

# Prevalence of actinic skin lesions in patients with basal cell carcinoma of the head: a case-control study

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## SUMMARY

**Objective:** To evaluate the prevalence of actinic skin lesions in patients with basal cell carcinoma of the head. **Methods:** A case-control study was carried out. Cases were patients with primary, solid basal cell carcinoma of the head, less than two centimeters in diameter; and as controls, patients with other dermatoses. Constitutional and behavioral variables were analyzed, as well as actinic lesions. **Results:** One hundred twenty cases and 360 controls were evaluated. Facial milia (OR = 2.3), leukoderma punctata of the upper limbs (OR = 2.9), and *cutis rhomboidalis nuchae* (OR = 1.8) were associated with neoplasms regardless of other variables, suggesting a risk phenotype. There was also association with light hair and eye color phenotypes, family genetics, and cumulative sun exposure. Sunburn, smoking, and alcoholism were not identified as risk factors. The use of sunscreens showed no evidence of protection; however, the control group consisted of dermatology patients who are often prescribed sunscreens. **Conclusion:** Actinic lesions were more prevalent in patients with solid basal cell carcinoma of the head than in controls, especially milia, *cutis rhomboidalis nuchae*, and leukoderma punctata, regardless of other known risk factors.

**Keywords:** Head and neck neoplasias; basal cell carcinoma; epidemiology; case-control studies; UV rays; risk factors.

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## INTRODUCTION

Basal cell carcinoma (BCC) is the most common neoplasia in humans, especially among fair-skinned individuals. It constitutes 70% to 80% of malignant skin tumors and represents an important demand on and cost to the health system<sup>1,2</sup>. According to a German sample, throughout life, the cumulative risk of its development in the Caucasian population is over 30%<sup>3</sup>. The expected incidence in 2011 in Brazil is approximately 120,000 cases<sup>1</sup>. Over the past 50 years, there was an increase in the incidence in several countries, including the involvement of younger patients<sup>4,5</sup>.

This neoplasia has a low degree of malignancy and mortality due to the typical slow growth and reduced potential to metastasize, in addition to its early diagnosis, as it is preferentially located in areas exposed to sunlight. However, its morbidity is high due to local invasion, tissue destruction, and the possibility of recurrence, affecting patients' quality of life<sup>4,6-8</sup>.

In contrast, a smaller fraction of malignant neoplasms of the skin (20-30%) consists mainly of squamous cell carcinoma (SCC) and melanomas, which are aggressive forms, with clear metastatic potential. Whereas the SCC favors sun-exposed and mucosal areas, melanomas also occurs in less irradiated areas such as the back, upper thighs, and extremities, which can lead to diagnostic delay<sup>1</sup>.

Ultraviolet radiation (UVR) is the main environmental risk factor associated with the genesis of the BCC, as shown by a higher frequency of lesions in sun-exposed areas. In addition to the immunosuppressive action on the skin, compromising the local antitumor monitoring activity<sup>2-4,9</sup>, UVB radiation generates mutagenic photoproducts in the DNA, which promotes mutations in genes such as PTCH and p53. In turn, UVA radiation has mainly indirect effects by generating cytotoxic and mutagenic free radicals<sup>9-12</sup>.

The most important constitutional risk factors are: fair skin (difficulty to tan and predisposition to sunburns), light-colored eyes and hair, family history of BCC, and freckles in childhood. Noteworthy behavioral factors are: professional activity unprotected from UVR, rural activities, and sunburns in youth<sup>7,13</sup>.

Although most authors point to a greater role of intermittent sun exposure, especially in youth, in the genesis of the BCC, some recent studies have suggested that nodular BCC would be more related to chronic sun exposure<sup>14,15</sup>.

As their genesis is associated with exposure to UVR, chronic actinic skin lesions may be indicators of the risk for the development of BCC. Skin lesions such as actinic keratosis, solar lentigines, solar elastosis, and facial telangiectasias are commonly found in patients with this cancer, but have not been systematically studied, nor considered regarding the other epidemiological markers of risk<sup>13,16-18</sup>.

Early diagnosis is a key strategy to improve prognosis, and reduce sequelae (local and therapeutic) and costs for the health system. The identification of risk phenotypes can be favorable in public health interventions aiming at primary and secondary prevention.

The authors aimed to evaluate the prevalence of chronic actinic skin lesions in patients with solid, primary BCC of the head, and compared them with patients without skin cancer, in order to identify skin phenotypes associated with the risk of BCC.

## METHODS

This was a case-control study involving patients older than 40 years of age, of both genders, treated at the Department of Dermatology of the Medical School of UNESP - Botucatu, from March 2007 to December 2009.

The cases were defined as patients with solid, primary BCC (confirmed by histopathological analysis), less than two centimeters in diameter, located on the head, diagnosed less than a year before the interview. Controls were patients with other benign dermatoses, interviewed at a proportion of three respondents for each case, in a non-paired manner, to allow risk estimation and stratified analysis of constitutional variables such as gender, age, and skin type (Fitzpatrick classification)<sup>19</sup>.

Patients presenting with evidence of immunosuppression (medication-induced or associated with chronic diseases with significant reduction in immune response), genetic syndromes predisposing to cancer, diffuse skin dermatoses, skin type VI, presenting more than one BCC lesion or any other skin neoplasm at any time were excluded.

The demographic and behavioral information were obtained from standardized forms, and the actinic skin lesions were examined by a dermatologist. Systematic patient sampling was not used, thus including all those who were consecutively available.

The main dependent variable was the appearance of sporadic, solid BCC, less than two centimeters in diameter, located on the head. The independent variables were age, gender, skin type, constitutional characteristics, sunburns, photoaging measurement, dermatoses associated with chronic sun exposure, smoking, alcohol consumption, family occurrence of BCC, sun exposure related to occupational or leisure activity, and use of sunscreen.

Initially, a bivariate analysis was performed to estimate associations between the primary variables in each group. Categorical variables were expressed as the percentage of occurrence and compared by the chi-square tests or the chi-square test for trend, for ordinal characteristic. Continuous and discrete quantitative variables were represented by their means or medians, and analyzed by Student's *t*-test, or by the Mann-Whitney test if

the distribution was nonparametric. Normality of distributions was estimated by the Shapiro-Wilk's test.

Subsequently, the independent variables were adjusted from a non-conditional multiple logistic regression model of hierarchical structure to control confounding factors. The progressive inclusion of variables into the model, according to each hierarchical level, occurred with  $p < 0.25^{20-22}$ .

The hierarchical model of analysis to control confounding factors showed, in the first level (forced entry variables): gender, age, and skin type. At the second level, other constitutional variables included: light-colored eyes, light-colored hair, freckles in childhood, family history of BCC. In the third level, behavioral and exposure variables were included: rural activities, working in the sun, number of hours working in the sun (expressed by the product of hours/days and years of exposure =  $h/d \times \text{year}$ ), leisure activities in the sun, number of hours during leisure activities in the sun (expressed by the product of hours/week and years of exposure =  $h/wk \times \text{year}$ ), smoking (expressed as the product of packs/day and years of smoking =  $\text{packs}/d \times \text{year}$ ), alcoholism, use of sunscreen in the past 10 years (stratified as: never, when leaving the house/going to the beach, every day). In the last level, chronic actinic lesions were included: wrinkles, facial and upper limb actinic keratoses, telangiectasias, leukoderma punctata, facial milia, acne scars, comedones, facial and upper limb lentiginos, poikiloderma of Civatte, *cutis rhomboidalis nuchae*, stellar scars of the upper limbs, Bateman's purpura, actinic cheilitis, and palmar keratosis.

The groups were further analyzed and stratified by gender, skin types, and extremes of age tertiles. The additive effects of the interaction between variables were estimated by assessing the modification of the overall effect of the combination of variables<sup>20,22</sup>.

The association measures were represented as odds ratios, at a 95% confidence interval (CI), and a two-tailed p-value of 0.05 was considered significant.

Data were tabulated in MS Excel® 2003, and analyzed using the Statistical Package for the Social Sciences (SPSS) software version 17.0<sup>23</sup>.

The sampling was estimated based on a pretest with 50 cases and 150 controls, and calculated for a model of non-conditional multiple logistic regression, according to the estimation of variables for the final model<sup>24,25</sup>.

The project was approved by the institution's ethics and research committee (protocol number 331/2007). After all interviews, the patients signed the free and informed consent form.

## RESULTS

A total of 120 cases and 360 controls were evaluated. The main demographic data are shown in Table 1. There was a direct association of BCC with fair-skin phenotypes, older

age, predisposing family genetics, and work activity in the sun; 95% of the controls were exposed for less than 400 h/d x year. Smoking, regular alcohol consumption, sunscreen use, leisure activities in the sun, and sunburns were not risk factors for this sample.

Cases and controls mainly came from the city of Botucatu (45% and 41%) and surrounding regions (98% and 91%). No patients of Asian origin were interviewed and none of the cases or controls used tanning beds or phototherapy.

Among controls, 98 different dermatological diagnoses were identified, of which the main ones (> 2% of diagnoses) were onychomycosis, contact dermatitis, urticarial rash, melanocytic nevi, seborrheic keratoses, actinic keratosis, pyoderma, discoid lupus erythematosus, *tinea pedis*, stasis eczema, psoriasis, which are in agreement with the Brazilian dermatological outpatient sample for this age group<sup>26</sup>.

Table 2 specifies the frequency of chronic actinic lesions between the groups, showing a direct association between BCC and the skin lesions studied, except for lentiginos and facial acne scars.

Table 3 shows the final reduced hierarchical logistic model of the prevalence of actinic lesions. Milia, leukoderma punctata of the upper limbs, and *cutis rhomboidalis nuchae* were associated with the BCC, regardless of other covariates.

No significant interactions were identified between the independent variables, and there was no data loss in the sample. The final model showed no outliers ( $Z_{res} > 3$ ).

Female cases had lighter skin types, reported less alcohol consumption, and had higher sun exposure during work and leisure time than their controls of the same sex. Family history was more frequent (OR = 2.38) among cases, and skin lesions indicative of risk in this subgroup were milia (OR = 2.16) and stellar scars (OR = 2.55).

Male patients had the following skin lesions as indicative of risk: milia (OR = 3.85), acne scars (OR = 8.29), leukoderma punctata (OR = 3.71), and *cutis rhomboidalis nuchae* (OR = 4.17). Family history was more frequent among cases (OR = 23.83), which also showed lighter phenotypes, reported higher sun exposure during work and leisure periods, and more freckles in childhood in comparison to their controls. The presence of facial comedones showed a protective effect in these patients (OR = 0.28).

Overall, the women in the study worked fewer hours exposed to the sun as compared to men (average: 91.82 versus 182.94 h,  $p < 0.05$ ), and underwent less sun exposure during leisure time than men (average: 31.68 versus 53.33 h,  $p < 0.05$ ).

Cases with skin types I and II showed a higher sun exposure during work time than light skin type controls. The age of cases was younger than that of controls (OR = 0.95).

**Table 1** - Analysis of constitutional and behavioral demographic variables between the groups

Variables	Cases	%	Controls	%	Odds ratio	95% CI	p
n	120		360				
Constitutional and biological variables							
Female sex	76	63.3	241	66.9	0.85	0.55 to 1.31	0.47*
Skin type							
I	4	3.3	6	1.7	13.00	1.94 to 87.14	0.01**
II	42	35.0	67	18.6	12.22	2.80 to 53.29	
III	61	50.8	150	41.7	7.93	1.86 to 33.87	
IV	11	9.2	98	27.2	2.19	0.46 to 10.33	
V	2	1.7	39	10.8	1.00	-	
Light-colored hair	32	26.7	59	16.4	1.86	1.14 to 3.03	0.01*
Light-colored eyes	48	40.0	105	29.2	1.62	1.05 to 2.49	0.03*
Freckles in childhood	36	30.0	59	16.4	2.19	1.36 to 3.51	0.00*
Family history of BCC	31	25.8	46	12.8	2.38	1.35 to 3.53	0.00*
Median age (1 <sup>st</sup> -3 <sup>rd</sup> quartiles) years	64	(54-72)	56	(48-66)	1.04	1.02 to 1.06	0.00#
Behavioral and exposure variables							
Sun exposure at work	105	87.5	263	73.1	2.58	1.43 to 4.65	0.00*
Sun exposure at work - median (1 <sup>st</sup> -3 <sup>rd</sup> quartiles) hours/day x years	112.5	(24-350)	45	(5-150)	1.00	1.00 to 1.01	0.00#
Rural activity	58	48.3	101	28.1	2.40	1.57 to 3.67	0.00*
Leisure in the sun	42	35.0	102	28.3	1.36	0.88 to 2.11	0.17*
Sun exposure during leisure activities - median (1 <sup>st</sup> -3 <sup>rd</sup> quartiles) hours/week x years	0	(0-38)	0	(0-15)	1.00	1.00 to 1.01	0.21#
Painful sunburn	54	45.0	157	43.6	1.06	0.70 to 1.60	0.79*
Sunburn with blisters	23	19.2	71	19.7	0.97	0.57 to 1.63	0.89*
Smoking	49	40.8	176	48.9	0.72	0.48 to 1.10	0.13*
Tobacco load - median (1 <sup>st</sup> -3 <sup>rd</sup> quartiles) packs/days x years	0	(0-21)	0	(0-21)	1.00	1.00 to 1.01	0.36#
Regular alcohol consumption	18	15.0	81	22.5	0.61	0.34 to 1.06	0.08*
Sunscreen use for > 10 years							
Never	102	85.0	289	80.3	1.00	-	0.20**
Leaving the house/on the beach	8	6.3	26	7.2	0.87	0.38 to 1.99	
Everyday	10	8.3	45	12.5	0.63	0.31 to 1.30	

\*Chi-square test; \*\*Chi-square trend test; #Mann-Whitney test.

The injury most often associated with risk of BCC was facial telangiectasia (OR = 12.20).

Compared to controls with skin types IV and V, cases with darker skin types underwent higher sun exposure during leisure time. The age of the cases, which was older than controls (OR = 1.14), and the reference to family history (OR = 39.99) must be emphasized. The skin lesion most often associated was *cutis rhomboidalis nuchae* (OR = 8.32).

The cases in the youngest age tertile (< 60 years), compared to young controls presented lighter skin types, lower incidence of rural professions, and higher sun exposure during leisure time. We emphasize the strong influence of family history (OR = 7.65), and among the skin lesions, milia (OR = 6.39), facial telangiectasias (OR = 15.78), actinic keratosis of the upper limbs (OR = 3.67), and poikiloderma of Civatte (OR = 4.13).

**Table 2** – Bivariate analysis of prevalence of chronic actinic lesions between the groups

Variables	Cases	%	Controls	%	Odds ratio	95% CI	p
n	120		360				
<b>Actinic skin lesions</b>							
Facial telangiectasias	110	91.7	286	79.4	2.85	1.45 to 5.57	0.00*
Facial actinic keratosis	70	58.3	97	26.9	3.80	2.22 to 6.48	0.00*
Facial lentiginos	113	94.2	322	89.4	1.91	0.84 to 4.33	0.12*
None	7	5.8	38	10.6	0.55	0.24 to 1.29	0.49**
< 10 lesions	30	25.0	73	20.3	1.23	0.75 to 2.02	
≥ 10 lesions	83	69.2	249	69.2	1.00	–	
Acne scars	10	8.3	41	11.4	0.71	0.34 to 1.46	0.35*
<b>Facial wrinkles</b>							
Muscle movement	4	3.3	17	4.7	0.45	0.14 to 1.40	
Static	70	58.3	256	71.1	0.52	0.33 to 0.80	
Deep lines	46	38.3	87	24.2	1.00	–	0.00**
Cheilitis	13	10.8	19	5.3	2.18	1.06 to 4.49	0.04*
Facial milia	53	44.2	108	30.0	1.85	1.21 to 2.81	0.00*
Facial comedones	77	64.2	277	76.9	0.54	0.34 to 0.84	0.01*
<i>Cutis rhomboidalis</i>	70	58.3	104	28.9	3.45	2.10 to 5.66	0.00*
Poikiloderma of Civatte	71	59.2	169	46.9	1.64	1.08 to 2.48	0.02*
Lentigo on dorsum of hands	115	95.8	319	88.6	2.96	1.19 to 7.36	0.02*
None	5	4.2	41	11.4	0.31	0.12 to 0.80	0.00**
< 10 lesions	14	11.7	65	18.1	0.54	0.29 to 1.00	
≥ 10 lesions	101	84.2	254	70.6	1.00	–	
Bateman's purpura	51	42.5	85	23.6	2.39	1.56 to 3.67	0.00*
Leukoderma punctata	112	93.3	291	80.8	3.32	1.60 to 6.87	0.00*
None	8	6.7	69	19.2	0.29	0.13 to 0.63	0.00**
< 10 lesions	22	18.3	66	18.3	0.83	0.49 to 1.43	
≥ 10 lesions	90	75.0	225	62.5	1.00	–	
Stellar scars	26	21.7	38	10.6	2.34	1.37 to 4.02	0.00*
None	94	78.3	322	89.4	1.00	–	0.03**
< 10 lesions	19	15.8	19	5.3	3.42	1.74 to 7.74	
≥ 10 lesions	7	5.8	19	5.3	1.26	0.52 to 3.09	
Palmar keratosis	13	10.8	16	4.4	2.61	1.24 to 5.51	0.01*
Actinic keratosis of UULL	71	59.2	101	28.1	3.72	2.20 to 6.29	0.00*
None	49	40.8	259	71.9	1.00	–	0.00**
< 10 lesions	34	28.3	47	13.1	3.82	2.24 to 6.54	
≥ 10 lesions	37	30.8	53	14.7	3.62	2.16 to 6.08	

UULL, upper limbs; \*Chi-square test; \*\*Chi-square trend test.

The cases in the oldest tertile (> 78 years), when compared with older controls, showed lighter phenotypes and higher sun exposure during work. The associated actinic lesions in this subgroup were milia (OR = 3.63), *cutis rhomboidalis nuchae* (OR = 4.73), leukoderma punctata (OR = 6.80), and actinic cheilitis (OR = 6.35).

## DISCUSSION

The chronic actinic lesions were more prevalent among patients with solid BCC on the head than in the controls of the studied population. Especially, facial milia, leukoderma punctata of the upper limbs, and *cutis rhomboidalis nuchae* remained significant in the comparison, even

**Table 3** – Logistic model adjusted for the other risk factors

Variable	Odds ratio	95% CI	p
Age	1.01	0.99 to 1.04	0.26
Female sex	0.64	0.34 to 1.23	0.18
Skin type			0.00
I and II	7.15	2.57 to 19.91	
III and IV	3.70	1.67 to 8.20	
V and VI	1.00	–	
Freckles in childhood	1.53	0.85 to 2.75	0.16
Light-colored eyes	0.54	0.27 to 1.06	0.08
Family history of BCC	2.63	1.43 to 4.84	0.00
Rural activity	1.44	0.79 to 2.63	0.24
Professional sun exposure (100h)	1.30	1.06 to 1.58	0.01
Sun exposure in leisure (100h)	1.56	1.20 to 2.02	0.00
Regular alcohol consumption	0.59	0.28 to 1.23	0.16
Facial milia	2.25	1.33 to 3.81	0.00
Leukoderma punctata of UULL	2.90	1.11 to 7.60	0.03
<i>Cutis rhomboidalis nuchae</i>	1.82	1.03 to 3.21	0.04
Facial telangiectasias	1.52	0.66 to 3.53	0.33
Acne scars	1.83	0.77 to 4.35	0.18
Facial comedones	0.59	0.33 to 1.06	0.08
Constant	–		0.00

Hosmer and Lemeshow Test  $p = 0.35$ ; correct classification = 81.3%;  $R^2_{\text{Nagelkerke}} = 0.37$ .

when adjusted for age, skin type, gender, family history of BCC, and number of hours of work and leisure activities in the sun.

Milia are keratinocytic cysts that are formed in the upper dermis as a result of sun exposure, burns, trauma, sweat or sebaceous gland obstruction, or recurrent cicatricial processes as it occurs in porphyria and epidermolysis bullosa. They also occur in Gorlin, Bazex-Dupr -Christol, and Rombo syndromes, which course with multiple BCCs<sup>4,27,28</sup>. To date, no study had investigated its association with BCC.

*Cutis rhomboidalis nuchae* is a manifestation of exuberant dermal actinic elastosis that occurs in the neck. It commonly affects fair-skinned elderly individuals who were chronically exposed to UVR. The exacerbated production of thick and disarrayed elastic fibers is due to a chronic inflammatory process, with mast cell degranulation and activation of fibroblasts that produce collagen-degrading metalloproteinases. The association of BCC with photoaging, elastosis, and Favre-Racouchot syndrome has been described before<sup>16,17,29</sup>. Facial wrinkles are skin lesions associated with elastosis, which have been identified as a possible protective factor in a German series<sup>30</sup>. This,

however, was not demonstrated in this sample, as the direct analysis showed that wrinkles represent risk factors that are proportional to their intensity.

Leukoderma punctata or idiopathic guttate hypomelanosis is common in fair-skinned adults and occurs mainly in sun-exposed surfaces of the upper and lower limbs. It is caused by local melanocytic hypoplasia with reduced melanin pigmentation. It has been previously identified as a risk element for BCC after multivariate adjustment<sup>29</sup>.

Leukoderma punctata, milia, and *cutis rhomboidalis* are not neoplastic lesions, and their physiopathogenesis occurs independently from each other; in addition, they do not share other factors in the biological chain of the BCC, except chronic exposure to UVB. The concomitant susceptibility of these actinic lesions with BCC must derive from an individual phenotype of common risk.

Solar lentigines, actinic keratoses, actinic cheilitis, facial telangiectasia, and solar elastosis were not variables independently associated with BCC in this population, unlike other studies<sup>16,17,29-31</sup>. This discrepancy may result from the confounding effect caused by the types of lesions studied, which was minimized in this work by including several other predictive variables in the multivariate

analysis, such as milia, leucoderma, and *cutis rhomboidalis*. Other explanations for this difference may result from the selection of patients with BCCs in other topographies, other histological types and multiple forms; moreover, the control individuals come from a group of adult dermatology patients, in whom a higher frequency of skin lesions than in the normal population is to be expected<sup>14</sup>.

Prospective studies should be carried out to corroborate these findings and disclose the physiopathology of individual sensitivity to BCC that predisposes the simultaneous expression of these actinic dermatoses to the detriment of others.

The literature indicates lower-sensitiveness skin types and sun exposure as the most important risk factors for BCC. Some studies also report association with previous sunburns, light hair and eyes, positive family history, and presence of actinic lesions<sup>7,16,17,31-36</sup>.

In the present study, there was a direct association of BCC with lighter skin types, load of sun exposure during professional activities, family history, and actinic lesions. There was no association with previous sunburns, smoking, and alcohol, and the regular use of sunscreen did not protect against BCC.

Contrary to what occurs in SCC, there is no consensus with regard to smoking and subsequent development of BCC<sup>37,38</sup>. The same goes for the protection provided by the regular use of sunscreen (in the past 10 years), and most studies also found no such association for this neoplasia<sup>29,34,39-41</sup>.

The population studied, typically coming from lower social classes, presented a report of current smoking at a proportion that was similar to that found in the state capital of São Paulo (20.4% versus 19.9%)<sup>42</sup>. However, the regular use of sunscreen, even occasionally, was reported with a lower frequency than the result obtained from the Brazilian population survey (18.5% versus 38.4%), where the rate reaches up to 53.3% in the highest-income class<sup>43</sup>. It is noteworthy that, in this study, the estimated use of sunscreen considered the past 10 years, which underestimates the frequency compared to the national survey; however, it is more consistent with the long latency time for the development of BCC, and in accordance with the study aim<sup>3</sup>.

In addition to the fact that the genesis of BCC could have occurred more than 10 years before the study, the sunscreen protection factor (SPF > 30), the spectrum (UVA and UVB), the amount of product used, and reapplication frequency were not analyzed among patients who reported daily use, which can interfere with the accuracy of the conclusion about its role in preventing BCC, and therefore it should not discourage the recommendation for the regular use of the product, with broad spectrum and SPF > 30, especially in populations at risk for UVR-induced skin cancer<sup>4</sup>.

The lack of association of BCC with a history of sunburn in this study may be due to the exclusion of tumors of the trunk and superficial types, associated with the most intense intermittent exposure and sunburns, while solid facial tumors are associated mainly with chronic exposure<sup>14,29,44</sup>.

When the genders are analyzed separately, the association of risk for *cutis rhomboidalis nuchae* only for men highlights the protection of long hair on women. As for stellar scars of the upper limbs only associated with women, it may indicate aspects of personal protection at work, or the possibility that hair on male forearms can offer some protection. Facial milia were lesions that indicated risk in both sexes.

Men also had acne scars as a risk factor for BCC, in disagreement with previous studies that correlated them with a protective effect, as it is referred for oily skin. The evidence that facial comedones exert a protective effect is consistent with this hypothesis, but contradicts the findings on acne scars<sup>4,45</sup>. The restricted choice of primary BCCs of the head and the solid subtype prevents the direct comparison of these findings with the literature, and adequate designs to investigate this aspect should be used.

There are peculiarities in the epidemiology of gender-related neoplasias. In the case of BCC, in addition to clothing and professional aspects, it can be suggested that sun exposure occurs daily for women, although it is little perceived during housework activities; they less often report frequent smoking and alcohol consumption, and, moreover, there are protective factors against cancer specifically related to gender that are observed in carcinogen initiation-promotion animal models, but that need to be evaluated in humans<sup>46,47</sup>.

The cases with lighter skin types develop BCC earlier, when compared to controls. In addition to the fact that they have higher sun exposure, the importance of early recommendations regarding behavioral factors, particularly in this group of individuals, is emphasized. These data are consistent with the observation of the emergence of BCCs in patients younger than 40 years, mainly among lighter skin types<sup>2,48-50</sup>.

In contrast, in darker skin types, the important influence of family genetics is emphasized, indicating susceptibility to BCC, regardless of protective melanin, which justifies recommendations on the risks of unprotected sun exposure, even in groups that do not burn easily. The possibility of BCC in black individuals supports this observation<sup>51-53</sup>.

In the comparison between young cases and young controls, sun exposure during leisure time was higher among cases, but not sunburns, supporting the hypothesis that solid BCCs are not induced by sunburns, but mainly by cumulative exposure to UVR<sup>14,44</sup>.

Light skin types and positive family history of BCC were elements that were strongly associated with the development of BCC in younger individuals, mainly in those with actinic lesions and unprotected sun exposure. These elements identify subgroups that benefit from preventive primary and secondary measures, as an increased incidence of BCC in individuals younger than 40 years has been identified<sup>17,50</sup>.

Older cases had higher number of sun exposure hours, higher incidence of *cutis rhomboidalis*, actinic cheilitis, and leukoderma punctata than controls of the same age, reinforcing the importance of chronic sun exposure as a risk factor for BCC in this group.

The limitations of this study are related to the possibility of memory bias, the selection of a control group among dermatology patients - who have a higher frequency of actinic lesions -, and momentary assessment of the presence of lesions. However, the sample size, the choice of three controls for each case, and the magnitude of the associations found by multivariate analysis of these elements reduce the impact on the results.

The identification of actinic lesions as risk for BCC, despite the exclusion of patients with skin type VI, who would mainly compose the control group and would reduce the prevalence of actinic lesions in this group, is another element that strengthens the results of the study.

Memory bias may occur regarding smoking, alcohol consumption, sunburns, sunscreen use, family history, freckles in childhood, light-colored hair in youth, rural activities, sun exposure in leisure and work activities; a greater reference to these factors is expected in the case group. The controls, who are outpatients, favor compliance with the study and decrease memory and information bias when compared to healthy subjects<sup>31,54</sup>.

With the exception of family history and sun exposure during work and leisure activities, none of the other factors remained significant in the final risk model, minimizing the influence of these elements in the analysis. Furthermore, family history and hours of sun exposure are risk factors substantiated by other studies and related to other actinic lesions<sup>2,7,16,36</sup>.

The quality of information regarding the type of skin neoplasia in the family, and especially sun exposure and habits are classically difficult to assess<sup>55,56</sup>. The authors adopted the cumulative quantification of these latter variables to maximize the differences between the groups regarding exposure to these factors.

The accuracy of the dermatologic diagnosis of actinic lesions and its quantification is a matter of attention regarding the results. While there is little reproducibility in the counting of skin lesions<sup>57</sup>, the arbitrary choice of a cut-off of 10 lesions, and the clear evidence that the absence of lesions increases the accuracy of estimating the number of

lesions, was a decision considered also by other studies<sup>16,58</sup>. Furthermore, histological lesion verification would make the sample size unfeasible, in addition to the ethical limits of this procedure. Another confounding factor arises from the different classifications and choices among authors for lesions such as comedones, lentigines, cysts, and photoaging criteria<sup>16,17,31,59</sup>.

The choice of controls from the dermatology outpatient clinic of the institution benefits the homogeneity of the social and geographical origin of patients; however, it may overestimate the occurrence of actinic lesions, due to the nature of dermatological care, and modify the current reference to photoprotection by medical indications. Even so, the common social structure of groups reduces the generalization of the results to other populations and socioeconomic realities.

Still, the higher frequency of actinic lesions among cases and the maintenance of this profile after adjustment for other covariates support the association between BCC and actinic lesions.

Subsequent comparative studies to investigate the general population should substantiate our findings, may evidence greater magnitude of these associations, and even reveal the existence of other actinic lesions associated with BCC. They would also allow the stratification of the analysis by social status and ethnic groups, which would contribute to the generalization of the results.

The study of risk factors for the development of BCC allows the creation of statistical risk models, the identification of individuals susceptible to tumor development, and the planning of strategies for primary prevention in these groups, such as campaigns for periodic dermatological examinations, resulting in the increase of the diagnostic index, earlier treatments, and more effective national campaigns to prevent skin cancer<sup>60</sup>.

## CONCLUSION

Actinic lesions were more prevalent in patients with solid basal cell carcinoma of the head than in controls, especially milia, *cutis rhomboidalis nuchae* and leukoderma punctata, regardless of other known risk factors.

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