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Report

Exposome and basal cell carcinoma: a multicenter case–control study

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Abstract

Background While ultraviolet radiation (UVR) present in sunlight is recognized as the main etiological agent of skin cancer, the most frequent form of which is basal cell carcinoma (BCC), other exposome factors like pollution, diet, and lifestyle may also contribute. This study aimed to investigate the association of BCC and exposome-related factors in the Spanish population.

Methods BCC cases (n = 119) and controls (n = 127) with no history of skin cancer were recruited between April 2020 and August 2022 by 13 dermatologists throughout Spain in this prospective multicenter case–control study.

Results The BCC group had a higher proportion of outdoor workers, more years of UVR exposure, and a greater consumption of drugs (statins, ASA, hydrochlorothiazide, ACE inhibitors and omeprazole), $P < 0.05$. Avoidance of sun exposure was the most used photoprotection measure in both groups. The use of hats or caps was higher in the BCC group ($P = 0.01$). The solar protection factor (SPF) used 15 years previously was higher in the control group ($P = 0.04$). The control group had a higher daily screen time ($P < 0.001$), and practiced more relaxation activities ($P = 0.03$). Higher linolenic acid intake and lower coffee consumption were the only dietary variables associated with BCC ($P < 0.05$). Statistical significance for all the aforementioned variables was maintained in the multivariate analysis ($P < 0.05$).

Conclusions The study found a significant association between BCC and multiple exposome-related factors in addition to chronic sun exposure in the Spanish population. Primary prevention strategies should target specific populations, such as outdoor workers, promoting sun-safe behaviors and stress-reducing activities, and also adequate skin photoprotection in patients on certain medications associated with increased BCC risk.

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Introduction

The exposome encompasses all forms of environmental exposure throughout human life, and the study of its effect on human health constitutes a new approach.[1] The EXPOsOMICS project aims to assess environmental exposure, mainly pollution and water contaminants, using "omics" techniques that can associate exposure data with biochemical and molecular changes, leading to a better understanding of how they influence the risk of developing skin diseases.[2]

Skin cancer is the most frequent cancer in humans. Its incidence has increased over the last 20 years, and in the next 20 years an exponential increase of close to 100% is predicted, leading to epidemic levels of prevalence.[3] In Spain, the crude incidence rates for basal cell carcinoma (BCC) are 113.05 cases per 100,000 person-years (CI 95%, 89.03–137.08).[4]

The skin is our outermost organ, and therefore, the one most directly exposed to the effects of the environment. Ultraviolet radiation (UVR) present in sunlight is recognized as the main etiological agent of skin cancer.[5] However, a growing body of evidence indicates that environmental pollution and contaminants in water, food, or one's lifestyle can also exert an important influence.[2] Furthermore, in any holistic concept of health, taking into account the interaction between the skin and the nervous, endocrine, and immune systems, as well as one's diet, it is also necessary to consider the influence of stress and sleep, on the development of cancer.[6]

The aim of this study was to analyze the association between BCC and exposome variables related to sun exposure, diet, pollution, stress, and lifestyle within the Spanish population.

Materials and methods

Study design

A multicenter, case–control study was carried out by 13 dermatologists from different hospitals in Spain between April 1, 2020 and August 31, 2022. The case group consisted of patients diagnosed with BCC (maximum 3 months before the beginning of the study), while the control group consisted of individuals who attended dermatology consultations accompanying BCC patients, and had no history of skin cancer. The exclusion criteria were as follows: aged <18 years; patients with photosensitive diseases; patients who did not provide written informed consent.

Data regarding age, sex, marital status, income, height, weight, place of residence (rural/urban), profession, phenotype and phototype, and chronic medication were collected. Sun exposure and photoprotection habits were evaluated using a validated questionnaire previously used by our group[7,8]; dietary habits were evaluated using the validated PREDIMED questionnaire[9]; exposure to pollution, toxic substances and ionizing radiation was reported by participants; perceived stress was evaluated using the Perceived Stress Scale (PSS)[10,11]; and the number of hours of sports (outdoors and indoors) and number of hours of sleep were measured (Figure S1).

Statistical analyses

Descriptive statistical analysis was performed for all variables. Continuous variables were presented as the number of valid cases, mean, standard deviation (SD), and 25th and 75th percentiles depending on the results of the Kolmogorov–Smirnov test. Categorical variables were presented as the mean of absolute and relative frequencies of each category over the total number of valid values (*N*).

Categorical variables were compared using the chi-squared test. In the case of continuous variables, ANOVA was used. Logistic regression was used to determine which variables were associated with a diagnosis of BCC. For all comparisons, statistical significance was set at $P < 0.05$.

Statistical analyses were performed using SAS (Statistical Analysis System) version 9.4.

Ethical concerns

The study was observational and the protocol was approved by the Aragón Ethical Committee for Clinical Research (C.I.

Table 1 Demographic characteristics of the study population

Variable	BCC	Control	*P*-value
Sex, *N* (%)			
Male	50 (42.0%)	42 (33.3%)	0.160
Female	69 (58.0%)	84 (66.7%)	
Age, Mean (SD) [P25;P75]	66.91 (12.66) [61.0; 75.0]	55.77 (15.00) [45.5; 67.0]	<0.001
Height (cm), Mean (SD) [P25;P75]	164.75 (8.91) [158.0; 170.0]	165.73 (8.86) [160.0; 172.0]	0.392
Weight (kg), Mean (SD) [P25;P75]	72.08 (13.46) [61.5; 81.0]	70.51 (15.13) [59.0; 81.0]	0.395
BMI (kg/m^2), Mean (SD) [P25;P75]	26.42 (4.16) [23.9; 28.7]	25.56 (4.57) [22.2; 28.2]	0.127
Hair color, *N* (%)			
Red	4 (3.4%)	0 (0%)	0.035
Blonde	25 (21.2%)	13 (10.7%)	
Light brown	39 (33.1%)	42 (34.4%)	
Dark brown	36 (30.5%)	49 (40.2%)	
Black	14 (11.9%)	18 (14.8%)	
Eye color, *N* (%)			
Blue	64 (17.5%)	13 (10.9%)	0.086
Green	47 (12.8%)	15 (12.6%)	
Dark green/brown	42 (11.5%)	13 (10.9%)	
Light brown	96 (26.2%)	27 (22.7%)	
Dark brown	117 (32.0%)	51 (42.9%)	
Phototype, *N* (%)			
I	11 (9.4%)	3 (2.4%)	0.028
II	35 (29.9%)	33 (26.6%)	
III	52 (44.4%)	52 (41.9%)	
IV	8 (6.8%)	21 (16.9%)	
V	11 (9.4%)	15 (12.1%)	
Personal history of skin cancer, *N* (%)			
Yes	56 (47%)	—	—
Type of skin cancer			
BCC	44 (78.5%)	—	—
Squamous cell carcinoma	7 (12.5%)	—	—
Melanoma	5 (8.9%)	—	—
Family history of skin cancer, *N* (%)			
Yes	30 (25.4%)	27 (22.7%)	0.267
No	75 (63.6%)	70 (58.8%)	
Unknown	13 (11.0%)	22 (18.5%)	
Marital status, *N* (%)			
Single	11 (9.2%)	26 (20.8%)	0.011
Married	85 (71.4%)	87 (69.6%)	
Divorced	8 (6.7%)	7 (5.6%)	
Widow/widower	15 (12.6%)	5 (4.0%)	
Annual income, *N* (%)			
<€15,000/year	21 (21.0%)	21 (20.8%)	0.784
€15,000–25,000/year	43 (43.0%)	39 (38.6%)	
€25,000–50,000€/year	32 (32.0%)	34 (33.7%)	
>€50,000/year	4 (4.0%)	7 (6.9%)	
Residential environment, *N* (%)			
Urban	88 (75.2%)	101 (80.8%)	0.293
Rural	29 (24.8%)	24 (19.2%)	
Current workplace, *N* (%)			
Indoors	84 (85.7%)	110 (94.8%)	0.022
Outdoors	14 (14.3%)	6 (5.2%)	
Previously worked outdoors, *N* (%)			
Yes	29 (42.0%)	11 (22.4%)	0.026
No	40 (58.0%)	38 (77.6%)	
Daily hours of occupational exposure, Mean (SD) [P25;P75]	6.16 (2.91) [4.0; 8.0]	4.36 (2.66) [2.0; 7.0]	0.042
Years of exposure, Mean (SD) [P25;P75]	29.96 (14.25) [20.0; 40.0]	15.45 (10.82) [5.0; 20.0]	0.004

Table 1 Continued

Variable	BCC	Control	*P*-value
Exposure to chemicals, *N* (%)			
Yes	14 (12.2%)	13 (10.4%)	0.891
No	94 (81.7%)	105 (84.0%)	
Exposure to ionizing radiation, *N* (%)			
Yes	6 (5.2%)	8 (6.5%)	0.473
No	104 (89.7%)	105 (84.7%)	

BCC, basal cell carcinoma; BMI, Body Mass Index, *N*, number of subjects; P25, 25th percentile; P75, 75th percentile; SD, standard deviation.

PI19/311). All participants provided written informed consent prior to their enrolment.

Results

Demographic and clinical characteristics of the sample/study population

The study population consisted of a BCC case group [n = 119; 58% female; mean (SD) age, 66.9 (12.6)] and a control group [n = 127; 66.7% female; mean (SD) age, 55.7 (15)], which differed significantly in age ($P < 0.001$). There were no differences in anthropometric variables [weight, height, and body mass index (BMI)] between groups. However, differences were observed in hair color and phototype: the BCC group had significantly lighter hair color (redhead and blonde; $P = 0.03$), and a lighter phototype (I-III; $P = 0.02$). The characteristics of the study population are summarized in Table 1.

The most frequent location of BCC was the head and neck (62.2%), followed by the trunk (37.8%) and lower (8.4%) and upper extremities (5.9%). No differences in the frequency of family history of skin cancer were observed between cases and controls (25.4% vs 22.7%). Among BCC patients, 47% had had a previous diagnosis of skin cancer (BCC, 78.5%; SCC, 12.5%; melanoma, 8.9%).

Most participants in the BCC and control groups were married (71.4% and 69.6%, respectively). However, the control group contained more single people (20.8%) and fewer widows/widowers (4%) than the BCC group (9.2% and 12.6% respectively). There were no differences between groups in annual income. Most participants earned €15,000–25,000/year (43% of the BCC group and 38.6% of controls), and the majority of both groups lived in urban environments (75.2% and 80.8%, respectively). However, the groups differed in terms of workplaces: 14.3% of the BCC group worked outdoors at the time of diagnosis and 42% had previously worked outdoors, as compared to 5.2% and 22.4% in the control group. Among the participants who worked outdoors, the mean (SD) of the number of daily working hours spent outdoors was higher in BCC patients than in controls [6.16 (2.91) vs. 4.36 (2.66) hours; $P = 0.04$], as was the number of years spent working outdoors [29.96 (14.25) vs. 15.45 (10.82); $P = 0.004$].

There were no significant differences between groups in terms of exposure to other possible carcinogens, such as chemicals (pesticides, arsenic, coal tar, anthracenes, paraffins, asphalt, mineral oils, petroleum, others), and ionizing radiation.

Table 2 Chronic medications taken by the study population

Medication (*N*, %)	BCC	Control	*P*-value
Acetylsalicylic acid	6 (5.5%)	1 (0.9%)	0.046
NSAIDs	12 (11.0%)	10 (8.7%)	0.560
Anxiolytics	17 (15.6%)	15 (13.0%)	0.585
Antidepressants or hypnotics	13 (11.9%)	8 (7.0%)	0.202
Contraceptives	4 (3.7%)	5 (4.3%)	0.796
Antioxidants	1 (0.9%)	2 (1.7%)	0.592
Antipsychotics	3 (2.8%)	—	0.073
Beta blockers	8 (7.3%)	6 (5.2%)	0.512
Statins	29 (26.6%)	17 (14.8%)	0.028
Hydrochlorothiazide	13 (11.9%)	2 (1.7%)	0.002
Hydroxyurea	—	—	—
ACE inhibitors (Captopril, enalapril, ramipril)	24 (22.0%)	7 (6.1%)	<0.001
Metformin	10 (9.2%)	6 (5.2%)	0.250
Omeprazole	31 (28.4%)	19 (16.5%)	0.032
Vitamin D	13 (11.9%)	15 (13.0%)	0.800

ACE, angiotensin-converting enzyme; *N*, Number of subjects; NSAIDs, non-steroidal anti-inflammatory drugs.

Chronic medication

A higher percentage of BCC patients versus controls consumed acetylsalicylic acid (5.5% vs. 0.9%; $P = 0.04$), statins (26.6% vs. 14.8%; $P = 0.02$), hydrochlorothiazide (11.9% vs. 1.7%; $P = 0.002$), angiotensin-converting enzyme (ACE) inhibitors (22% vs. 6.1%; $P < 0.001$), and omeprazole (28.4% vs. 16.5%; $P = 0.03$). The chronic medications taken by the study population are summarized in Table 2.

Sun exposure habits and practices

Sun exposure and photoprotection measures are summarized in Table 3.

There were no differences between groups in recreational sun exposure (e.g., sunbathing and UVR exposure during sports), with a similar number of days per year and hours per day of sunlight exposure.

Avoiding the hours of highest UVR incidence (12–4 PM) either always or habitually was the most common

Table 3 Sun exposure and photoprotection measures

Variable	BCC	Control	*P*-value
Outdoor sunbathing (days/year), *N* (%)			
Never	33 (28.0%)	29 (23.0%)	0.382
1–5 days	19 (16.1%)	19 (15.1%)	
6–30 days	37 (31.4%)	53 (42.1%)	
31–90 days	21 (17.8%)	21 (16.7%)	
>90 days	8 (6.8%)	4 (3.2%)	
Days/year practicing outdoor sports, *N* (%)			
Never	29 (24.6%)	31 (24.6%)	0.088
1–5 days	14 (11.9%)	21 (16.7%)	
6–30 days	20 (16.9%)	35 (27.8%)	
31–90 days	24 (20.3%)	16 (12.7%)	
>90 days	31 (26.3%)	23 (18.3%)	
Outdoor sunbathing (h/day), *N* (%)			
1–2 h	69 (76.7%)	76 (71.7%)	0.598
3–4 h	15 (16.7%)	25 (23.6%)	
5–6 h	4 (4.4%)	4 (3.8%)	
>6 h	2 (2.2%)	1 (0.9%)	
Practicing outdoor sport (h/day), *N* (%)			
1–2 h	72 (82.8%)	92 (86.8%)	0.307
3–4 h	13 (14.9%)	13 (12.3%)	
5–6 h	2 (2.3%)		
> 6 h		1 (0.9%)	
Staying in the shade, *N* (%)			
Never/Rarely	29 (24.8%)	28 (22.6%)	0.346
Sometimes	17 (14.5%)	27 (21.8%)	
Habitually/Always	71 (60.7%)	69 (55.6%)	
Use of sunglasses, *N* (%)			
Never/Rarely	45 (38.5%)	36 (28.8%)	0.267
Sometimes	17 (14.5%)	23 (18.4%)	
Habitually/Always	55 (47.0%)	66 (52.8%)	
Use of a hat or cap, *N* (%)			
Never/Rarely	49 (41.9%)	67 (53.6%)	0.015
Sometimes	24 (20.5%)	32 (25.6%)	
Habitually/Always	44 (37.6%)	26 (20.8%)	
Use of clothes, *N* (%)			
Never/Rarely	60 (51.3%)	49 (39.8%)	0.197
Sometimes	31 (26.5%)	42 (34.1%)	
Habitually/Always	26 (22.2%)	32 (26.0%)	
Sun exposure from 12:00 to 16:00, *N* (%)			
Never/Rarely	13 (11.1%)	23 (18.7%)	0.245
Sometimes	22 (18.8%)	23 (18.7%)	
Habitually/Always	82 (70.1%)	77 (62.6%)	
Use of sunscreen, *N* (%)			
Never/Rarely	26 (22.2%)	20 (16.3%)	0.421
Sometimes	18 (15.4%)	24 (19.5%)	
Habitually/Always	73 (62.4%)	79 (64.2%)	
Exposure to sunlight 15 years ago *N* (%)			
Yes	93 (79.5%)	78 (62.9%)	0.004
No	24 (20.5%)	46 (37.1%)	
SPF used 15 years ago, *N* (%)			
Unknown	36 (32.1%)	22 (18.2%)	0.047
2–10	14 (12.5%)	11 (9.1%)	
11–20	16 (14.3%)	17 (14.0%)	
21–50	28 (25.0%)	37 (30.6%)	
>50	18 (16.1%)	34 (28.1%)	
SPF used now, *N* (%)			
Unknown	12 (10.5%)	10 (8.3%)	0.209
2–10	—	3 (2.5%)	
11–20	2 (1.8%)	6 (5.0%)	
21–50	24 (21.1%)	30 (25.0%)	
>50	76 (66.7%)	71 (59.2%)	

Table 3 Continued

N, number of subjects; SPF, sun protection factor.

photoprotection measure in both the BCC (70.1%) and the control group (62.6%), followed by the use of sunscreen (SPF ≥30) always or habitually (62.4% and 64.2%, respectively), with no significant differences. In the BCC and control groups, staying in the shade always or habitually (60.7% and 55.6%, respectively) and the use of sunglasses always or habitually (47% and 52.8%, respectively) was similar, while the use of a hat or cap always or habitually was more frequent in the BCC group (37.6% and 20.8%, respectively; $P = 0.01$). Finally, the use of protective clothing always or habitually was the least common measure adopted, with no differences between groups.

Higher sun exposure 15 years ago as compared to now was reported more frequently by the BCC group (79.5%) than the controls (62.9%) ($P < 0.001$). Regarding the SPF used 15 years ago, most of the BCC and the control group answered SPF >21 (25% and 30.6%, respectively) or >50 (16.1% and 28.1%; $P = 0.04$). However, regarding current use, both groups reported using an SPF of at least 21, and the majority, an SPF of >50 (BCC, 66.7%; controls, 59.2%; $P = 0.209$).

Diet

The dietary intake of 59 nutrients was calculated using the PREDIMED questionnaire (Table S1). Linolenic acid was the only nutrient that was significantly associated with BCC. Patients with BCC had a higher linolenic acid intake than controls (1.74 vs. 1.40 μg/day; $P = 0.02$). Caffeinated coffee intake was higher in the controls than in the BCC group (3.55 vs. 2.88 coffees/day; $P = 0.05$). No significant differences were observed in the remaining dietary variables.

Lifestyle and stress

The lifestyle characteristics and stress levels are presented in Table 4. A larger proportion of the control group practiced relaxation exercises, meditation, mindfulness, or yoga than the BCC group (23.2% vs. 12.7%; $P = 0.03$). The number of hours of screen time was also higher in the controls than in the BCC group (>3 h: 50% vs. 29.8%; $P < 0.001$). No significant differences were observed in the practice of sports, perceived stress, hours of sleep, or smoking.

Multivariate analysis

All variables for which significant associations were observed in the bivariate analysis were included in a multivariate analysis (Table 5).

Table 4 Lifestyle and stress-related variables in the study population

Variable	BCC	Control	*P*-value
Relaxation activities, *N* (%)			
Yes	15 (12.7%)	29 (23.2%)	0.033
No	103 (87.3%)	96 (76.8%)	
Sport, *N* (%)			
Yes	80 (67.8%)	80 (65.0%)	0.657
No	38 (32.2%)	43 (35.0%)	
Years practicing sport, Mean (SD) [P25;P75]	21.77 (16.91) [8.0; 40.0]	20.84 (16.14) [10.0; 30.0]	0.736
Location of sport, *N* (%)			
Indoor	18 (22.5%)	21 (26.6%)	0.117
Outdoor	57 (71.3%)	46 (58.2%)	
Indoor/outdoor	5 (6.3%)	12 (15.2%)	
Hours/week, Mean (SD) [P25;P75]	5.85 (3.71) [3.0; 7.0]	5.58 (3.00) [3.0; 7.0]	0.618
Screen time, *N* (%)			
<1 h	51 (44.7%)	27 (22.1%)	0.0005
1–2 h	29 (25.4%)	34 (27.9%)	
>3 h	34 (29.8%)	61 (50.0%)	
Smoker, *N* (%)			
Yes	17 (14.4%)	30 (23.8%)	0.061
No	65 (55.1%)	71 (56.3%)	
Former smoker	36 (30.5%)	25 (19.8%)	
Cigarettes/day, Mean (SD) [P25;P75]	9.90 (6.51) [3.0; 15.0]	8.86 (4.29) [6.0; 10.0]	0.640
Hours/day of sleep in the last 5 years, *N* (%)			
<6 h	15 (12.7%)	13 (10.4%)	0.154
6 h	28 (23.7%)	24 (19.2%)	
7 h	38 (32.2%)	54 (43.2%)	
8 h	31 (26.3%)	33 (26.4%)	
>10 h	6 (5.1%)	1 (0.8%)	
Perceived stress,[a] Mean (SD) [P25;P75]	19.17 (8.57) [12.5; 25.0]	19.69 (8.99) [14.0; 26.0]	0.660
Sunburns in the last year, *N* (%)			
0	80 (80.0%)	78 (78.8%)	0.051
1	8 (8.0%)	14 (14.1%)	
2	6 (6.0%)	7 (7.1%)	
≥3	6 (6.0%)	—	

N, number of subjects; P25, 25th percentile; P75, 75th percentile; SD, standard deviation.
[a]Individual scores on the PSS can range from 0 to 40 with higher scores indicating higher perceived stress: scores ranging from 0 to 13 are considered low stress, from 14 to 26 moderate stress, and from 27 to 40 high stress.

Variables for which associations persisted in the multivariate analysis included genetic variables such as hair color and phototype, as well as variables related to sun exposure (workplace, hours, and years of exposure), and photoprotection (use of a hat or cap). Practicing relaxation activities and screen time were also identified as protective factors. Finally, chronic treatment with drugs, such as acetylsalicylic acid, statins, hydrochlorothiazide, ACE inhibitors, and omeprazole, as well as the linolenic acid intake, were identified as risk factors for the development of BCC, while caffeine intake was found to be a protective factor.

Table 5 Logistic regression findings: variables significantly associated with the presence of BCC

Variable	Coefficient	*P*-value
Hair color	0.09745	0.004
Phototype	0.05610	0.021
Current workplace (indoors)	−0.30581	0.011
Previous outdoor work	0.24359	0.013
Daily hours of sun exposure	0.06631	0.042
Years of sun exposure	0.01301	0.006
Use of a hat or cap	0.04960	0.038
Higher exposure to ultraviolet radiation 15 years ago	0.21638	0.003
Relaxation activities	−0.19181	0.025
Screen time	−0.13829	<0.001
Acetylsalicylic acid	0.38249	0.046
Statins	0.18100	0.028
Hydrochlorothiazide	0.40734	0.002
ACE inhibitors (captopril, enalapril, ramipril)	0.33378	<0.001
Omeprazole	0.17172	0.032
Linolenic acid	0.06926	0.022
Coffee	−0.02525	0.059

ACE, angiotensin-converting enzyme.

Discussion

The present analysis of the exposome in BCC patients corroborates the role of UVR-related variables, specifically chronic occupational sun exposure, and past photoprotection habits, especially in people with a low phototype. The fact that screen time and the practice of relaxing activities, which tend to occur indoors, were more frequent among controls reinforces the association between outdoor exposure and BCC. Systemic factors, for instance, exposure to drugs such as acetylsalicylic acid, statins, hydrochlorothiazide, ACE inhibitors, and omeprazole, and certain nutrients such as linolenic acid, along with no coffee consumption appear to also contribute to the development of BCC.

The characteristics of BCC patients in our sample are similar to previous reports. BCC appears to be more common in Fitzpatrick skin phototypes I and II, and it is associated with light eye color, freckles, and blonde or red hair.[12,13] The most frequent locations of BCC are photoexposed areas: 70% on the face, and 15% on the trunk,[14] which corresponds to our findings. Furthermore, individuals with a personal history of BCC are at increased risk of developing subsequent lesions. Approximately 40–50% of patients who have had one BCC lesion will develop another within 5 years,[15] also in line with our findings.

Differences in marital status between cases and controls are likely because of the difference in age: the mean age of controls was less than that of BCC patients. We observed no differences in economic status between groups. However, other authors have shown that differences in income can be linked to variations in the form and presentation of skin cancer. A German study reported a direct correlation between higher income and educational level and increased prevalence of melanoma and non-melanoma skin cancer (NMSC),[15] while a multicenter study including five European countries found that higher socioeconomic status was associated with an increased risk of skin cancer among middle-aged, but not older patients.[16]

Although most of our population lived in an urban environment, the BCC group worked more outdoors, and for longer, than controls. Interest in occupational UVR exposure increased over recent years, and several studies have reported a higher risk of NMSC in outdoor workers, including mountain guides, farm laborers, and ski resort workers.[8,17,18] These findings underscore the importance of promoting and supporting photoprotective behaviors and the proper use of sunscreen among outdoor workers.

Ionizing radiation is a known cause of NMSC, and the occupational exposure of radiology technicians to low-to-moderate doses of radiation can increase the risk of BCC, especially in individuals with low phototypes.[19] Exposure to substances such as pesticides, especially when occupational, has also been reported to increase the risk of other skin tumors, including melanoma.[20]

Notwithstanding, ionizing radiation and chemical exposure may be underestimated in our sample, and indeed, in the general population: as both are invisible, exposure often occurs unbeknownst to the affected individual.

There are contradictory findings regarding the association between acetylsalicylic acid consumption and the development of BCC. Frankel et al.[21] reported that acetylsalicylic acid decreased the risk of BCC, and argued that the opposing finding reported in other studies may be because of the absence of matched controls, and the confounding effects of age and sex; however, in our study, these factors are controlled.

Similarly, contradictory findings have been reported for statins: a meta-analysis found no significant association between statin use and NMSC.[22] Preclinical studies have suggested that statins may act as chemopreventive agents.[23] However, other authors have argued that their photosensitizing and immune-modulating effects could increase the risk of skin cancer, as we have observed in our results.[24,25]

Thiazides and ACE inhibitors have been associated with an increased risk of NMSC.[26,27] In agreement with our findings, previous studies have suggested that tumor risk may be increased by antihypertensive drugs, particularly hydrochlorothiazide, owing to its photosensitizing properties.[28] Finally, while no studies showed evidence of an association between omeprazole use and BCC risk, omeprazole is included among the photosensitizing drugs which could explain this relationship.[24,29]

Differences in photoprotection measures were observed between groups, especially the increased use of hats in the BCC group, probably because they had tumors located mainly on the head and neck, and were therefore more conscientious about protecting these areas. While most head coverings protect the scalp and forehead, many fail to cover the rest of the face and neck: large brimmed hats afford greater facial protection, except around midday.[30] Regarding photoprotection in the previous 15 years, the majority reported that they used sunscreens of a lower SPF and less frequently compared to nowadays, perhaps because of a poorer knowledge of sun damage and its implications. In recent years, campaigns promoting photoprotection measures have increased exponentially, enhancing awareness among the general public. Our findings corroborate the importance of prolonged photoexposure (at least 15 years) prior on the appearance of BCC (years later) and indicate that adequate photoprotection is insufficient to reverse previous sun damage.[31]

Of the 59 dietary components analyzed in this study, association with BCC was observed only for linolenic acid and caffeinated coffee. Previous studies have reported a link between linolenic acid intake and increased BCC risk.[32] Park et al.[33] found that linolenic acid intake was associated with a higher risk of BCC, in conformity with our findings. Moreover, studies in animals have reported that omega-6 fatty acids enhance UVR-induced carcinogenesis. Specifically, the concentration of omega-6 fatty acid intake increased proportionally with that of prostaglandin E synthase type 2, which exerts pro-inflammatory and immunosuppressive effects, and has been associated with aggressive growth patterns of NMSC.[34,35] Although biological processes link levels of polyunsaturated fatty acid (PUFAs) to protection against general cancer, observational studies examining its relationship with NMSC (BCC and SCC) have reported contradictory findings.[36] Cohort studies with larger number of patients and longer exposure periods are therefore required to further investigate this association.

The observed association between coffee consumption and BCC is in agreement with the findings of a meta-analysis[37] supporting a dose-dependent chemopreventive effect of caffeinated coffee in BCC. Specifically, the study reported relative risks of NMSC of 0.96 (CI 95% 0.92–0.99) for 1 cup; 0.92 (CI 95% 0.88–0.97) for 2 cups; 0.89 (CI 95% 0.86–0.93) for 2–3 cups; and 0.81 (CI 95% 0.77–0.85) for >3 cups of coffee per day.

No association was detected between sports and skin cancer in this study, although many studies have reported much higher levels of UVR exposure, and therefore higher risk of skin cancer among athletes who practice outdoor sports, especially winter sports in which snow reflectance amplifies UVR exposure.[38] The UVR exposure practicing these types of sports and other recreational activities, such as sunbathing, have been associated with increased risk of BCC.[39]

Chronic stress can increase susceptibility to skin cancer by suppressing type 1 cytokines and protective T cells, while increasing regulatory/suppressor T cells.[40] While there were no differences between groups in perceived stress using the PSS scale, we observed differences in relaxation activities, which were more common in the control group. This finding has not been previously reported.

No differences were observed between groups in any other lifestyle variables (e.g., smoking status, hours of sleep), except for the median number of hours per day of screen time, which was higher in the control group. This last finding may be explained by the fact that the control group was younger and was more likely to work indoors.

One limitation of the present study is the sample size, which may have resulted in inadequate statistical power to detect differences in many exposome variables. The fact that control participants were selected from individuals accompanying BCC patients to medical consultations may have introduced bias, given that some may share common exposures with the BCC group. Furthermore, the mean age of the control group was 10 years younger than that of the BCC group. The primary strength of our study is that, to our knowledge, it is the first to simultaneously evaluate the association between BCC and all possible exposome factors.

Conclusion

The present analysis of exposome-related variables in BCC patients confirms sun exposure, specifically chronic, occupational exposure, as the exposome variable most strongly associated with BCC, especially in people with low phototypes, who are genetically predisposed. Insufficient photoprotection at younger ages may be an important risk factor, the effects of which are unlikely to be modified by improved photoprotection habits later in life. Chronic consumption of photosensitizing drugs should also be considered a risk factor for BCC, and patients on these regimens should be targeted by awareness campaigns emphasizing the importance of adequate photoprotection. Consumption of caffeinated coffee may provide beneficial effects in the fight against BCC. A good balance between indoor and outdoor activities, including screen time, relaxation activities, and sports is important to reduce BCC incidence. Given the possibility that climate change may increase the time spent outdoors, as well as the levels of radiation to which outdoor workers are exposed, campaigns targeting this specific group, as well as the general population, are required to promote safe behaviors in the sun, and to instill healthy photoprotective habits from childhood.

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IRB approval status

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Questionnaires.

Table S1. The dietary intake of nutrients calculated using the PREDIMED questionnaire.