk factors contribute to increase the risk of BCC, including intermittent intense sun exposure, painful sunburn

(especially during childhood and adolescence), fair skin, red or blond hair, light eye color, and an inability to tan; several genetic syndromes such as nevoid BCC or xeroderma pigmentosum; certain autoimmune conditions such as rheumatoid arthritis; and finally, a variety of therapies like photosensitizing medications, immunosuppressants, UV-A light, or ionizing radiation–based treatments (5, 6).

Diet is a modifiable environmental factor associated with several kinds of tumors (7) and, therefore, could also be related to BCC risk (8, 9). However, the epidemiologic studies investigating a possible relation between diet and risk of BCC have mainly focused on single nutrients, such as fat, some vitamins (A, C, D, E), carotenoids, alcohol, and certain foods, often reporting inconsistent results (5, 10–19). Therefore, to date, there is only some evidence that drinking coffee and consuming alcoholic drinks might, respectively, decrease and increase the risk of BCC (20). Such inconsistency could be due to different reasons, including an inappropriate focus based only on a single nutrient or food instead of focusing on the overall food pattern. It is possible that the assessment of dietary patterns may be superior for identifying a relation between diet and BCC risk (21–23). However, to date, few studies have investigated dietary patterns in relation to BCC risk.

The Mediterranean diet and the Dietary Approaches to Stop Hypertension (DASH) diet have been shown to be associated with reduced cancer risk (24, 25), including that of melanoma (26, 27). Moreover, a recent prospective cohort study in French women aged 40–65 y suggested a possible inverse association of adherence to the Mediterranean diet with the risk of BCC (28). However, this is the only available prospective evidence, and these results need to be confirmed by other independent prospective studies. Moreover, there is little information about the association of dietary patterns rich in plant-based foods and poor in animal-based foods, such as the Pro-vegetarian diet, with the risk of BCC. However, some bioactive compounds abundant in plant-derived foods have been speculated to have photo-protective effects and to inhibit carcinogenesis (29). In the light of this previous evidence, we hypothesized that 3 high-quality dietary patterns, defined a priori (the Mediterranean food pattern, the DASH diet, and the Pro-vegetarian diet), could be associated with a lower risk of BCC.

Therefore, we evaluated the relations between adherence to each of these 3 a priori–defined dietary patterns and the risk of BCC.

Methods

Study population

We conducted a nested case-control study, selecting the subjects from people included in the SUN (Seguimiento Universidad de Navarra) follow-up project. The SUN project is a prospective multipurpose dynamic Spanish cohort study that includes former students of the University of Navarra, Spanish-registered professionals, and other university graduates. Baseline information with regard to dietary habits, lifestyles, and health conditions was gathered using mailed or e-mailed questionnaires. After the baseline evaluation, the information was updated every 2 y with follow-up questionnaires. The recruitment of the participants started on 21 December, 1999, and it is permanently

ongoing. The overall follow-up rate is >90% (30). Before April 2016 a total of 22,492 participants had completed the baseline questionnaire. Of these participants, we excluded participants without follow-up questionnaires (2036), participants with a diagnosis for any skin cancer at baseline (98), incident cases of melanoma (22) or squamous cell carcinoma (SCC) (7), and subjects who reported extremely low or high values of energy intake (1905). Some individuals met >1 of these exclusion criteria. At this time point, for each incident case of BCC, 4 controls matched for sex, age (same decile), and analysis time were randomly selected. A total of 101 cases and 404 controls were included in the study (**Figure 1**).

This study was conducted in accordance with the guidelines of the Declaration of Helsinki and all procedures involving human subjects were approved by the Human Research Ethical Committee at the University of Navarra (091/2008). Participants received written information on their specific data to be requested by future questionnaires, the protections in place to safeguard their privacy, and the future feedback they would receive from the research team. We also informed all potential candidates of their right to refuse to participate in the SUN study or to withdraw their consent to participate at any time without reprisal, according to the principles of the Declaration of Helsinki. A series of comprehensive procedures and information were applied in order to ensure that their completion of the baseline questionnaire could be considered to imply informed consent. The Research Ethics Committee of the University of Navarra approved this method to request the informed consent of participants.

Exposure assessment

Dietary intake was assessed at baseline using a semiquantitative FFQ (136 food items) previously validated in Spain (31). A trained dietitian updated the nutrient databank by means of the latest available information included in food composition tables for Spain. Adherence to the Mediterranean diet was evaluated using the Trichopoulou score (32). Briefly, for each of the 6 protective components (MUFA:SFA ratio, legumes, cereal, fruits and nuts, vegetables, or fish), a participant received 1 point if his/her intake was over the sample median. The participant received 1 point if his/her intake was below the median for the 2 nonprotective components (whole-fat dairy products and meat/meat products). For ethanol, 1 point was awarded only for moderate amounts of intake (5–25 g/d for women and 10–50 g/d for men). The final score ranged from 0 (minimal adherence) to 9 (maximal adherence). Adherence to the DASH diet was evaluated using the score proposed by Taylor et al. (33). For each of the components, the participants were classified into quintiles according to their intake ranking. The component score for each of fruits, vegetables, nuts and legumes, low-fat dairy products, and whole grains was the participant's quintile ranking (i.e., quintile 1 was assigned 1 point and quintile 5 was assigned 5 points). For sodium, red and processed meats, and sweetened beverages, low intake was desirable: the lowest quintile was given a score of 5 points and the highest quintile a score of 1 point. Therefore, the overall DASH score ranged from 8 to 40. Finally, to build the Pro-vegetarian diet score, we adjusted the consumption (g/d) of 7 food groups of plant origin (fruit, vegetables, nuts, cereals, legumes, olive oil, and potatoes) and 5 food groups of animal origin (added animal fats, eggs, fish, dairy
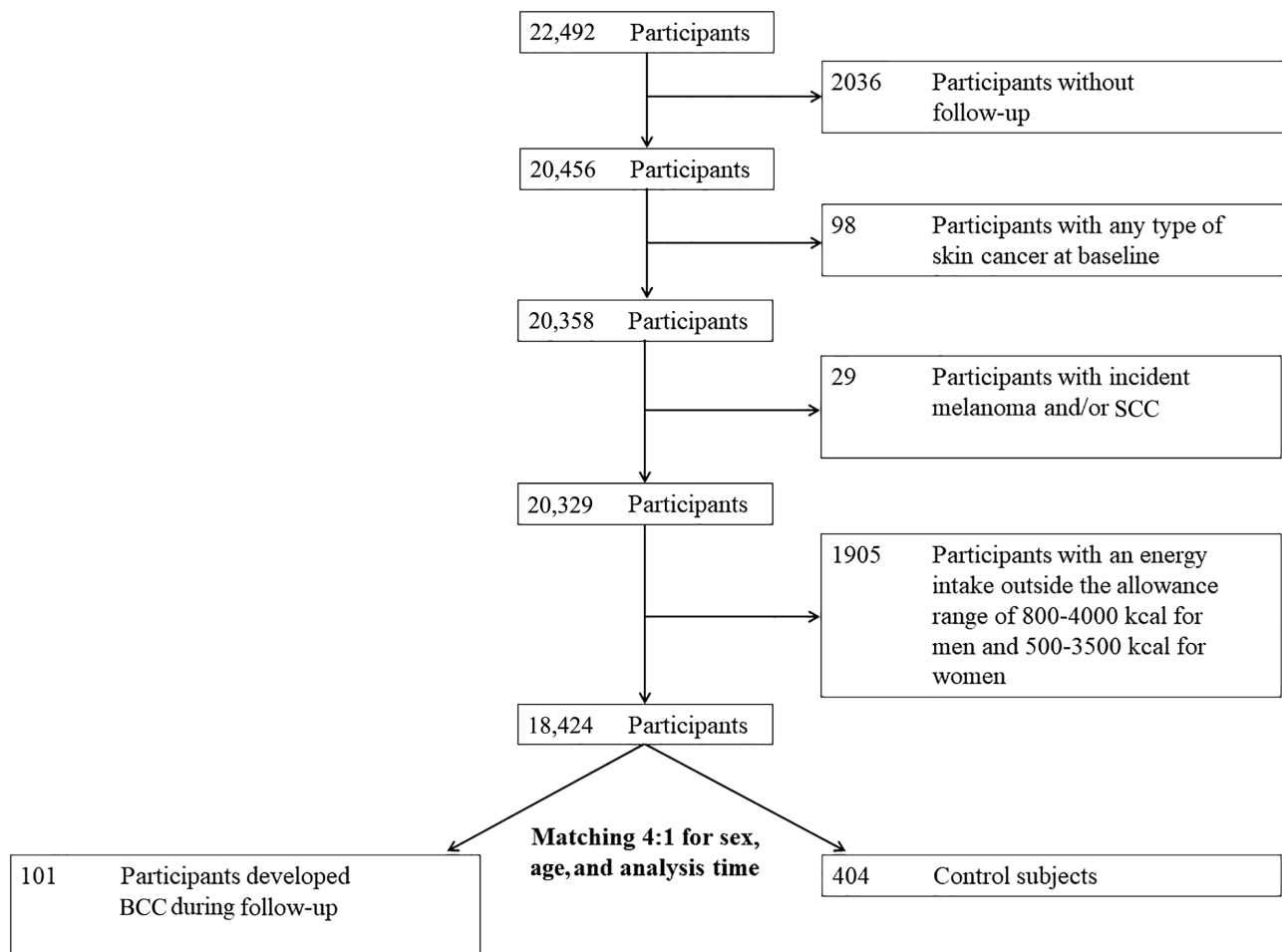
FIGURE 1 Flowchart for the nested case-control study within the Seguimiento Universidad de Navarra (SUN) cohort study. After exclusion of participants without follow-up questionnaires (2036), participants with a diagnosis for any skin cancer at baseline (98), incident cases of melanoma (22) or SCC (7), and subjects who reported extremely low or high values of energy intake (1905), 101 cases of BCC were matched with 404 controls randomly selected. Matching took into account sex, age (same decile), and analysis time. BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

products, and meats and meat products) for total energy intake by using the residual method separately for men and women. The energy-adjusted estimates were ranked according to their sex-specific quintiles. The quintile values for animal products were reversed (assigning a value of 5 for the first quintile, 4 for the second quintile, and successively until a value of 1 was assigned to the fifth quintile). To obtain the Pro-vegetarian diet score, quintile values of plant foods and reverse quintile values of animal foods were summed; thus, the final scores could range from 12 (lowest adherence) to 60 (highest adherence) following the approach described by Martínez-González et al. (34).

Covariate assessment

The baseline questionnaire was intended to gather information with regard to sociodemographic characteristics (e.g., sex and age), anthropometric variables (e.g., weight and height), lifestyle (e.g., smoking status and physical activity), history of chronic diseases (e.g., cardiovascular disease, diabetes, and cancer), family history of skin cancer, past painful sunburns (e.g., history of sunburns during childhood and adolescence, including number of sunburn incidents during adolescence), use of sunscreen during sun exposure, and presence of freckles. Physical activity was assessed through a validated physical activity questionnaire, with data on 17 activities (35). Leisure-time activities were computed by assigning a metabolic equivalent score to each activity, multiplying by the time that was spent on each activity, and summing up all activities. The prevalence and history of any type of cancer were ascertained at baseline. Energy and nutrient intakes were also calculated on the basis of the information collected from the semiquantitative FFQ that was administered at baseline.

Outcome assessment

We defined participants as having incident BCC when they were free of BCC at baseline and responded positively to the following question in any of the follow-up questionnaires: "Have you ever been diagnosed with basal cell carcinoma by a medical doctor?" Subsequently, each self-reported physician-made BCC diagnosis was validated by a medical oncologist, blinded to the

exposure, against the medical history reported in the clinical records available at the university clinic.

Statistical analysis

Most continuous variables had non-Gaussian distributions, and all are reported as medians with IQRs. Discrete variables are reported as *n* (%). The residuals method was used to adjust baseline food consumption (g/d) for total energy intake (36). Negative values of household consumption resulting from this adjustment were set to 0 for interpretability. Conditional logistic regression models taking the matching into account were fitted to assess the relations of dietary patterns with the risk of BCC. ORs and their 95% CIs were calculated by including the exposure variables (dietary pattern scores and the energy-adjusted consumption of individual foods) categorized into quintiles, considering the lowest quintile as the reference category. To control for potential confounding factors, the results were adjusted for age (continuous; y), height (continuous; cm), smoking (discrete; 0 = not smoking, 1 = ex-smoker, 2 = smoker, 3 = missing), physical activity (continuous; metabolic equivalent tasks-h/week), recruitment year (continuous), total energy intake (continuous; kcal/d), family history for skin cancer (discrete; 0 = no, 1 = yes, 2 = missing), use of sunscreen during sun exposure (discrete; 0 = not taking sun, 1 = yes, 2 = no, 3 = missing), history of sunburns during childhood and adolescence (discrete; 0 = never burned, 1 = only some reddening, 2 = ≥1 burns, 3 = missing), number of sunburns during adolescence (discrete; 0 = never, 1 = 1–2 times, 2 = ≥3 times, 3 = missing), and presence of freckles (discrete; 0 = no, 1 = yes, 2 = missing). Tests of linear trend across increasing categories of adherence were conducted by assigning the median value to each category and treating it as a continuous variable. Multivariable fractional polynomials were used to test whether the multivariable relations between continuous variables and the outcome were linear. A *P* value < 0.05 was considered statistically significant. Statistical analysis was performed using STATA version 12.0 (StataCorp).

Results

Table 1 reports the main characteristics of the recruited subjects.

The association of potential confounders (presented in Table 1) with the risk of BCC was investigated using the multivariate conditional logistic regression model as described in the statistical analysis section without the inclusion of dietary exposure variables. We found that history of sunburns during childhood and adolescence (multivariate OR: 4.54; 95% CI: 1.48, 13.89; *P* = 0.008) and the presence of ≥15 freckles on the body (multivariate OR: 3.35; 95% CI: 1.54, 7.31; *P* = 0.002) were associated with an increased risk of BCC. In addition, we found a nonsignificant reduction in BCC risk associated with increased BMI (multivariate OR: 0.92; 95% CI: 0.85, 1.01; *P* = 0.078 per 1-kg/m^2 BMI increment). When we assessed height instead of BMI, the multivariate OR for the association (per 10-cm increase in height) with BCC was 0.98 (95% CI: 0.65, 1.48; *P* = 0.927).

When we included dietary patterns in the multivariate conditional logistic regression analysis, we found inverse relations of adherence to the Mediterranean diet and adherence to the DASH diet with the risk of BCC (**Table 2**). We observed that subjects in the highest quintile of adherence to the Mediterranean diet had a 72% lower RR (multivariate OR: 0.28; 95% CI: 0.10, 0.77; *P* = 0.014) than those in the lowest quintile, and for the DASH diet this RR reduction for the comparison between extreme quintiles was 68% (multivariate OR: 0.32; 95% CI: 0.14, 0.76; *P* = 0.009). Moreover, a significant dose–response relation was found (*P*-trend = 0.014 for the Mediterranean diet and *P*-trend = 0.013 for the DASH diet). No association was found between a Pro-vegetarian dietary pattern and BCC risk.

In the analysis relating food consumption to BCC occurrence (**Table 3**), the consumption of fruit and of low-fat dairy products were associated with lower risk of BCC. The multivariate ORs for quintiles 2–5 of fruit and low-fat dairy product consumption as compared with the lowest quintile were 0.92, 0.67, 0.38, and 0.27 (95% CI: 0.11, 0.64; *P*-trend < 0.001) and 1.04, 0.71, 0.59, and 0.39 (95% CI: 0.16, 0.92; *P*-trend = 0.014), respectively. A higher risk of BCC was observed in the third quintile of alcohol consumption than in the lowest one (multivariate OR: 2.45; 95% CI: 1.02, 5.90). However, the 2 upper quintiles did not exhibit any association with the risk of BCC.

Discussion

To our knowledge, this is the first study investigating the association of different healthy dietary patterns with the risk of BCC in a population whose sun exposure history and family history of skin cancer were documented.

Previous studies have mainly focused on the association between a limited group of nutrients and foods and the risk of BCC. However, it is well known that an approach based on studying a single nutrient does not take into account the synergistic and/or antagonistic interactions existing between nutrients, and it probably has a suboptimal statistical power to assess associations with the risk of disease (37). Moreover, evidence of nutritional research using overall dietary patterns is more amenable to translation into public health practice and food politics (23). In fact, there is a strong rationale to support the study of dietary patterns, so as to translate such findings into disease-specific dietary guidelines even before the mechanisms underlying the observed associations are fully understood (37).

We found strong inverse associations between 2 high-quality dietary patterns (Mediterranean diet and DASH diet) and the risk of BCC. These results replicate the findings of a recent prospective cohort study in French women aged 40–65 y (28) and suggest that also the DASH diet is associated with a lower BCC risk. Finally, this study did not find any significant association of the Pro-vegetarian dietary pattern with the risk of BCC. The lower BCC risk associated with the Mediterranean and DASH dietary patterns seems to be related to the consumption of fruit and low-fat dairy products. However, it is also possible that other food groups have small individual effects that are visible only as part of an overall dietary pattern, when cumulative and synergistic effects are being considered (21).

In agreement with some (38, 39), but not all (40), previous studies, we did not find any association between the consumption of vegetables and the risk of BCC. However, in agreement with Kune et al. (40), we found an inverse association between fruit consumption and BCC risk. Fruit is one of the major sources of

TABLE 1 Characteristics of the recruited subjects[1]

	Controls ($n = 404$)	Cases ($n = 101$)	Total ($n = 505$)
Age, y	48 [40–56]	47 [39–56]	48 [40–56]
Height, m	1.67 [1.61–1.73]	1.67 [1.60–1.75]	1.67 [1.61–1.73]
Weight, kg	67 [58–78]	65 [56–76]	67 [57–78]
BMI, kg/m^2	24.0 [21.5–26.2]	23.8 [21.0–25.6]	24.0 [21.3–26.0]
Physical activity, METs-h/wk	15 [7–28]	21 [10–33]	16 [8–29]
Energy intake, kcal/d	2234 [1777–2665]	2341 [1851–2818]	2242 [1806–2691]
Vegetables consumption, servings/d	2.10 [1.45–2.87]	1.98 [1.41–2.76]	2.06 [1.43–2.85]
Fruit consumption, servings/d	2.16 [1.34–3.60]	1.96 [1.19–2.92]	2.12 [1.33–3.49]
Nuts consumption, servings/wk	0.93 [0.47–1.47]	0.93 [0.47–1.47]	0.93 [0.47–1.47]
Meat and meat products consumption, servings/d	1.55 [1.12–2.04]	1.62 [0.98–2.27]	1.56 [1.12–2.07]
Fish consumption, servings/wk	4.87 [3.33–6.91]	4.40 [3.40–6.40]	4.87 [3.33–6.90]
Cereals consumption, servings/d	1.36 [0.92–2.50]	1.57 [1.00–2.79]	1.43 [0.92–2.63]
Legumes consumption, servings/wk	1.97 [1.40–3.00]	2.00 [1.40–2.93]	2.00 [1.40–3.00]
Low-fat dairy products consumption, servings/d	1.00 [0.14–2.14]	1.00 [0.07–1.50]	1.00 [0.13–2.07]
Whole-fat dairy products consumption, servings/d	1.13 [0.56–2.00]	1.27 [0.49–1.99]	1.14 [0.56–2.00]
Carbonated beverages consumption, servings/wk	0.47 [0–1.00]	0.47 [0–1.47]	0.47 [0–1.00]
Coffee consumption, servings/d	1 [0–2.5]	1 [0–2.5]	1 [0–2.5]
Olive oil consumption, g/d	14 [9–27]	12 [8–27]	14 [9–27]
Alcohol intake, g/d	4 [1–10]	3 [1–7]	3 [1–10]
Mediterranean score	5 [3–6]	4 [3–5]	4 [3–6]
DASH score	24 [21–28]	24 [20–27]	24 [21–28]
Pro-vegetarian score	37 [33–40]	37 [33–39]	37 [33–40]
Sex			
Male	180 (44.6)	45 (44.6)	225 (44.6)
Female	224 (55.4)	56 (55.4)	280 (55.4)
Smoking			
Not smoking	125 (30.9)	46 (45.5)	171 (33.9)
Ex-smoker	180 (44.6)	35 (34.7)	215 (42.6)
Smoker	80 (19.8)	17 (16.8)	97 (19.2)
Missing	19 (4.7)	3 (3.0)	22 (4.4)
Family history of skin cancer			
No	318 (78.7)	78 (77.2)	396 (78.4)
Yes	14 (3.5)	8 (7.9)	22 (4.4)
Missing	72 (17.8)	15 (14.9)	87 (17.2)
Use of sunscreen during sun exposure			
Not taking sun	73 (18.1)	14 (13.9)	87 (17.2)
Yes	274 (67.8)	77 (76.2)	351 (69.5)
No	50 (12.4)	9 (8.9)	59 (11.7)
Missing	7 (1.7)	1 (1.0)	8 (1.6)
History of sunburns during childhood and adolescence			
Never	76 (18.8)	7 (6.9)	83 (16.4)
Only redness	149 (36.9)	27 (26.7)	176 (34.9)
Burns	172 (42.6)	66 (65.3)	238 (47.1)
Missing	7 (1.7)	1 (1.0)	8 (1.6)
Number of sunburns during adolescence			
Never	274 (67.8)	56 (55.4)	330 (65.3)
1–2 times	86 (21.3)	26 (25.7)	112 (22.2)
≥3 times	38 (9.4)	18 (17.8)	56 (11.1)
Missing	6 (1.5)	1 (1.0)	7 (1.4)
Freckles on the body			
None	136 (33.7)	23 (22.8)	159 (31.5)
1–5	110 (27.2)	19 (18.8)	129 (25.5)
6–14	68 (16.8)	22 (21.8)	90 (17.8)
≥15	47 (11.6)	26 (25.7)	73 (14.5)
Missing or intentionally not reported	43 (10.6)	11 (10.9)	54 (10.7)

[1] Values are medians [IQRs] or n (%). DASH, Dietary Approaches to Stop Hypertension; MET, metabolic equivalent task.

TABLE 2 Association of dietary patterns with the risk of basal cell carcinoma[1]

	Quintile 1 (reference)	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P-trend
MED						0.014
Cases/controls	40/116	16/81	20/82	14/60	11/65	
Median	2	4	5	6	7	
OR (95% CI)	1.00	0.45* (0.22, 0.96)	0.69 (0.34, 1.42)	0.47 (0.20, 1.11)	0.28* (0.10, 0.77)	
DASH						0.013
Cases/controls	31/89	19/83	21/100	16/57	14/75	
Median	18	22	25	28	31	
OR (95% CI)	1.00	0.45* (0.21, 0.95)	0.43* (0.21, 0.88)	0.45 (0.19, 1.03)	0.32** (0.14, 0.76)	
PROVEG						0.384
Cases/controls	20/92	21/71	26/106	19/72	15/63	
Median	30	34	37	40	44	
OR (95% CI)	1.00	1.67 (0.77, 3.62)	1.20 (0.60, 2.39)	1.58 (0.71, 3.48)	1.54 (0.61, 3.91)	

[1]ORs and 95% CIs were obtained from conditional regression models adjusted for age (continuous), height (continuous), smoking (discrete), physical activity (continuous), recruitment year (continuous), total energy intake (continuous), family history of melanoma (discrete), use of sunscreen during sun exposure (discrete), sunburns during childhood and adolescence (discrete), number of sunburns during adolescence (discrete), and presence of freckles (discrete). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. DASH, Dietary Approaches to Stop Hypertension; MED, Mediterranean diet; PROVEG, Pro-vegetarian diet.

polyphenols, a large group of natural compounds possessing anti-inflammatory, immunomodulatory, and antioxidant properties. Several in vitro and in vivo studies have shown the efficacy of naturally occurring polyphenols against UV radiation–induced inflammation, oxidative stress, DNA damage, and suppression of immune responses (41), and, for this reason, there has been some speculation about their involvement in the chemoprevention of melanoma and NMSC (42).

We found an increased risk of BCC in the third quintile of alcohol consumption. However, the OR estimates for each of the 2 upper quintiles did not show significantly increased odds of BCC. Contrarily, a recent meta-analysis reported a positive dose–response relation between alcohol consumption and BCC risk (43). We acknowledge the possibility that our partially null finding for alcohol may be related to the inherent weaknesses of the case-control study design, especially regarding the preservation of the temporal sequence. Also, previous case-control studies failed to find any association between alcohol intake and BCC risk (44, 45). A most likely reason could be related to the fact that almost all alcohol drinkers in our study were only moderate alcohol consumers. The median daily consumption of alcohol in the highest consumption category was only 22 g/d (corresponding to 157 mL or 1.3 glasses of wine per day), a value within the Mediterranean diet adherence range. This suggests that there were almost no heavy drinkers in our population. Therefore, our finding does not contradict the possibility that heavy alcohol consumption is harmful for BCC risk. In addition, because alcohol could be related to BCC risk through interaction with the harmful and carcinogenic effects of UV light (46), it is possible that in our sample the total exposure to UV light or the use of sunscreen were lower and higher than those in other studies, respectively, which would make participants in our sample less susceptible to any cocarcinogenic effect of alcohol (45).

Dairy products are a good source of calcium and vitamin D. Several in vitro and in vivo studies have shown that both calcium and vitamin D signaling through their respective receptors are important for keratinocyte proliferation and differentiation, and the disruption of these signals can lead to skin cancer development (47, 48). This could explain the inverse association we observed between the consumption of low-fat dairy products and BCC risk. However, given the lack of specifically designed trials, it must be said that evidence of the effect of simultaneous calcium and vitamin D supplementation on the risk of skin cancer in humans is very limited. To the best of our knowledge, only the Women's Health Initiative calcium/vitamin D clinical trial, a study specifically designed to test the hypotheses that dietary calcium and vitamin D supplementations would reduce hip fractures and colorectal cancer in postmenopausal women, investigated whether these supplementations reduced the risk of NMSC and melanoma (18). The study observed no association between the supplementation of calcium and vitamin D and the overall incidence of NMSC or melanoma. Only in the women with a history of NMSC did the supplementation reduce the risk of melanoma. However, as reported by the authors themselves, the reasons for the partial failure could be many: insufficient calcium and vitamin D supplementation, the study was not specifically designed for this topic, the nonvalidation of NMSC cases (they were self-reported by the patients), and the nondifferentiation of the latter into BCC and SCC (18). Therefore, it is premature to assign or exclude a role of dietary calcium and vitamin D in the development of BCC in humans.

The main strength of our study was its prospective nature, because the measurement of participants' dietary habits was carried out before the onset of the disease, which reflects the optimal temporal relation between exposure and disease occurrence (14). Second, we adjusted our analysis for sunburn and family history of skin cancer, known risk factors for BCC. A further strength of the present study was the validation of the BCC diagnosis. Indeed, our diagnoses were self-reported, so to avoid misclassification each diagnosis was confirmed by an oncologist blind to the exposure via the medical history reported in participants' medical records at the university clinic.

We are well aware that our study was not free of limitations. Although larger than some previous studies, the sample size was a limitation. This was due to the limited number of BCC incident cases registered during the follow-up period. However, the distribution of skin cancer types was in line with the literature.

TABLE 3 Association of food consumption and the risk of basal cell carcinoma[1]

	Quintile 1 (reference)	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P-trend
Vegetables						0.528
Cases/controls	21/80	24/77	19/82	19/82	18/83	
Median, g/d	209	360	481	605	869	
OR (95% CI)	1.00	1.13 (0.53, 2.39)	1.00 (0.41, 2.42)	0.98 (0.46, 2.12)	0.83 (0.38, 1.82)	
Fruit						<0.001
Cases/controls	25/76	26/75	22/79	16/85	12/89	
Median, g/d	111	240	321	447	676	
OR (95% CI)	1.00	0.92 (0.44, 1.95)	0.67 (0.31, 1.45)	0.38* (0.17, 0.85)	0.27** (0.11, 0.64)	
Nuts						0.719
Cases/controls	22/79	20/81	16/85	25/76	18/83	
Median, g/d	0	2	5	7	21	
OR (95% CI)	1.00	0.97 (0.42, 2.25)	0.70 (0.28, 1.76)	1.79 (0.76, 4.21)	0.83 (0.36, 1.94)	
Red and processed meat						0.960
Cases/controls	26/75	14/87	21/80	16/85	24/77	
Median, g/d	80	124	159	192	242	
OR (95% CI)	1.00	0.32* (0.13, 0.80)	0.69 (0.30, 1.59)	0.37* (0.17, 0.80)	0.81 (0.34, 1.93)	
Fish						0.110
Cases/controls	23/78	20/81	20/81	19/82	19/82	
Median, g/d	39	68	96	126	167	
OR (95% CI)	1.00	0.78 (0.35, 1.74)	0.81 (0.38, 1.73)	0.65 (0.32, 1.29)	0.54 (0.24, 1.21)	
Cereals						0.156
Cases/controls	18/83	19/83	17/83	21/80	26/75	
Median, g/d	18	65	94	127	186	
OR (95% CI)	1.00	1.01 (0.46, 2.20)	0.81 (0.36, 1.81)	1.10 (0.44, 2.78)	1.76 (0.79, 3.92)	
Legumes						0.335
Cases/controls	19/82	28/73	19/82	16/85	19/82	
Median, g/d	7	14	19	23	34	
OR (95% CI)	1.00	1.41 (0.64, 3.07)	0.88 (0.38, 1.98)	0.70 (0.29, 1.71)	0.86 (0.35, 2.09)	
Low-fat dairy products						0.014
Cases/controls	25/76	21/80	21/80	20/81	14/87	
Median, g/d	0	31	179	267	523	
OR (95% CI)	1.00	1.04 (0.45, 2.39)	0.71 (0.33, 1.50)	0.59 (0.27, 1.25)	0.39* (0.16, 0.92)	
Whole-fat dairy products						0.867
Cases/controls	22/79	18/83	20/81	19/82	22/79	
Median, g/d	20	64	117	214	375	
OR (95% CI)	1.00	0.64 (0.28, 1.45)	0.68 (0.28, 1.70)	0.75 (0.33, 1.75)	0.76 (0.34, 1.67)	
Olive oil						0.288
Cases/controls	24/77	22/79	21/80	17/84	17/84	
Median, g/d	4	10	17	26	34	
OR (95% CI)	1.00	0.93 (0.43, 1.99)	1.16 (0.57, 2.38)	0.66 (0.30, 1.43)	0.76 (0.33, 1.73)	
Carbonated beverages						0.600
Cases/controls	16/85	17/84	23/78	24/77	21/80	
Median, g/d	0	2	13	28	99	
OR (95% CI)	1.00	1.32 (0.53, 3.29)	1.80 (0.76, 4.28)	2.28 (0.96, 5.43)	1.67 (0.69, 4.02)	
Coffee						0.665
Cases/controls	22/79	21/80	15/86	19/82	24/77	
Median, servings/d	0	1.0	1.1	2.5	2.7	
OR (95% CI)	1.00	1.06 (0.46, 2.45)	0.86 (0.39, 1.91)	0.95 (0.45, 2.02)	1.26 (0.56, 2.85)	
Alcohol						0.020
Cases/controls	20/82	23/77	28/73	19/82	11/90	
Median, g/d	0	2	4	9	22	
OR (95% CI)	1.00	1.74 (0.69, 4.36)	2.45* (1.02, 5.90)	1.02 (0.38, 2.78)	0.63 (0.25, 1.59)	

[1]ORs and 95% CIs were obtained from conditional regression models adjusted for age (continuous), height (continuous), smoking (discrete), physical activity (continuous), recruitment year (continuous), total energy intake (continuous), family history of melanoma (discrete), use of sunscreen during sun exposure (discrete), history of sunburns during childhood and adolescence (discrete), number of sunburns during adolescence (discrete), and presence of freckles (discrete). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Of the cancer cases we recorded during the follow-up period, 80% of skin cancer cases were represented by BCC cases. This limits the likelihood of an under-registration of BCC cases. Furthermore, dietary habits were evaluated only at baseline, so the possibility that they changed over time cannot be excluded. Finally, the SUN project mainly includes university graduates and this can affect the generalizability of our results. External validation of our results by further studies is therefore required.

In conclusion, our data suggest that both the Mediterranean diet and the DASH diet are associated with a lower risk of BCC. However, further confirmatory studies are required before using these findings to support recommendations on specific dietary guidelines for BCC.

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