Impact of Sunscreens on Preventing UVR-Induced Effects in Nevi: In Vivo Study Comparing Protection Using a Physical Barrier vs Sunscreen

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IMPORTANCE Sun damage is the most important environmental factor associated with malignant melanoma. To address the health threat, as well as the economic burden, primary prevention and early detection are crucial.

OBJECTIVE To test the efficacy of a topical sunscreen in the prevention of UV-induced effects in nevi.

DESIGN Prospective study of nevi protected by sunscreen vs a physical barrier.

SETTING AND PATIENTS Twenty-three nevi from 20 patients attending a referral hospital.

INTERVENTION Half of each nevus was protected by either a physical barrier or a sunscreen. Lesions were completely irradiated by a single dose of UV-B.

MAIN OUTCOMES AND MEASURES In vivo examination before and 7 days after irradiation and histopathologic-immunopathologic evaluation after excision on the seventh day.

RESULTS The most frequent clinical changes after UV radiation were pigmentation, scaling, and erythema; the most frequent dermoscopic changes were increased globules/dots, blurred network, regression, and dotted vessels. Both physical barrier- and sunscreen-protected areas showed some degree of these changes. More than 30% (7) of nevi did not show any change on clinical examination, and 18% (4) had no dermoscopic change. Immunohistopathologic differences between the halves of each nevus were demonstrable even when in vivo examination detected nothing. Parakeratotic scale, increased number and activation of superficial melanocytes, and keratinocyte proliferation were the most remarkable features. The only difference between both barriers was more enhanced melanocytic activation and regression features in the sunscreen group. No phenotypic features were found to predict a specific UV-B response.

CONCLUSIONS AND RELEVANCE Both physical barriers and sunscreens can partially prevent UV-B effects on nevi. Subclinical UV radiation effects, not always associated with visible changes, can develop even after protection. Sunscreens are not quite as effective as physical barriers in the prevention of inflammatory UV-B-induced effects.

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S un damage is the most important environmental factor associated with skin cancer, which is the most frequent type of malignant neoplasm in humans. Malignant melanoma (MM) incidence has increased dramatically in the past decades, especially among young women, in part related to the tanning fashion trend. Indeed, it poses a significant health threat, since it is the sixth most commonly diagnosed cancer in the United States and its care represents a major economic burden for health insurance systems. Therefore, great effort in primary prevention and early detection of MM is crucial in reducing this expense.

Ultraviolet radiation (UVR) has been widely demonstrated to be implicated in nevogenesis and melanomagenesis, being the most relevant environmental and exogenous risk factor. Recently, for the first time, proper sunscreen use has been demonstrated to reduce the incidence of MM in Australia and the United States. Previously, this benefit had been proven only for solar erythema, sunburn, actinic keratosis, and squamous cell carcinoma development; however, it is well accepted that basal cell carcinomas and MM seem to follow a more complex pathway and relationship to sun exposure. A beneficial effect of sunscreen use in prevention of MM could not be demonstrated or quantified until now, when a recent prospective epidemiologic study documented a reduction in MM incidence among Australian sunscreen users, and with a better prognosis because the sunscreen group presented earlier-stage melanomas compared with nonusers. On the other hand, melanocytic nevi are considered potential MM precursors and simulators, as well as the most important independent phenotypic risk factor for MM development. It has been reported since the 1980s that UVR may promote changes in sun-exposed melanocytic nevi. Seasonal variation and the influence of phototherapy have been described in nevi. Several prospective interventional studies on UVR in melanocytic nevi have been carried out since 1995. This issue has been reviewed in depth in a publication in which the present study model was described. Among the most remarkable effects reported using different methodologies, UVR can induce clinical changes, such as increased pigmentation, scale formation, and erythema, as well as dermoscopic changes in pigmentation, such as globules and dots (size and number), regression features (bluish gray granules), blurred pigmented network, and increased vascularity. At the histopathologic level, the most relevant events are the appearance of parakeratotic hyperplasia; lymphocytic perivascular infiltrates; cell-cycle activation of keratinocytes and melanocytes; activation of melanocytes, consisting of larger nuclear and cytoplasm size of cells; and prominent dendrites in addition to suprabasal location of melanocytes. Some of these studies highlighted the importance of the recognition that acute UV-B irradiation can provoke demonstrable and quantifiable changes in melanocytic lesions similar to those found in early MM.

The first interventional model for in vivo evaluation of the effects of UV-B irradiation on nevi and adjacent skin, depending on the use of a physical barrier or a commercial topical sunscreen, was developed in 2008. With use of this model, in the present study, the main objective was to test the effectiveness of a topical sunscreen in preventing the different UVR effects on nevi. A secondary aim was to evaluate the different types of measurable UVR effects on clinical, dermoscopic, and histopathologic examinations depending on the different phenotype of the patients. To the best of our knowledge, this was the first prospective interventional in vivo study of the efficacy of a topical sunscreen in preventing UV-B-induced damage to melanocytic nevi and surrounding skin.

**Methods**

We recruited 20 volunteers with multiple dysplastic nevi attending the Pigmented Lesion Unit in the Dermatology Department of the Hospital Clinic of Barcelona. The study was performed according to the Declaration of Helsinki principles, and our local ethics committee reviewed and approved the interventional protocol. Criteria for patient inclusion were age older than 18 years, a signed informed consent form explaining the complete protocol, and adherence to strict photoprotection conditions before and during the study. Patient exclusion criteria were a history of skin cancer or photodermatoses, phototoxic/allergic drug intake, active dermatoses, phototherapy or intentional photoexposure in the previous 3 months, immunosuppressive treatment, or pregnancy.

According to the previously published model to induce UV-B effects on nevi by a single, double minimal erythema dose (2 MED) detailed by Carrera et al., in the present study 23 melanocytic nevi were consecutively included in 2 groups. Criteria for selecting nevi were diameter greater than 5 mm, at least 1 axis symmetry, and no suspicion of melanoma. In the first group (n = 14) half of each nevus was covered with a physical opaque barrier before irradiation, whereas in the second group (n = 9), half of each nevus was protected by a topical sunscreen (2 mg/cm²) and the remaining half was covered by a patch to avoid diffusion of the cream. The sunscreen (broad-spectrum protection, sun protection factor 50) contained octocrylene, avobenzone (Parsol 1789), titanium dioxide, ecamsul (Mexoryl SX), and Mexoryl XL and was applied 30 minutes prior to UVR. Ultraviolet-B was administered by a lamp (UV800; Waldmann) a 2.5-mJ/cm²/s dose on a 2-cm² skin area that was centered on the nevus and 20 cm from the lamp.

Complete clinical patient history was recorded, including familial history, previous photoexposure, and phenotype. Clinical and dermoscopic images of the 23 nevi included were taken using digital cameras (G7 [Canon, Inc.], and Coolpix 4500 [Nikon Corp.]) and a polarized dermoscope (Dermlite Foto; 3Gen). Clinical evaluation was based on clinical ABCD-E (asymmetry, irregular borders, multiple colors, diameter >6 mm, and evolution and enlargement), and dermoscopic study on pattern analysis. Each in vivo feature was evaluated before and 7 days after irradiation (baseline time and final time), and features were assessed comparing the unprotected and protected halves of each nevus 7 days after irradiation. All lesions were removed 7 days after UV-B, the protected half of each being labeled. Histopathologic and immunohistochemical studies for human melanoma black-45 antigen (HMB-45 monoclonal mouse IgG1; Dako) and for mela-
noma antigen recognized by T-cells (Melan-A monoclonal antibody A-HU, A103; mouse IgG1; Dako) were performed using standard methods. Semiquantitative scales were established for continuous values for the in vivo and ex vivo evaluations in a blinded manner by 2 of the 3 readers (J.P. and S.P.). In immunostaining, intensity and percentage of positive cells were examined, comparing both halves of each nevus and the adjacent skin. The scale for immunostaining in nevi was as follows: 0, negative or weak (<20% of nevicells); 1, 20% to 30%; 2, 31% to 50%; 3, 51% to 80%; 4, greater than 80% to 100% of nevicells. For adjacent surrounding skin, measurements were performed in 0.5-mm intervals (diameter of the ×40 magnification objective): 0, no positive cells; 1, 1% to 2% of keratinocytes; 2, 3% to 5%; 3, 5% to 10%; and 4, 11% to 20%.

Statistical analysis was carried out using commercial software (SPSS, version 18.0; SPSS Inc). The chi2 test was applied for all category features, and the Fisher exact test was applied if any cell value in the 2×2 table was expected to be less than 5. Mean and median values were assessed for quantitative and semiquantitative variables and compared using a 2-tailed, unpaired t test for dependent samples, comparing in vivo lesions before and after UVR and unprotected vs protected halves of the same lesion, as well for independent samples, comparing the effects of physical barrier vs sunscreen. Significance was considered to be P < .05.

### Results

#### Patients

There were no significant differences between the study groups (physical barrier and sunscreen) in characteristics or nevus features. Sex distribution and mean (SD) age were similar in both groups (women, 12 [60%]; age, 36.5 [9.5] years; range, 22-55 years). Most patients had a history of intense sun exposure, inadequate sun protection behavior, and frequent sunburns in infancy and youth. Three patients (15%) were common sunbed users over the past years, and physical examination showed sun-damaged skin in 15 patients (75%). Fourteen patients (70%) had fair skin type (phototype I or II). Mean UV-B MED was 90 [27] mJ/cm². As many as 12 patients (60%) presented a very low UV-B MED (≤50 mJ/cm²), including 5 (30%) of those who experienced sun tolerance and tanning (ie, phototype III or IV). The only significant association found between clinical features was the intense sun-exposure history and higher number of nevi (P < .02).

#### Basal Examination of Nevi

As inclusion criteria required, all lesions were located on the trunk, with a minimum diameter of 5 mm and a maximum diameter of between 6 and 10 mm. All were symmetric on at least 1 axis to permit the division of each into 2 similar halves. Clinical

### Table 1. Clinical and Dermoscopic Changes Detected Among 46 Halves of the 23 Irradiated Nevi

<table>
<thead>
<tr>
<th>Changes 7 Days After UVR</th>
<th>Overall Nevi, No. (%) (N = 23)</th>
<th>Statistical Significancea</th>
<th>Physical Barrier (n = 14)</th>
<th>Sunscreen (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unprotected Halves</td>
<td>Protected Halves</td>
<td>P Value</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased erythema</td>
<td>13 (57)</td>
<td>1 (4)</td>
<td>&lt;.001</td>
<td>2.9 (1.7-5.0)</td>
</tr>
<tr>
<td>Increased pigmentation</td>
<td>14 (61)</td>
<td>1 (4)</td>
<td>&lt;.001</td>
<td>3.2 (1.8-5.6)</td>
</tr>
<tr>
<td>Scaling</td>
<td>13 (57)</td>
<td>0</td>
<td>&lt;.001</td>
<td>3.3 (1.9-5.5)</td>
</tr>
<tr>
<td>No clinical changea</td>
<td>7 (30)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dermoscopy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased pigmentation</td>
<td>4 (17)</td>
<td>1 (4)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Decreased pigmentation</td>
<td>2 (9)</td>
<td>2 (9)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Blurred pigment network</td>
<td>12 (52)</td>
<td>1 (4)</td>
<td>&lt;.001</td>
<td>2.8 (1.7-4.6)</td>
</tr>
<tr>
<td>Increased dotted vessels</td>
<td>7 (30)</td>
<td>2 (9)</td>
<td>&lt;.03</td>
<td>1.8 (1.1-3.0)</td>
</tr>
<tr>
<td>Increased erythema</td>
<td>10 (43)</td>
<td>6 (26)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Increased size of globules and dots</td>
<td>2 (9)</td>
<td>0</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Increased bluish gray regression</td>
<td>10 (43)</td>
<td>9 (39)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>No dermoscopic changea</td>
<td>4 (17)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No in vivo change detecteda</td>
<td>2 (9)</td>
<td>0</td>
<td>0</td>
<td>1 (7)</td>
</tr>
</tbody>
</table>

Abbreviations: NS, not significant; RR, relative risk of appearance of each change in unprotected compared to protected halves; UVR, UV radiation.

a Categorical changes between baseline and 7 days after a double minimal erythematous dose of UV-B were analyzed by the χ2 and Fisher exact tests (unprotected vs protected halves).

b Mean differences were significant within the subgroups (P < .05).

c Values given are for both halves.
cal and dermoscopic examination showed variable degrees of atypia, similar to the rest of nevi in such a population attending our unit, but none of the lesions was suspicious for MM. There were no significant differences between nevi characteristics included in the 2 groups (physical vs sunscreen).

In Vivo UV-B–Induced Effects: Comparison Between Baseline Image of the Nevi and 7 Days After UV-B Irradiation

Clinical and dermoscopic changes in the nevi are reported in Table 1. The most relevant changes were the appearance of erythema (13 [57%]), increase in pigmentation (14 [61%]), and presence of surface scaling (13 [57%]) (Figure 1). Most of these changes were more evident at the periphery of the lesions. No clinical change was detected in 7 cases (30%).

Dermoscopic Features
Changes observed were the appearance of diffuse pigmentation (4 nevi [17%]) (Figure 2), blurring of pigment network (Figure 3) (12 [52%]), increase in dotted vessels in the nevus and surrounding skin (7 [30%]), presence of diffuse erythema (10 [43%]), changes in the size of globules and dots (2 [9%]), and increase in regression structures (10 [43%]) (Figure 4 and Figure 5). Only 4 (17%) of the lesions did not show any dermoscopic change. Two lesions (9% of nevi) did not present any change either clinically or dermoscopically 7 days after irradiation.

Comparison Between Both Halves of Each Nevus 7 Days After Irradiation
In a comparison between protected halves and unprotected halves, regardless of the type of protection used, all 3 clinically evaluated features were different (P < .001). Scale formation was observed only in the unprotected areas; however, changes in pigmentation and erythema could be detected in both protected and unprotected areas, but to a lower, yet statistically significant, degree in the protected halves (Table 1 and Figure 1).

Unexpectedly, all dermoscopic changes evaluated also were observed in protected halves, some of them even with no significant differences when compared with the unprotected (Table 1) halves. In fact, the presence of regression structures in both halves of the nevus appeared in 67% of the sunscreen-protected group and in less than 30% of the physically
protected group (21% of the physically protected halves vs 29% of the unprotected halves). The increase in regression was more important in the sunscreen group but for both the protected \((P = .04)\) and unprotected \((P = .04)\) halves compared with the protected and unprotected halves of the physical barrier group. Other dermoscopic changes observed in the protected halves were an increase in dotted vessels (9%) and blurred network (4%), but these change were significantly less than in the unprotected halves \((P < .001\) and \(P = .03\), respectively). Pigmentation changes (increase or decrease) present in 13% of the protected halves were not significantly different compared with the unprotected halves (Table 1).

**In Vivo Changes Depending on Protection**

All clinical UV-induced changes were partially prevented by protection in both groups. However, changes in overall pigmentation, vascularity, and regression structures on dermoscopy were not significantly different between the protected and unprotected halves of the nevi. Considering the intensity and semiquantitative scale of these changes regarding the type of protection, blurred network was the only change signifi-
cantly prevented by the sunscreen barrier ($P < .008$); the in-
crease in dotted vessels was prevented by the physical bar-
rier ($P = .05$).

**Ex Vivo Study of Excised Lesions**

**Histopathologic Evaluation**

Diagnosis of melanocytic nevus was made in 21 of the 23 cases (91%), 12 of them (53%) with congenital-type features (18 compound and junctional nevus), and cases were considered as lentiginous melanocytic hyperplasia without nesting. Two patients decided to delay the removal of their nevi, and further histopathologic evaluation of these 2 cases was not included in the analysis of this series (ex vivo study was performed in 21 cases [9%]: 12 in group 1 and 9 in group 2). Architectural atypiawaspresent in 15 cases (71%) to a variable degree, and in 6 of these (29%), from moderate to marked. Parakeratotic epithelial hyperplasia was observed in almost all lesions (97% of cases, $P < .001$; OR, 4.5; 95% CI, 2.1-9.6; and 81% of cases, $P < .001$; OR, 3.3; 95% CI, 1.6-6.2, respectively), suprabasal solitary melanocytes (52.4% of cases, $P < .001$; OR, 3.1; 95% CI, 1.6-5.8), and prominent and elongated melanocyte dendrites (52% of cases, $P < .001$; OR, 3.1; 95% CI, 1.6-5.8). Differences in superficial perivascular inflammatory infiltrates and regression features were observed but were not significant between halves of each ne-
vus in any of the groups.

Immunohistochemical staining for melanocytic markers (HMB-45 and Melan-A) were intensely positive in all lesions (marked intensity and >80% of nevus cells) and helped to quant-
ify and demonstrate melanocytic activation (Figures 6, 7, and 8), more evident in the unprotected halves (Table 2). Regarding the quantification of HMB-45 staining in nevus cells, there was a significant difference depending on the type of protection (Figure 7). The physical barrier group (protected vs un-
protected halves) had a greater difference in expression than the sunscreen group, and this also was demonstrated when the intensity of the protected halves was compared ($P < .04$). How-
ever, the quantification of staining between unprotected groups was also different, with the expression of HMB-45 being more...
intense in the physical barrier group (P < .04). On the contrary, Melan-A in nevus cells was significantly increased in the unprotected halves, but it also was higher in the halves protected with sunscreen than with physical barrier (P < .04) despite it being similar on unprotected halves. Evaluation of adjacent peripheral areas highlighted the differences with both antibodies that were more intensely stained in unprotected areas than protected ones (Figure 7 and Table 2).

Discussion

The results of the present study demonstrate that both physical barriers and sunscreens are able to decrease or even prevent most of the UV-B–induced biological changes in nevi and surrounding skin. However, some UV-B–induced changes appeared in protected areas, such as regression structures and vessels (erythema and dotted vessels) (Figures 4 and 5). Interestingly, regression structures appeared in 75% of nevi in the sunscreen group but in less than 30% of the lesions in the physical barrier group. Thus, neither sunscreen nor physical barrier prevented inflammation in the protected halves. At the histopathologic level, the main difference between the protected and unprotected halves was the presence of activated melanocytes in the unprotected halves and the adjacent peripheral skin, which was more intensely stained with both antibodies in unprotected areas. Sunscreen seems to be less effective than a physical barrier against melanocyte activation, as evidenced by the intensity and percentage of Melan-A–positive staining (Figure 7). Despite HMB-45 staining being more activated in the sunscreen group, it was slightly higher in both the protected and unprotected halves, so it cannot be used as a measure for comparing the effectiveness of protection type.

Another interesting and previously undescribed fact is the discordance between the different presentations of UVR ef-

![Figure 5. Dermoscopic Evaluation Before (A) and 7 Days After (B) UV Irradiation](image)

The left half of the lesion was protected by sunscreen, and the right side was unprotected. Mild erythema was present only on surrounding unprotected skin, but a decrease in whole pigmentation and globules (squares) was noted in both sunscreen-protected and unprotected areas.

Table 2. Histopathologic Evaluation; Demonstrated Differences Between Protected and Unprotected Halves of Each Nevus in All Cases

<table>
<thead>
<tr>
<th>Type of Evaluation</th>
<th>Overall Nevi Unprotected, No. (%) (n = 21)</th>
<th>Physical Barrier (n = 12)</th>
<th>Sunscreen (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histopathology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parakeratotic scale</td>
<td>19 (90.5)</td>
<td>11 (84.6)a</td>
<td>8 (88.9)a</td>
</tr>
<tr>
<td>↑ Nevus melanocytic HPL</td>
<td>14 (66.7)</td>
<td>8 (66.7)a</td>
<td>6 (66.7)a</td>
</tr>
<tr>
<td>↑ Adjacent melanocytic HPL</td>
<td>17 (81)</td>
<td>9 (75)a</td>
<td>8 (88.9)a</td>
</tr>
<tr>
<td>↑ Suprabasal melanocytes</td>
<td>11 (52.4)</td>
<td>4 (36.4)</td>
<td>7 (63.6)a</td>
</tr>
<tr>
<td>↑ Melanocytic dendrites</td>
<td>11 (52.4)</td>
<td>4 (36.4)</td>
<td>7 (63.7)a</td>
</tr>
<tr>
<td>↑ Inflammatory infiltrates</td>
<td>11 (52.4)</td>
<td>6 (50)a</td>
<td>5 (55.6)a</td>
</tr>
<tr>
<td><strong>Immunostaining</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑ HMB-45+ nevus cells</td>
<td>11 (52.4)</td>
<td>9 (75)a</td>
<td>2 (22.2)</td>
</tr>
<tr>
<td>↑ HMB-45+ adjacent cells</td>
<td>16 (76.2)</td>
<td>8 (66.7)a</td>
<td>8 (88.9)a</td>
</tr>
<tr>
<td>↑ Melan-A+ nevus cells</td>
<td>13 (61.9)</td>
<td>9 (75)a</td>
<td>4 (44.4)</td>
</tr>
<tr>
<td>↑ Melan-A+ adjacent cells</td>
<td>19 (90.5)</td>
<td>10 (82.3)a</td>
<td>9 (100)a</td>
</tr>
</tbody>
</table>

Abbreviations: HMB-45, human melanoma black-45 antigen; HPL, hyperplasia; ↑, increase in; +, positive.

* Features identified in unprotected halves were assumed to be those avoided by protection, since they were considered differences between irradiated with or without protection, although it was not possible to rule out the histologic asymmetry characteristic in dysplastic nevi. All differences observed between both halves were significant (P < .001) by χ² test and Fisher exact correction.

** Significant differences between protected and unprotected halves within each subgroup (ie, feature avoided by that specific protection). Despite an increase in activation of immunostaining, there were no significant differences in the sunscreen group, that is, protected halves showed the same activation as unprotected halves.
More than 30% of the nevi did not show any change on clinical examination, and only 18% exhibited changes on dermoscopic examination. However, in an unexpected finding, all cases, even those without in vivo changes, showed some difference between the protected and unprotected halves at the histopathologic level. That is, we observed cases with no visible clinical changes despite the presence of dermoscopic changes (Figure 4), as well some cases (8%) with neither clinical nor dermoscopic changes but with immunopathologic findings related to UVR, such as parakeratotic scale, inflammatory infiltrates, and melanocytic activation. Therefore, the importance of this finding should be emphasized, as it indicates the existence of subclinical biological effects beyond clinical erythema or pigmentation. In our model, with correlation between clinical, dermoscopic, and histopathologic changes, we demonstrated that it is possible, even in the absence of any clinical UV-B effect (erythema or pigmentation changes), that melanocytic nevi could develop some kind of damage.

Topical sunscreens are supposed to be a suitable tool for preventing UVR effects and are probably the best-accepted method of photoprotection by the general, especially the younger, population. For the first time in dermatology, a prospective study in Australia has demonstrated that proper sunscreen use can prevent MM, but the biological effect of sunscreens in vivo on nevi remains poorly understood. In 1989, Stierner et al demonstrated that UV-B could promote melanocytic activation both in irradiated and in protected skin, and the possible role of keratinocyte interaction seems to play a crucial role. Recent studies have shown that both opaque tape and commercial sunscreen can prevent clinical and dermoscopic changes in acquired nevi exposed to repeated equally suberythemogenic UV-B-NB and UV-A-1 radiation. However, since the authors did not find significant differences at the histopathologic level between nevi covered by an opaque barrier or a commercial sunscreen or left unprotected, they proposed that repeated suberythemogenic UVR doses are not a risk factor for the malignant transformation of nevi, since this irradiation does not induce changes at the cellular level. In our model, we tested the more frequent sunbathing dose in summer exposure (twice the erythemogenic dose), and our nevi could be directly compared against themselves (the previous investigators studied different nevi—ones completely covered by an opaque barrier or a commercial sunscreen or left unprotected).
In our experience, no patient phenotype or phototype could be associated with a predictable or specific UVR response. This is a possible bias, since the 20 patients studied herein are representative of our clinically atypical nevi syndrome and high-risk MM population. Most of them have dark-colored eyes and hair, with phototype II or III but with a very low UV-B MED. Compared with other photosensitive populations, such as those in Northern countries or patients with photodermatoses, our sample presented a very high UVR sensitivity. Up to 60% of patients presented a very low MED (≤50 mJ/cm²), similar to those reported in Northern European populations or patients with photodermatoses (unpublished data from 65 consecutive photosensitive patients studied in our Photobiology Unit, January 2005 through January 2007). Compared with a previous series on irradiated nevi (summarized by Carrera et al³⁹), we have observed more intense inflammatory changes other than darkening or other than an increase in the number and size of globules and the network. We cannot find a relationship between which lesions or patients presented a specific change. Another limitation in our interpretation of the results is that it is not clear why the sunscreen-protected nevi showed a higher degree of regression.

In contrast to those results, histopathologic differences between both halves were demonstrated in all cases in our study. As previously described,²⁷,²⁸ chronic sun exposure can promote an increase in melanocyte density and activation in normal skin that can be misdiagnosed as melanocytic proliferations. In view of our findings, it should be taken into account that acute UVR also could interfere with the appropriate surgical margin assessment for melanocytic tumors.

Figure 7. Human Melanoma Black-45 Antigen (HMB-45)–Positive Nevus Cells (Original Magnification ×100) in Unprotected (A) and in Sunscreen-Protected (B) Halves

More intense staining and marked activation of dendritic larger melanocytes were noted in unprotected areas. Significant differences were noted between protected and unprotected halves for intensity of immunohistochemical staining (C and D). Unexpectedly, the intensity of the immunostain in sunscreen-protected areas were higher than physically protected areas (P < .04) both for HMB-45 and Melan-A. NS indicates nonsignificant. See the legend to Figure 1 for an explanation of the graphic elements (C and D).
features. Even though this limitation could be a consequence of the small size of the sample, some other explanation may be hypothesized. It could be suggested that physical barriers prevent UV damage and that immunosuppression and sunscreens also may protect against immunosuppression but not against all UV damage inducing inflammation and the presence of regression structures.

In conclusion, we have demonstrated for the first time that the protective role of sunscreen in avoiding UVR-induced effects on nevi is at least similar to a physical barrier under Mediterranean summer weather conditions.

Two findings of the study were the most remarkable. First, neither all patients nor all nevi had the same UVR response after 2 MED UV-B irradiation. Actually, we were not able to distinguish which patients or lesions would be more affected by UVR. Even with no visible changes, histopathologic examination showed some UVR-related effects in all lesions. Thus, UVR provokes effects other than pigmentation and erythema, sometimes not visible in vivo. Second, not all changes after UVR were confined to unprotected areas. Therefore, neither physical nor sunscreen protection could completely prevent the UVR effects. Some local inflammatory effects in addition to erythema and pigmentation changes probably could affect protected areas. There were very weak differences between a physical barrier and sunscreen, not enough to conclude that sunscreen creams are not effective but enough to suggest that sunscreens do not provide the same effect as a physical barrier to prevent 2 MED UV-B irradiation in nevi.

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