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ORIGINAL ARTICLE

Solar Elastosis in Cutaneous Squamous Cell Carcinoma

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KEYWORDS

Solar elastosis;
Ultraviolet rays;
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Abstract

Introduction: Solar elastosis, or basophilic degeneration of collagen, may be a histologic sign of chronic sun damage.

Material and methods: We reviewed 222 cases of squamous cell carcinoma (SCC) to identify the presence of solar elastosis and its possible invasion of the upper, middle, or deep reticular dermis. We also analyzed clinical variables such as SCC location, location in exposed areas of the skin, age, sex, and immunosuppression. Patients included had undergone surgical excision of an SCC.

Results: Severe solar elastosis was found in most cases (182 patients, 82%): 87 extended to the middle reticular dermis and 95 had reached the deep reticular dermis. Only 6 (2.7%) patients had no solar elastosis. In some cases elastosis was so severe that it had affected the subcutaneous cellular tissue or venous or arteriolar walls. Deeper solar elastosis was significantly associated with older age and female sex.

Conclusions: Solar elastosis was found in most patients with SCC and seems to indicate chronic severe solar damage. Exposure to ultraviolet radiation would be the main cause of SCC, although other factors might also be implicated, particularly in patients who did not have severe solar elastosis. Systemic or localized immunosuppression was associated with nearly all the SCC cases studied, consistent with the marked immunosuppressant effects of sun exposure, the aging process, or both.

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PALABRAS CLAVE

Elastosis solar;
Radiación ultravioleta;
Carcinoma
espinocelular

Elastosis solar en carcinomas espinocelulares cutáneos**Resumen**

Introducción: El hallazgo de elastosis solar (degeneración basófila del colágeno) se podría considerar como un signo histológico del daño solar crónico.

Material y método: Se ha realizado un estudio retrospectivo sobre 222 carcinomas espinocelulares (CE). Se ha valorado si existía elastosis solar y si esta se extendía hasta la dermis reticular superficial, media o profunda. También se han analizado otras variables clínicas como la localización, la ubicación en áreas fotoexpuestas, así como la edad, el sexo y la inmunodepresión de los pacientes a los que se extirparon estos CE.

Resultados: En la mayoría de CE (182 CE, un 82%) se observa una intensa elastosis solar: 87 CE presentaban elastosis solar hasta la dermis reticular media y 95 CE hasta la dermis reticular profunda. Sólo hubo 6 CE (2,7%) que no presentaban elastosis solar. En algunos CE la elastosis solar era tan intensa que se extendía hasta el tejido celular subcutáneo o afectaba a la pared de venas y/o arteriolas. Existía una relación significativa entre la observación de elastosis solar a más profundidad y una edad mayor, así como con el sexo femenino.

Conclusiones: En la mayoría de CE se observa elastosis solar, lo que podría traducir un intenso daño solar crónico. La radiación ultravioleta sería el principal factor etiopatogénico en la mayoría de CE, aunque también podrían estar implicados otros factores etiopatogénicos, sobre todo en aquellos CE sin una elastosis solar intensa. Casi todos estos CE estudiados se asociarían a inmunodepresión (sistémica o localizada), basándonos en los importantes efectos inmunosupresores que producen las radiaciones solares, la edad avanzada o ambas.

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Introduction

The first to associate chronic sun exposure with the appearance of skin cancer was Unna in 1896; currently, UV rays are considered the main factor in the pathogenesis of skin tumors, particularly in squamous cell carcinoma (SCC).¹ More important than the intensity of exposure would be the total number of hours of UV radiation accumulated, as there is a statistically significant association between the appearance of SCC and lifetime cumulative sun exposure exceeding 70000 hours.^{2,3}

Histologic evidence of solar elastosis (basophilic degeneration of collagen) may be an objective sign of skin damage caused by sun exposure. Our aim was to study the presence of solar elastosis in tissue from 222 excised SCC tumors. Although SCC usually develops in locations where there is chronic actinic damage and, therefore, solar elastosis is usually present, we wished to determine whether it was absent or less severe in some cases and to measure intensity in terms of whether the upper, middle, or deep reticular dermis (RD) had been affected.

Material and Methods

We retrospectively studied 222 SCC histology samples of tumors removed over a 5-year period at Hospital Vega Baja de Orihuela in Alicante, Spain, and stored by the pathology department. Each SCC tumor was considered a case, even if several such tumors had been excised from a single patient; the 222 SCC tumors came from 199 patients.

SCC lesions located on the lip, anogenital region, or mucosal tissues were not included. Also excluded were SCC samples that could not be fully evaluated (tissue samples with narrow tumor margins, from partial biopsies or from curettage and electrocoagulation, etc) and those that did not allow comparison to the epidermis or might be recurrences of previously excised SCC tumors.

The following variables were analyzed:

1. Solar elastosis: presence of solar elastosis (basophilic degeneration of collagen⁴) in the dermis adjacent to the tumor, and extension of solar elastosis to the upper, middle, or deep RD. The measurement of depth of elastosis may be less objective in certain locations where the dermis is thinner, such as on the cheeks or forehead. As solar elastosis was present in nearly all the SCC cases, this variable was grouped according to whether it was mild (without elastosis or involving only the upper RD), moderate (reaching the middle RD) or intense (reaching the deep RD). Although we could have evaluated elastosis in terms of the presence of large nodules or the relative abundance of thickened fibers or thin fibers (corresponding to severe, moderate, and mild elastosis, respectively), we felt that classifying according to depth would be more objective and reproducible. We also thought there might be cases in which the appearance of one of these types of elastosis as opposed to another would be affected by skin phototype or a history of sunburn or other injury.
2. Clinical variables recorded were age, known immunodepression, sex, tumor location (later grouped

as head-scalp, trunk-limbs, or hands), and location in sun-exposed areas or not. We considered the head and neck, dorsal side of the hands and lower limbs in women to be sun exposed. In men, unexposed areas were the trunk, arms, and legs in men.

Statistical Analysis

The data were processed using SPSS statistical software, version 12.0 for Windows.

Statistical associations between deeper solar elastosis and the various clinical variables were explored. The possible relation between qualitative variables was analyzed by preparing contingency tables and applying Pearson's χ^2 test. Less than a 5% risk of error ($P < .05$) was considered significant. Correlations between qualitative variables and continuous variables such as age were analyzed by analysis of variance.⁵ Dichotomized variables or normally distributed variables were also analyzed by logistic regression analysis to calculate odds ratios (OR) as an estimate of the independent relationship of each variable with the outcome of interest (ie, ruling out collinearity).⁶

Results

Intense solar elastosis was evident in most of the cases of SCC (Figures 1-6). In nearly 82% of the SCC cases (182 lesions), elastosis reached the middle or deep RD. In 95 (42.79%), elastosis had reached the deep RD or beyond (cases with subcutaneous tissue involvement were classified as deep RD). Solar elastosis extending to the middle RD was observed in 87 tumors (39.2%). Elastosis only in the upper RD was seen in 34 (15.3%). Six lesions (2.7%) had no solar elastosis. Finally, elastosis was so intense in 5 cases that venous wall (3 cases) or arteriolar wall (2 cases) involvement could be observed (Figures 2 and 3).

The mean age of patients was 73.4 years; the median age was 73 years (interquartile range [IQR], 67-80 years); men numbered 154 and women, 68. Women (mean age, 77.2 years; median, 78 [IQR, 71-84] years) were significantly older than men (mean age, 71.7 years; median, 72 [IQR, 66-78] years) ($P < .001$). The most frequent location was the head-neck (151 lesions). Sixteen SCC lesions were from immunocompromised patients— 7 men who were younger (mean age, 61.5 years; median, 62 years; $P < .001$) than the immunocompetent patients. The 16 tumors from these 7 immunocompromised patients had less severe elastosis (none or only superficial involvement, $P = .006$) than the rest of the tumors. Specifically, 3 had no solar elastosis, 4 had elastosis reaching the upper RD, 7 had elastosis in the middle RD, and 2 had elastosis in the deep RD.

More intense solar elastosis (reaching the deep RD) was seen in older patients ($P = .001$). The mean age of patients with deep elastosis was 76 years (median, 77 years) whereas the mean was 72.1 years (median, 72 years) for patients with middle RD involvement and 70.3 years (median, 70 years) for patients with no elastosis or involvement of only the upper RD.

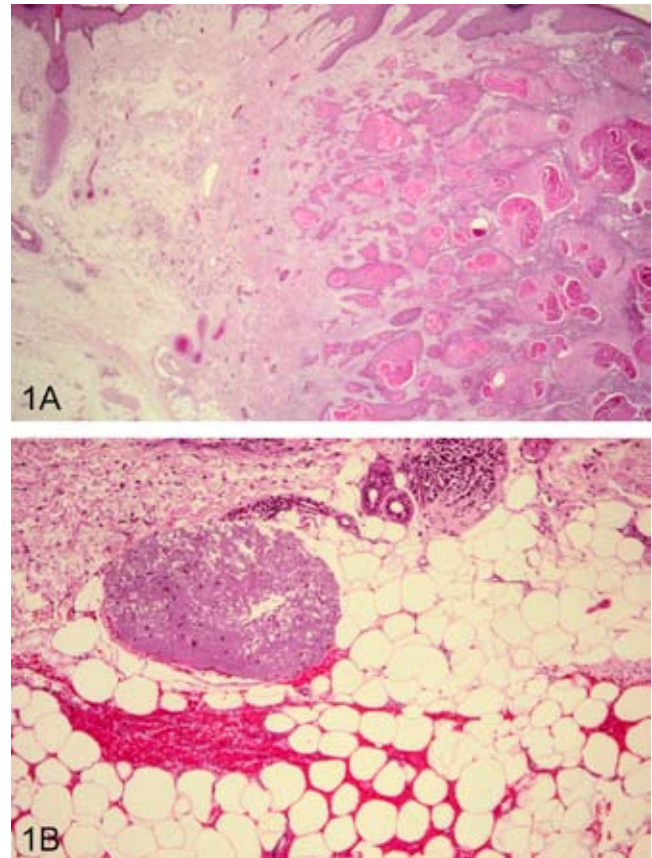


Figure 1 A, Intense solar elastosis in the area adjacent to a squamous cell carcinoma (hematoxylin-eosin stain, original magnification $\times 16$). B, Localized solar elastosis in subcutaneous cellular tissue (hematoxylin-eosin stain, original magnification $\times 200$).

Men had less solar elastosis than women, and in men the degeneration more often only reached the middle RD whereas in women degeneration more often reached the deep RD ($P = .002$).

To rule out that the correlation between older age and deeper solar elastosis might be related to sex (given that women were older) or immunodepression (given that these patients were younger and all men), we performed logistic regression analysis of these normally distributed variables, considering solar elastosis in 2 categories (no elastosis or only superficial elastosis vs involvement of the middle or deep RD). This analysis showed that the independent relationship between age and solar elastosis was reflected by an OR of 1.038 (95% confidence interval, 1.004-1.073); the OR for sex was 2.162 (95% confidence interval, 1.170-3.994). This indicates that solar elastosis is related to older age (a factor independent of sex or immunodepression) and female sex (a factor independent of age).

We observed a significant correlation between more intense solar elastosis (reaching the deep RD) and location on the hands or head-neck ($P = .002$). Tumors on the trunk-limbs had less intense elastosis (none or only in the upper RD) ($P = .002$). Twenty-six lesions were located in areas of the body that were usually unexposed. However, solar

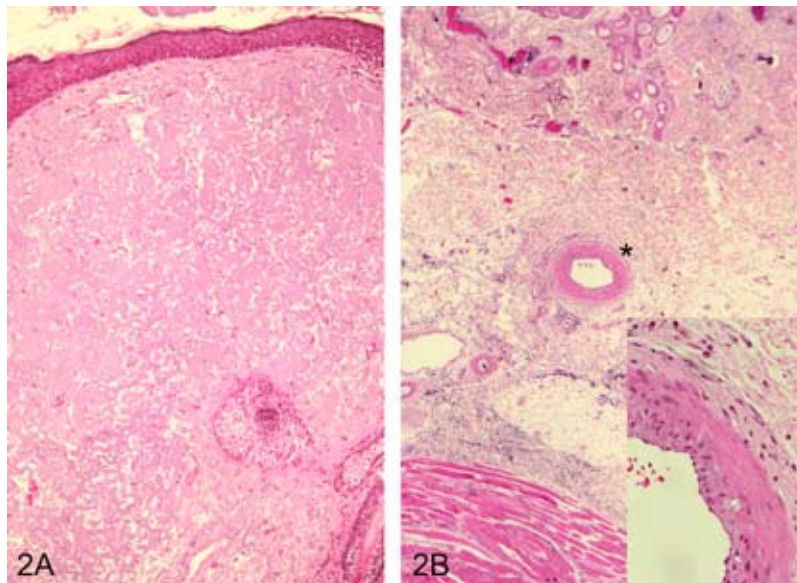


Figure 2 A, Solar elastosis affecting the entire dermis in the zone adjacent to a squamous cell carcinoma (hematoxylin-eosin stain, original magnification $\times 200$). B, Solar elastosis extending to the deep reticular dermis and even an arterial wall (*) (hematoxylin-eosin stain, original magnification $\times 200$). (Detail, lower right corner, hematoxylin-eosin stain, original magnification $\times 400$.)

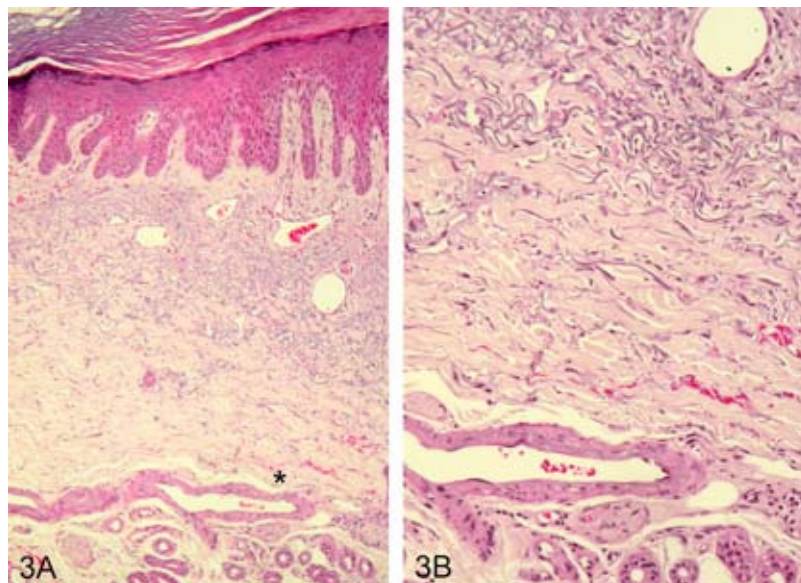


Figure 3 A, Solar elastosis in the dermis around the tumor and extending to the arterioles (*) (hematoxylin-eosin stain, original magnification $\times 100$). B, Detail, solar elastosis in the arteriolar wall that is slightly more intense than in the nearby epidermis, which receives more sun exposure (hematoxylin-eosin stain, original magnification $\times 200$).

elastosis was observed in nearly all these lesions (only 4 lacked elastosis altogether); 5 of these lesions even had elastosis reaching the middle or deep RD. Thus, as these areas had also been exposed to the sun we did not pursue the analysis of this variable.

Langerhans cells were seen to be reduced in number or nearly absent from some SCC lesions, on immunohistochemical staining for the S100 protein. To

rule out the presence of melanocytes in 6 SCC lesions we stained for CD1A (positive in Langerhans cells), confirming that these cells were absent or fewer in number in the tumor than in the adjacent tissue (Figure 4A). We also stained for CD1A in 3 SCC tumors removed from unexposed zones (2 from the genital area and 1 from behind the ear (all without solar elastosis), confirming that the number of Langerhans cells was not reduced (Figure 4B).

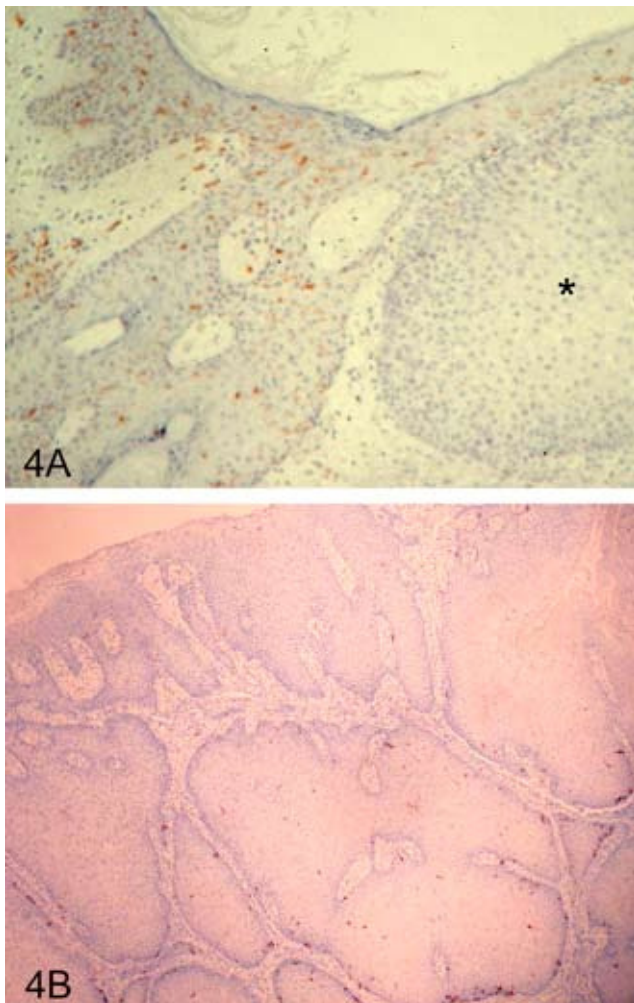


Figure 4 A, Marked reduction in or near absence of Langerhans cells in the portion of tissue corresponding to the squamous cell carcinoma (*) in comparison with the adjacent tissue (CD1A stain, original magnification $\times 100$). B, Squamous cell carcinoma tumor in a unexposed location (vulva). Numerous Langerhans cells are still present in the tumor (CD1A stain, original magnification $\times 40$).

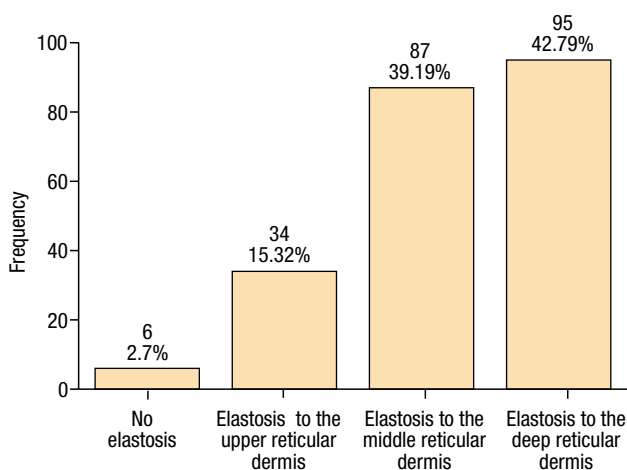


Figure 5 Intensity of solar elastosis in squamous cell carcinoma tumors.

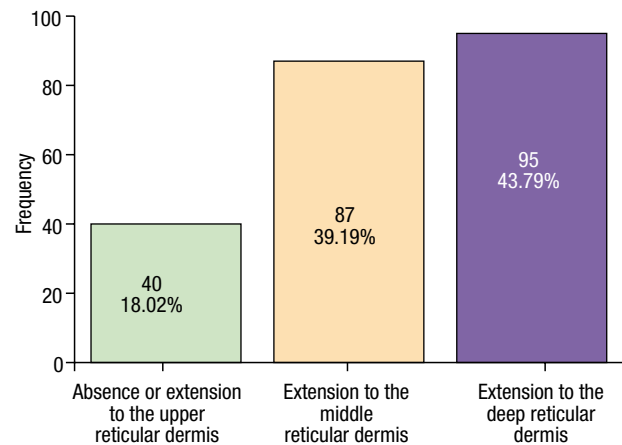


Figure 6 Distribution of mild, moderate, and intense solar elastosis.

Discussion

Solar elastosis can be considered as an objective sign of chronic sun damage. Most SCC cases in our study showed signs of solar elastosis: 97.3% of the lesions had this sign, which involved the middle or deep RD in 82%. Very intense elastosis was present in nearly half: 42.8% extended to the deep RD and subcutaneous cells and vessel walls were even involved in some cases. These findings confirm that the main pathogenic factor in the development of most cases of SCC is sun exposure.^{2,3} However, 18% of the SCC cases showed only mild or no solar elastosis (none in 6 tumors, 3 of which were from immunocompromised patients; 34 with elastosis only reaching the upper RD, only 4 of which were from immunocompromised patients). Various studies of SCC suggest that additional oncogenic factors play roles in the etiology of the disease; examples are immunodepression or human papillomavirus infection.⁷ Such factors would be more evidently implicated in cases with milder elastosis.

The 16 SCC tumors from immunocompromised patients were significantly related to less intense elastosis and younger age. In these patients, who had received transplants and were younger, immunosuppression was probably the main oncogenic factor.⁸

Given the considerable immunosuppressant effects of solar radiation,^{9,11} most immunocompetent patients who have intense solar elastosis might be considered to have at least local immunodepression.^{12,13} Older age may also be an immunosuppressant factor¹⁴ and in our study age was associated with more intense solar elastosis. Practically speaking, in fact, we might consider that nearly all the SCC cases in this study were related to at least localized, cutaneous immunodepression. When we applied CS1A immunohistochemical staining to study 6 SCC samples, we observed markedly fewer Langerhans cells in the tumor in comparison with the adjacent tissue (Figure 4A). This effect was not observed in SCC samples from unexposed locations, indicating that the action of solar radiation was responsible. It may be that the decreased number of Langerhans cells was transient or recoverable (as is the case when this effect is observed in psoriasis patients who

have undergone psoralen-UV-A therapy¹⁰); however, our observations are also consistent with the theory of localized immunodepression at the tumor site. A recent study of 12 basal cell carcinomas demonstrated that fewer Langerhans cells are found in the epidermis overlying a tumor, as opposed to the area around the tumor,¹⁵ consistent with our observations. A larger number of tumors would have to be studied in order to confirm these interpretations. It would also be useful to study whether other signs of localized immunodepression are present at the site of the tumor (for example, if the CD8+ T-cell count is higher than the CD4+ T-cell count, or if there is a decrease in the number of natural killer cells, or elevated levels of immunosuppressor interleukins and cytokines, etc).^{7,9-11}

Although we found few studies on solar elastosis in skin cancer,¹⁶⁻¹⁹ it is interesting to compare our results on SCC to those observed in other tumors, such as basal cell carcinomas. Much less solar elastosis has been seen in basal cell carcinoma¹⁶⁻¹⁹ than we saw in SCC, consistent with the hypothesis that UV radiation plays a much more important role in the pathogenesis of SCC.^{3,20} Also supported is the hypothesis that SCC is related to chronic, sustained sun exposure (work-related exposure, which has been associated with the development of solar elastosis)³ whereas basal cell carcinoma has been linked to intense but sporadic exposure (recreational sun exposure)³, which leads to less solar elastosis.

Regarding the remaining variables analyzed, we noted that the largest proportion of the SCC tumors were located on the head-neck and hands, consistent with the literature.²¹ Furthermore, these SCC tumors had more intense solar elastosis than those located on the trunk-limbs. That pattern is logical, we think, given that the limbs and trunk are not regularly exposed to the sun unless, in some patients, clothing choices, work, or leisure activities might lead to more frequent exposure. We found that the areas we classified as unexposed also developed solar elastosis; the measurement of elastosis itself, therefore, is a more objective factor than the supposition that some locations receive exposure while others do not.

Regarding the factors of age and sex, we saw that solar elastosis was more intense in older patients, consistent with the fact that these patients would have more cumulative exposure.¹⁻³ Age was independent of sex or immunodepression, as confirmed by logistic regression analysis.

We were surprised to find that solar elastosis was more intense in women than in men and thought that the older age of women in this study might account for this difference. However, the relation between sex and elastosis was independent of age (when controlling for age, women continued to present deeper solar elastosis). This finding runs counter to the notion that men have more chronic sun damage, especially in relation to the tendency of men to engage in outdoor work such as agriculture or fishing.¹ One explanation might be that in the geographical area represented in our study, many women also work in agriculture.

The principal limitation of our study is that it is retrospective; it is therefore possible that some relevant clinical variables were not included in patient charts

(examples would be the use of certain drugs or certain comorbidities that lead to immunosuppression). It would also have been interesting to include skin phototype among the variables to compare, as it is possible that subjects with a fair phototype might have deeper solar elastosis at an earlier age; this remains to be determined.

In summary, of the 222 SCC tumors we studied, most had solar elastosis. Nearly half of these tumors had intense elastosis, indicating intense chronic sun damage. More intense solar elastosis was associated with older age, female sex, and tumor location on the head-neck or back of the hands. More studies are required to determine if this chronic sun damage can cause localized or cutaneous immunodepression.^{12,13} It would also be useful to further compare solar elastosis in SCC to elastosis in basal cell carcinoma or other skin tumors.

Conflict of interest

The authors declare that they have no conflicts of interest.

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