Discordance Between Facial Wrinkling and the Presence of Basal Cell Carcinoma

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Background: During routine surgical treatment of basal cell carcinomas (BCCs), we observed an apparent inverse relationship between the presence of a BCC and significant wrinkling of the face. To ascertain the veracity of this observation, we performed a clinical and questionnaire-based case-referent study.

Observation: One hundred eighteen successive white patients (mean±SD age, 71.9±9.5 years) attending the hospital for surgical treatment of a BCC and 121 control (no skin cancer) patients (mean±SD age, 69.1±10.8 years) were assessed for grade of facial wrinkling using a previously validated photonumeric scale of photoaging and completed a questionnaire about sun exposure. Despite being older ($P=.03$), patients with a BCC were found to have a lower mean grade of wrinkling than controls ($P=.001$). Using logistic regression, increasing grade of wrinkling was associated with a progressive reduction in risk of developing a BCC.

Conclusion: Mechanisms responsible for the production of facial wrinkles may either be separate to or mitigate against the development of a BCC of the face.

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WHILE conducting clinical studies on facial photoaging and during surgical treatment of facial basal cell carcinomas (BCCs), we observed that patients who develop this form of skin cancer appeared to have smoother, less wrinkled facial skin than those who do not (Figure 1). Patients with a BCC did not seem to develop the deep coarse facial wrinkling commonly designated as one of the markers of significant sun exposure. Another observation seemingly in favor of this hypothesis is the apparent scarcity of BCCs on the heavily sun-exposed nape of the neck but the presence of characteristic deep wrinkling at this site—cutis rhomboidalis nuchae. Thus, we performed a case-referent study to determine if patients with a BCC on the face had a significantly lesser degree of facial wrinkling compared with those in the same age range who did not have a BCC.

RESULTS

Despite being older ($P=.03$, t test), patients with a BCC had a lower mean grade of wrinkling than controls ($P=.001$, Mann-Whitney test) (Figure 2). Using logistic regression and adjusting for age, sex, and smoking history, an increase in grade of wrinkling was associated with a progressive reduction in the likelihood of developing a BCC. As the frequency of grade 2 wrinkling alone was small (n=9), grades 2 and 3 were combined to form the referent or comparison group. In this study, no subjects had a wrinkle grade of 0 or 1. There was some evidence of a threshold effect, with the maximum protective effect being observed at wrinkling grade 5 (Table). Multivariate analysis indicated that those subjects with a wrinkling of grade 5 were 90% less likely to have a BCC than were subjects with a lower amalgamated wrinkle grade—grades 2 and 3.

When analyzed by Fitzpatrick phototype, after adjusting for age, compared with those who always tan (Fitzpatrick grade IV), those with lower grades (tans slowly or not at all) were more likely to develop a BCC (grade II or III: odds ratio, 2.7 [95% confidence interval, 1.1-4.9]; and grade I: odds ratio, 1.7 [95% confidence interval, 0.7-4.0]).

COMMENT

The results of this study indicate that BCCs are more likely to occur on facial
skin that, although photoaged, is relatively unwrinkled. This observation implies that the mechanisms responsible for producing wrinkles associated with photaging are different from those involved in the development of BCCs.

The clinical hallmarks of high cumulative sun exposure in whites are coarse wrinkles, actinic keratoses, telangiectasia, and actinic lentigines (“age spots”), features known alternatively as photoaging. In individual cases, the features of photoaging often differ despite equivalent sun exposure; for instance, some people have wrinkles predominantly while others have relatively smooth facial skin with telangiectasia. Indeed, it appears that individuals with cutis rhomboidalis nuchae often have smooth unwrinkled faces. English et al demonstrated that on traditionally wrinkled but less BCC-prone sites—the back of the hand and the nape of the neck—wrinkling as assessed by cutaneous microtopography or a clinical severity scale, respectively, showed moderate agreement with reported sun exposure. However, their study did not assess facial wrinkling. Photoaging also occurs in nonwhite skin but with different phenotypes—actinic lentigines predominate in Far East Asians, whereas wrinkles can be a feature of long-term sun exposure in black skin.

Relatively little is known about the cellular biological features of sun-induced wrinkling, although it is accepted that this may be due in part to loss of extracellular matrix components subjacent to the dermoepidermal junction. Such components include type I, III, and VII collagens and fibrillin—a cumulative loss resulting from a combination of decreased synthesis and increased breakdown from sun-induced activation of matrix metalloproteinase production.

There is an increasing body of evidence to indicate that the relationship between sun exposure and the subsequent development of a BCC is nonlinear. The chronicity of sun exposure is directly linked to the subsequent development of a squamous cell carcinoma. By contrast, the intermittency of intense sun exposure appears to be a stronger determinant of BCC risk than an equivalent amount of sun exposure delivered over a longer period.

Others have found that BCC and squamous cell carcinoma of the skin are more likely to occur in people who tan with difficulty, equating to Fitzpatrick phototypes I to III. Our observations are in keeping with this but identify a particular nonwrinkled phenotype within this group that more likely presents with a BCC. Although we studied BCC, as this is the more prevalent nonmelanoma skin cancer, it is possible that squamous cell carcinoma may also occur more commonly on nonwrinkled as opposed to wrinkled sun-exposed skin. While acknowledging the potential for observer bias, as one observer carried out all the photomeric assessments of patients and controls, this study strongly suggests that the underlying mechanisms responsible for the production of facial wrinkles may be different from those producing BCC. Intriguingly, particularly as BCCs are rare or comparatively rare on the nape of the neck and back of the hand, this could also imply that wrinkling protects against the development of a BCC. An explanation for this could lie in the hypothesis that there are perhaps 2 forms of the collagen repair process in the papillary dermis following sun exposure—a nonfibrotic response, with loss of collagen leading to a wrinkled clinical phenotype and relatively few BCCs; and a fibrotic re-
response, with preservation of collagen resulting in a clinical phenotype with few if any wrinkles but a tendency to develop BCCs. One speculative mechanism that could underlie these processes is predicated on a role for transforming growth factor \( \beta \),\(^{16} \) which stimulates collagen formation, thereby facilitating wrinkle repair, but is locally angiogenic and immunosuppressive, leading to telangiectasia and growth of BCCs, respectively.

Whatever the pathomechanisms that link clinical phenotype and BCCs, this study has provided some clues, through clinical observation, to factors that determine a predisposition to nonmelanoma skin cancer of the face.

### Figure 1.
Two examples of basal cell carcinomas occurring on a background of nonwrinkled but photoaged and telangiectatic skin: in a 72-year-old man (A) and in a 55-year-old man (B).

### Figure 2.
Distribution of wrinkling severity among all patients. Facial wrinkling is less for patients with basal cell carcinoma compared with control patients without basal cell carcinoma.

### Odds Ratios and 95% Confidence Intervals (CIs) for Grade of Facial Wrinkling and Development of Basal Cell Carcinoma, Adjusted for Age, Sex, and Smoking History

<table>
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<th>Variable</th>
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<th>Multivariate Analysis</th>
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<tr>
<td>Age</td>
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<td></td>
<td>Female</td>
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<td>Smoked</td>
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<td></td>
<td>Ever</td>
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<td>Wrinkle grade</td>
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<td>4 (n = 56)</td>
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<td>5 (n = 30)</td>
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<td>7 (n = 24)</td>
<td>0.5 (0.2-1.2)</td>
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<tr>
<td></td>
<td>8 (n = 11)</td>
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*Referent group.
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REFERENCES