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.

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]).

The results of this study indicate that BCCs are more likely to occur on facial
PATIENTS AND METHODS

A clinical and questionnaire-based case-referent study was performed within the setting of a dermatology tertiary referral center in Manchester, England. We studied all identified white patients (n = 118 [30 men and 68 women]) older than 50 years (mean ± SD age, 71.9 ± 9.5 years) who presented to the Dermatology Centre at Hope Hospital, Manchester, during a 3-month period in 1999. Patients were attending the hospital either for surgical treatment of a BCC (thus giving histological verification of the diagnosis) or for a first diagnosis. Control patients were 121 white patients (59 men and 62 women) older than 50 years (mean ± SD age, 69.1 ± 10.8 years) who had never had a BCC and who were outpatients or inpatients under the care of other departments within the hospital. All identified patients in any department able to answer the questionnaire and give informed consent were included to minimize selection bias. There were no other exclusion criteria.

All subjects completed the same questionnaire and were assessed for extent of wrinkling by a single observer (S.A.N.) using a previously validated photonumeric assessment scale of facial wrinkling. This scale gives a range of severity for facial wrinkles from 0 (no wrinkling) to 8 (severe wrinkling). Although this design could result in observer bias, the alternative of using high-quality accurate photographs of each study participant suitable for third-person blinding was considered financially unfeasible. The questionnaire asked for demographic details; known confounders (eg, radiation treatment for acne); childhood arsenic ingestion as “tonics”; other skin problems and treatments for these, such as UV irradiation; smoking history; and occupational history. No patient or control self-declared any prior cosmetic procedure (dermabrasion, laser resurfacing, or a chemical peel for facial photoaging). Skin phenotype was established for all participants using the Fitzpatrick classification, which categorizes the sensitivity of white skin to UV radiation into 4 groups. Average sun exposure was included in the questionnaire but not controlled for because the relationship between sun exposure and the development of a BCC, although still causal, is less well defined than for that of squamous cell carcinoma.4,5 There is thought to be a plateau in the risk for a BCC at higher cumulative doses of UV radiation. In addition, recall bias can be introduced when trying to assess lifetime sun exposure, particularly for a group of patients who are aware that they have developed a carcinoma thought to be etiologically related.

All statistical analyses were carried out using Stata software, version 6.0 (Stata Corp, College Station, Tex).

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.6 Indeed, it appears that individuals with cutis rhomboidalis nuchae often have smooth unwrinkled faces. English et al8 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,9 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 dermoeidermal junction.10 Such components include type I, III, and VII collagens and fibrillin11-13—a cumulative loss resulting from a combination of decreased synthesis and increased breakdown from sun-induced activation of matrix metalloproteinase production.14

There is an increasing body of evidence to indicate that the relationship between sun exposure and the subsequent development of a BCC is nonlinear.7 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.3

Others15 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 photonumeric 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 β, 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.
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