








# A multicenter case-control study comparing sun exposure habits and use of photoprotection measures in patients diagnosed with different types of skin cancer

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## Abstract

**Background:** While skin cancer awareness programs have significantly furthered public understanding about the harmful effects of the sun, there is a disparity between photoprotection knowledge and protection practices.

**Objective:** To compare sun exposure habits and photoprotection measures in patients diagnosed with basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma versus controls.

**Methods:** Multicentre case-control observational study carried out by 13 Spanish dermatologists between April 2020 and August 2022. Patients diagnosed with BCC,

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SCC, or melanoma were considered cases. The control group consisted of individuals with no history of skin cancer.

**Results:** Of the 254 cases (56.2% female; mean age,  $62.67 \pm 15.65$ ), 119 (31.2%) had BCC, 62 (16.27%) SCC, and 73 (19.1%) melanoma. The control group consisted of 127 (33.33%) individuals. Avoiding sun exposure between 12:00 and 16:00 was the most commonly used photoprotection measure (habitually/always: 63.1%), followed by the use of sunscreen (habitually/always: 58.9%). Patients with melanoma were less likely to use clothing and shade to avoid sun exposure ( $p < .05$ ), whereas those with BCC and SCC reported greater use of head coverings ( $p = .01$ ). BCC and SCC groups reported greater sun exposure 15 years prior, whereas controls reported greater use of sunscreen. However, at the time of this study all groups reported using  $\text{SPF} \geq 21$ , and the majority  $\text{SPF} > 50$ . No differences were observed in photoprotection measures between people with and without a previous history of skin cancer.

**Conclusions:** We describe differences in photoprotection measures and sun exposure patterns among patients diagnosed with different skin tumor types. Whether these differences may influence the type of tumor each developed will require further investigation.

#### KEYWORDS

basal cell carcinoma, melanoma, photoprotection measures, squamous cell carcinoma

## 1 | INTRODUCTION

Sun exposure is necessary for life. It provides us with vitamin D, regulates the cardiovascular system, and modulates our mood. However, it can also have harmful effects, the most important of which include sunburn, skin cancer, and photoaging.

Distinct effects have been attributed to each of the different types of radiation: ultraviolet B (UVB) radiation (280–320 nm) causes DNA damage, immunosuppression, sunburn, vitamin D synthesis, and pigmentation stimulation; ultraviolet A (UVA) radiation (320–400 nm) produces free radicals and causes DNA damage (directly and indirectly via reactive oxygen species [ROS]), hyperpigmentation, and photoaging; blue-violet radiation (380–455 nm) induces hyperpigmentation and ROS; and near-infrared radiation (800–2500 nm) contributes to photoaging.<sup>1</sup>

Skin cancer is the primary harmful effect of sun exposure, and UV radiation exposure has been recognized by the WHO as the primary sun exposure-associated carcinogen.<sup>2</sup> Therefore, healthy sun exposure habits are required to obtain the benefits while avoiding harmful effects.

Ultraviolet radiation (UVR) is considered the single most important risk factor for basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma. However, the patterns of sun exposure associated with these three skin cancers vary substantially. Factors associated with the development of SCC include chronic cumulative lifetime sun exposure, skin type, and sensitivity to sunlight.<sup>3</sup> By contrast, the risk of BCC development is thought to vary depending

#### Summary statement

Exposure to sun radiation has been demonstrated to play an essential role in the development of both melanoma and non-melanoma skin cancer. However, no studies compare sun exposure habits and photoprotection measures among populations with different types of skin cancer and controls. We found significant differences in the exposure habits and photoprotection measures depending on the type of skin cancer and controls. These results suggest that photoprotection campaigns could specifically target the habits of these populations and increase their efficacy.

on histological subtype,<sup>4</sup> and available evidence suggests that intermittent sun exposure (recreational tanning, occupational exposure, or childhood sunburn) is a predominant risk factor and that chronic cumulative sun exposure may not play as critical a role as in SCC carcinogenesis.<sup>5</sup>

In the case of melanoma, Nagore et al.<sup>6</sup> identified several distinct sun exposure patterns associated with different forms of melanoma: a slow-growing form that tends to develop in intermittently exposed areas (trunk), the incidence of which is increasing almost epidemically and is linked to changes in lifestyle habits; a very slow-growing form, which tends to occur in chronically exposed areas (head and neck), is associated with aging, and also shows increasing incidence;

and a third, very fast-growing form with an aggressive course that tends to be located in non-exposed areas and has shown a stable incidence over time.

Skin cancer awareness programs have significantly improved public awareness and understanding about the harmful effects of sun exposure. Photoprotection measures include avoiding sun exposure during the middle hours of the day and using shade, especially in spring and summer, wearing appropriate clothing and head coverings, applying sunscreen, and wearing sunglasses. However, studies have demonstrated a disparity between photoprotection knowledge and skin protection practices.<sup>7</sup>

The objective of the present study was to evaluate the relationship between sun exposure and the use of photoprotection measures in patients diagnosed with the three most frequent types of skin cancer (melanoma, BCC, and SCC) and in healthy controls.

## 2 | PATIENTS AND METHODS

### 2.1 | Study population

A multicenter case-control design study was carried out between April 1, 2020, and August 31, 2022, in which 13 dermatologists from different hospitals in Spain participated. The study population consisted of incidental cases diagnosed with BCC, SCC, and melanoma, and a control group consisting of age- and sex-matched individuals who accompanied the aforementioned patients to dermatology consultations and had no prior history of skin cancer.

### 2.2 | Questionnaire

Sun exposure behavior and photoprotection measures were assessed using the validated Beach questionnaire.<sup>8</sup>

### 2.3 | Statistical analyses

A descriptive statistical analysis was performed for all variables. Continuous variables were expressed as number of valid cases, mean, standard deviation (SD), median, 25th and 75th percentiles (P25-P75), minimum and maximum depending on the results of the Kolmogorov-Smirnov test. Categorical variables were expressed as the mean of absolute and relative frequencies for each category over the total number of valid values (N). In the case of missing values, their number per group is reported.

Differences among groups in the categorical variables and continuous variables were assessed using Chi-squared and ANOVA tests, respectively. Statistical significance was set at  $p < .05$ .

Statistical analyses were conducted following the principles specified in the ICH E9 guidelines and relevant good clinical practice standards.

Statistical analysis was performed using the SAS (statistical analysis system) program, version 9.4, on the Windows platform.

## 2.4 | Ethical concerns

The present study was strictly observational and the protocol was approved by the Aragón Ethical Committee for Clinical Research (C.I. PI19/311). All participants provided written informed consent.

## 3 | RESULTS

The study population consisted of 254 patients (BCC, 119 [31.2%]; SCC, 62 [16.27%]; melanoma, 73 [19.1%]) and 127 controls (33.33%). Females accounted for 56.2% of the population. The mean ( $\pm$  SD) age was  $62.67 \pm 15.65$  years (range, 18-93 years). The distribution of Fitzpatrick phototype was similar across groups ( $p = .32$ ): phototypes II and III were the most frequent (28.8% and 42.2%), followed by phototypes IV (11.9%), V (9.6%), and I (7.6%).

The photoprotection measures used by the study population are presented in Table 1 and Figure 1. Avoiding sun exposure during the hours of greatest UV radiation, between 12:00 and 16:00, was the photoprotection measure most commonly used by all participants (always or habitually, 63.1%), followed by sunscreen (SPF  $\geq 30$ ), which was used always or habitually by 58.9% of the population. No significant differences were observed between the BCC, SCC, melanoma, and control groups ( $p = .09$  and  $p = .24$ , respectively). Use of shade (always or habitually, 53.5%) differed between groups ( $p = .05$ ): patients with melanoma used this measure the least (always or habitually, 37.5%). The use of sunglasses (50.5% always or habitually) was similar across groups, whereas the use of head coverings (always or habitually in all groups, 30.5%) differed ( $p = .01$ ): more BCC (37.6%) and SCC (44.1%) patients reported using head coverings always or habitually than melanoma patients (24.7%) or controls (20.8%). Finally, clothing was the least commonly used measure (always or habitually, 22.8%), with differences observed between groups ( $p < .001$ ): the melanoma group used clothing the least (13.7%) followed by the BCC group (22.2%), control group (26%), and SCC group (28.8%).

Given the important role of prior sun exposure in the pathogenesis of skin cancer, participants were asked about sun protection habits 15 years prior. Most (70.7%) reported greater exposure in the past than in the present, and significant differences were observed between groups ( $p < .001$ ): BCC and SCC patients (79.5% and 79.3%, respectively) reported greater exposure 15 years previously than melanoma patients and controls (63% and 62.9%, respectively). In the assessment of the SPF used 15 years prior, use of SPF of 21-50 and  $>50$  was reported by more controls (30.6% and 28.1%) than skin cancer patients (BCC, 25% and 16.1%; SCC, 17.3% and 9.6%; melanoma, 19.4% and 13.4%;  $p < .001$ ). However, for current SPF use, all groups reported using a minimum SPF of 21-50 (BCC, 21.1%; SCC, 22.2%; melanoma, 35.8%; controls, 25%), and the majority reported

TABLE 1 Photoprotection measures among study participants.

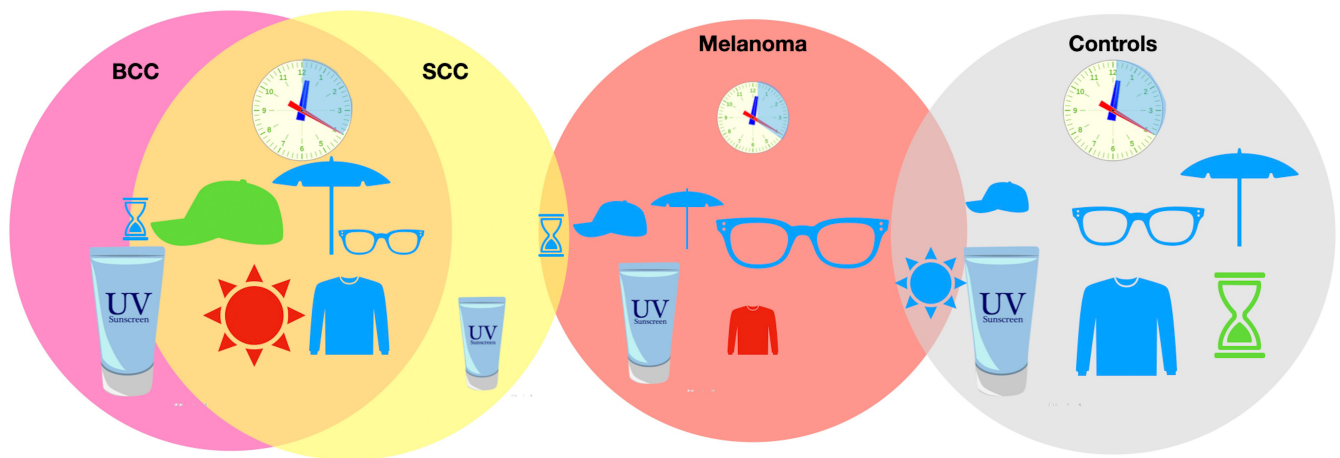
Variable	Total	BCC	SCC	Melanoma	Control	p-value <sup>a</sup>
Use of shade						
Total	370 (100.0%)	117 (100.0%)	57 (100.0%)	72 (100.0%)	124 (100.0%)	.0566
Never/rarely	99 (26.8%)	29 (24.8%)	17 (29.8%)	25 (34.7%)	28 (22.6%)	
Sometimes	73 (19.7%)	17 (14.5%)	9 (15.8%)	20 (27.8%)	27 (21.8%)	
Habitually/ always	198 (53.5%)	71 (60.7%)	31 (54.4%)	27 (37.5%)	69 (55.6%)	
N missing	11	2	5	1	3	
Use of sunglasses						
Total	372 (100.0%)	117 (100.0%)	59 (100.0%)	71 (100.0%)	125 (100.0%)	.3700
Never/rarely	125 (33.6%)	45 (38.5%)	25 (42.4%)	19 (26.8%)	36 (28.8%)	
Sometimes	59 (15.9%)	17 (14.5%)	8 (13.6%)	11 (15.5%)	23 (18.4%)	
Habitually/ always	188 (50.5%)	55 (47.0%)	26 (44.1%)	41 (57.7%)	66 (52.8%)	
N missing	9	2	3	2	2	
Use of hat or cap						
Total	374 (100.0%)	117 (100.0%)	59 (100.0%)	73 (100.0%)	125 (100.0%)	.0191
Never/rarely	173 (46.3%)	49 (41.9%)	20 (33.9%)	37 (50.7%)	67 (53.6%)	
Sometimes	87 (23.3%)	24 (20.5%)	13 (22.0%)	18 (24.7%)	32 (25.6%)	
Habitually/ always	114 (30.5%)	44 (37.6%)	26 (44.1%)	18 (24.7%)	26 (20.8%)	
N missing	7	2	3	0	2	
Use of clothing						
Total	372 (100.0%)	117 (100.0%)	59 (100.0%)	73 (100.0%)	123 (100.0%)	.0031
Never/rarely	180 (48.4%)	60 (51.3%)	21 (35.6%)	50 (68.5%)	49 (39.8%)	
Sometimes	107 (28.8%)	31 (26.5%)	21 (35.6%)	13 (17.8%)	42 (34.1%)	
Habitually/ always	85 (22.8%)	26 (22.2%)	17 (28.8%)	10 (13.7%)	32 (26.0%)	
N missing	9	2	3	0	4	
Avoid sun exposure from 12:00 to 16:00						
Total	371 (100.0%)	117 (100.0%)	58 (100.0%)	73 (100.0%)	123 (100.0%)	.0943
Never/rarely	61 (16.4%)	13 (11.1%)	10 (17.2%)	15 (20.5%)	23 (18.7%)	
Sometimes	76 (20.5%)	22 (18.8%)	9 (15.5%)	22 (30.1%)	23 (18.7%)	
Habitually/ always	234 (63.1%)	82 (70.1%)	39 (67.2%)	36 (49.3%)	77 (62.6%)	
N missing	10	2	4	0	4	
Use of sunscreen						
Total	372 (100.0%)	117 (100.0%)	59 (100.0%)	73 (100.0%)	123 (100.0%)	.2402
Never/rarely	83 (22.3%)	26 (22.2%)	18 (30.5%)	19 (26.0%)	20 (16.3%)	
Sometimes	70 (18.8%)	18 (15.4%)	13 (22.0%)	15 (20.5%)	24 (19.5%)	
Habitually/ always	219 (58.9%)	73 (62.4%)	28 (47.5%)	39 (53.4%)	79 (64.2%)	
N missing	9	2	3	0	4	
Greater exposure to ultraviolet radiation 15 years prior						
Total	372 (100.0%)	117 (100.0%)	58 (100.0%)	73 (100.0%)	124 (100.0%)	.0069
Yes	263 (70.7%)	93 (79.5%)	46 (79.3%)	46 (63.0%)	78 (62.9%)	
No	109 (29.3%)	24 (20.5%)	12 (20.7%)	27 (37.0%)	46 (37.1%)	
N missing	9	2	4	0	3	

TABLE 1 (Continued)

Variable	Total	BCC	SCC	Melanoma	Control	p-value <sup>a</sup>
SPF used 15 years ago						
Total	352 (100.0%)	112 (100.0%)	52 (100.0%)	67 (100.0%)	121 (100.0%)	.0001
I do not know	113 (32.1%)	36 (32.1%)	31 (59.6%)	24 (35.8%)	22 (18.2%)	
2–10	40 (11.4%)	14 (12.5%)	5 (9.6%)	10 (14.9%)	11 (9.1%)	
11–20	46 (13.1%)	16 (14.3%)	2 (3.8%)	11 (16.4%)	17 (14.0%)	
21–50	87 (24.7%)	28 (25.0%)	9 (17.3%)	13 (19.4%)	37 (30.6%)	
>50	66 (18.8%)	18 (16.1%)	5 (9.6%)	9 (13.4%)	34 (28.1%)	
N missing	29	7	10	6	6	
SPF used now						
Total	355 (100.0%)	114 (100.0%)	54 (100.0%)	67 (100.0%)	120 (100.0%)	.0625
I do not know	40 (11.3%)	12 (10.5%)	11 (20.4%)	7 (10.4%)	10 (8.3%)	
2–10	5 (1.4%)	0	2 (3.7%)	0	3 (2.5%)	
11–20	14 (3.9%)	2 (1.8%)	2 (3.7%)	4 (6.0%)	6 (5.0%)	
21–50	90 (25.4%)	24 (21.1%)	12 (22.2%)	24 (35.8%)	30 (25.0%)	
>50	206 (58.0%)	76 (66.7%)	27 (50.0%)	32 (47.8%)	71 (59.2%)	
N missing	26	5	8	6	7	

Abbreviations: BCC, basal cell carcinoma; SCC, squamous cell carcinoma; SPF, solar protection factor.

<sup>a</sup>ANOVA.



**FIGURE 1** Photoprotection measures adopted by the different groups. Green and red indicate measures for which positive and negative effects were observed, respectively. The size of each symbol corresponds to the proportion of patients that applied the corresponding measure. Sunscreen, use of sunscreen; hourglass, sunscreen used 15 years ago; cap, use of hat or cap; watch, avoidance of sun exposure from 12:00–16:00; sun, UVR exposure 15 years ago; T-shirt, use of clothing; glasses, use of sunglasses; umbrella, use of shade. Abbreviations: BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

using SPF > 50 (BCC, 66.7%; SCC, 50%; melanoma, 47.8%; controls, 59.2%). Finally, comparison of photoprotection measures in patients without skin cancer history versus those with previous history of skin cancer revealed no statistically significant differences (Table 2).

#### 4 | DISCUSSION

While many studies have investigated the relationship between photoprotection measures and skin cancer, most have focused on

the use of sunscreen, without considering protective clothing, sunglasses, head coverings, or use of shade when outdoors.<sup>9</sup> The most common photoprotection measure in our population was avoidance of sun exposure during the middle of the day, followed by the use of sunscreens. Moreover, we identified significant differences in photoprotection habits among the four groups. Those diagnosed with melanoma reported lower use of protective clothing and shade in comparison with the rest of the groups, whereas BCC and SCC patients reported greater use of head coverings, in comparison with melanoma patients, and all of the groups used hat/cap more than

**TABLE 2** Photoprotection measures of patients with incidental skin cancer compared with people without previous history of skin cancer.

Variable	Total	Skin cancer history	No skin cancer history	<i>p</i> -value <sup>a</sup>
<b>Use of shade</b>				
Total	341 (100.0%)	86 (100.0%)	255 (100.0%)	.0594
Never/rarely	92 (27.0%)	19 (22.1%)	73 (28.6%)	
Sometimes	68 (19.9%)	12 (14.0%)	56 (22.0%)	
Habitually/always	181 (53.1%)	55 (64.0%)	126 (49.4%)	
N missing	11	5	6	
<b>Use of sunglasses</b>				
Total	343 (100.0%)	89 (100.0%)	254 (100.0%)	.3882
Never/rarely	117 (34.1%)	33 (37.1%)	84 (33.1%)	
Sometimes	55 (16.0%)	17 (19.1%)	38 (15.0%)	
Habitually/always	171 (49.9%)	39 (43.8%)	132 (52.0%)	
N missing	9	2	7	
<b>Use of hat or cap</b>				
Total	345 (100.0%)	89 (100.0%)	256 (100.0%)	.3517
Never/rarely	156 (45.2%)	39 (43.8%)	117 (45.7%)	
Sometimes	84 (24.3%)	18 (20.2%)	66 (25.8%)	
Habitually/always	105 (30.4%)	32 (36.0%)	73 (28.5%)	
N missing	7	2	5	
<b>Use of clothing</b>				
Total	344 (100.0%)	89 (100.0%)	255 (100.0%)	.5529
Never/rarely	167 (48.5%)	39 (43.8%)	128 (50.2%)	
Sometimes	99 (28.8%)	27 (30.3%)	72 (28.2%)	
Habitually/always	78 (22.7%)	23 (25.8%)	55 (21.6%)	
N missing	8	2	6	
<b>Avoid sun exposure from 12:00 to 16:00</b>				
Total	342 (100.0%)	88 (100.0%)	254 (100.0%)	.1031
Never/rarely	53 (15.5%)	8 (9.1%)	45 (17.7%)	
Sometimes	72 (21.1%)	17 (19.3%)	55 (21.7%)	
Habitually/always	217 (63.5%)	63 (71.6%)	154 (60.6%)	
N missing	10	3	7	
<b>Use of sunscreen</b>				
Total	343 (100.0%)	89 (100.0%)	254 (100.0%)	.0908
Never/rarely	76 (22.2%)	14 (15.7%)	62 (24.4%)	
Sometimes	65 (19.0%)	14 (15.7%)	51 (20.1%)	
Habitually/always	202 (58.9%)	61 (68.5%)	141 (55.5%)	
N missing	9	2	7	

<sup>a</sup>ANOVA.

controls. The greatest difference between skin cancer patients and controls was observed for sun exposure 15 years prior, this parameter was higher for BCC and SCC patients, whereas sunscreen use was higher 15 years prior among the controls.

In their narrative review, Nahar et al.<sup>10</sup> assessed the prevalence of sun-safe behaviors in non-melanoma skin cancer survivors and, in line with our findings here, found that respondents did not protect themselves optimally from UV radiation exposure. This was attributed to low levels of perceived skin cancer risk, a lack of knowledge about

effective sun protection strategies, and a perception of sun-safe behaviors as inconvenient. The authors proposed that behavioral interventions should be developed and that skin cancer survivors should be educated about their increased risk of future skin cancer. Rowan-Robinson et al.<sup>11</sup> concluded that nurses play an important role in patient education and could educate patients about solar protective measures to reduce their risk of cancer.

In our study population, the use of shade as a photoprotection measure was reported by most participants. This significantly



reduces sun exposure, although the UVR reflected by surfaces such as sand, grass, and water must also be considered. Indeed, a randomized clinical trial found that a beach umbrella alone may not provide sufficient protection against prolonged UV exposure, and should be used in combination with sunscreen.<sup>12</sup> Moreover, it should be noted that the use of shade was lower among patients diagnosed with melanoma than those with BCC or SCC, and was similar to that recorded for controls. This is in line with the link between keratinocyte cancers and chronic, often occupational, UVR exposure. By contrast, melanoma has been associated with more intermittent and frequent recreational exposure, often in individuals with higher income. The use of head coverings may be more common in patients with keratinocyte carcinomas, which are more frequently located on the head and neck, in contrast to melanoma, which more often develops on the trunk.<sup>6</sup> Indeed, this association was observed in our Sol y Campo study,<sup>13</sup> in which head coverings were one of the most used photoprotection measures by farmers.

Patients with melanoma used less clothing to protect themselves from the sun than the other study groups. This may be explained by greater recreational and intermittent UVR exposure in this group, for example when practicing outdoor sports or sunbathing.<sup>14,15</sup> Soto et al.<sup>16</sup> compared the photoprotective behaviors of patients before and after being diagnosed with melanoma and found that clothing was one of the least used photoprotection measures before diagnosis, and Aleisa et al.<sup>17</sup> reported that this measure was less used than other photoprotection measures after diagnosis of melanoma. The use of clothing for photoprotection is increasing.<sup>18</sup> Lycra and elastane fabrics can both have an ultraviolet protection factor >50, although cotton clothing can also provide adequate photoprotection.<sup>19</sup>

Our findings indicate that the use of photoprotection measures was lowest in patients with melanoma, except sunscreen and sunglasses, which were used less by SCC patients than any other group.<sup>20</sup> Some randomized clinical trials have shown sunscreen use as the only photoprotection measure proven to prevent skin cancer, especially actinic keratoses, SCC,<sup>9,21-23</sup> and melanoma. In their clinical trial, Green et al.<sup>24</sup> compared daily versus discretionary sunscreen use and observed a reduced risk of melanoma after 10 years in daily use group (HR=0.50; CI95%, 0.24-1.02; p=.051). However, a lack of any clear protective effect of sunscreen has been reported in BCC<sup>9</sup> and, the current protective effect of sunscreen in overall skin cancer in general population could not be confirmed in a recent meta-analysis.<sup>25</sup> In spite of that, all international guidelines recommend the use of sunscreen to reduce the incidence of skin cancer.<sup>26,27</sup>

A worrying finding in our study was the absence of any differences in photoprotection habits among patients with a prior history of skin cancer versus people without a history of skin cancer. Several studies have shown that, despite adequate knowledge about photoprotection measures and risk factors for developing skin cancer, people do not correctly apply these measures.<sup>28,29</sup> Moreover, people with skin cancer history, even after receiving appropriate education following diagnosis, continued to develop sunburn<sup>30</sup> and show suboptimal adherence to photoprotection measures.<sup>31</sup>

Our study highlights the importance of maintaining adequate sun protection habits, and the influence of historical sunscreen use and

frequency of sun exposure on the risk of skin cancer development. All patients and controls in the present study reported lower use of photoprotectors 15 years prior, mainly SPF of 21-50, compared with the present in which they reported higher sunscreen use, mostly SPF > 50. This could possibly be explained due to poor knowledge at the time about sun damage and the implications thereof. Recent years have seen an exponential increase in photoprotection campaigns, which have considerably increased awareness among the general public.<sup>32-34</sup> Encouragingly, photoprotection habits in our study population had improved considerably compared with 15 years ago. Whether this translates into a decrease in skin cancer incidence in the future remains to be determined. Trends in Internet searches on sun protection, artificial tanning, and skin cancers could serve as markers to evaluate the reach and success of skin cancer awareness campaigns.<sup>35,36</sup> Nonetheless, in recent decades tanning has come to be considered attractive, and pursuit of a tan can put skin health at risk, favoring sunburn and in the long term increasing the risk of skin cancer and photoaging.

The present study has some limitations. A higher sample size could increase the statistical power to detect differences in photoprotection variables. Moreover, the selection of controls from the patients' environment. Although controls did not have history of skin cancer, some may have had photoprotection habits similar to those of the patients owing to proximity, potentially influencing the results obtained.

## 5 | CONCLUSIONS

Our findings indicate that photoprotection measures adopted by patients diagnosed with skin cancer differ to those of individuals without skin cancer, and reveal significant differences between patient groups depending on tumor type (melanoma, BCC, or SCC). Whether these differences have any relevance in terms of pathophysiology remains unclear. Efforts are required to promote and improve photoprotection habits among patients with a skin cancer diagnosis to prevent the development of new cutaneous tumors.

Photoprotection campaigns should not be overly general, instead focusing on the type of sun exposure of a given patient to optimize effectiveness.

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None.

### CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## IRB APPROVAL STATUS

Reviewed and approved by CEIC Aragón; approval C.I. PI19/311.

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