Effect of Smoking on Aging of Photoprotected Skin

Evidence Gathered Using a New Photonumeric Scale

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Objectives: To develop a reproducible photonumeric scale to assess photoprotected skin aging and to determine whether health and lifestyle factors, such as smoking, affect skin aging in photoprotected sites.

Design: Using standard photographs of participants’ upper inner arms, we created a 9-point photonumeric scale. Three blinded reviewers used the scale to grade the photographs. Participants answered multiple lifestyle questions.

Setting: Academic outpatient dermatology clinic.

Participants: Eighty-two healthy men and women aged 22 to 91 years.

Interventions: A professional medical photographer took standardized photographs of each participant’s upper inner arm. Participants answered standardized health and lifestyle questions.

Main Outcome Measures: (1) Interobserver agreement and reproducibility using the photonumeric scale and (2) health and lifestyle factors most predictive of the degree of aging in photoprotected skin.

Results: There was good blinded interobserver agreement as measured by the maximum range of disagreement scores for each participant (mean, 0.91; 95% confidence interval, 0.76-1.06). Results were reproducible. We developed a multiple regression model showing that the best model for predicting the degree of aging in photoprotected skin includes 2 variables: age and packs of cigarettes smoked per day.

Conclusions: This photonumeric scale demonstrates good interobserver agreement and good reproducibility. Using this scale, the degree of aging in photoprotected skin was significantly correlated with patient age and a history of cigarette smoking. Additional studies are needed to continue garnering information regarding independent risk factors for aging of photoprotected skin.

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The clinical features of photoaging—coarseness, coarse and fine wrinkling, telangiectasia, dyspigmentation, and sallowness—are well characterized, and various photographic and written scales have been developed for the assessment of photoaging.† The most reproducible scales are photonumeric scales, which use photographic standards to assign grades of severity to clinical patients.‡ No such scale exists for the assessment of aging in photoprotected skin, which is dominated by fine wrinkling but also includes changes in skin laxity and the development of benign neoplasms.†‡ As research into photoprotected skin aging progresses, a validated photonumeric scale assessing its severity will be needed.

To assess the degree of photoprotected skin aging, we developed a 9-point photographic scale. Because photoprotected skin aging is dominated by fine wrinkling, this photonumeric scale primarily assesses the degree of fine wrinkling. Three blinded reviewers used the scale to assess interobserver agreement and reproducibility. In addition, we investigated the correlation of fine wrinkling with age, sex, ethnicity, and many lifestyle factors.

METHODS

A total of 82 individuals aged 22 to 91 years were enrolled. The goal of recruitment was to include approximately equal numbers of participants with respect to sex and age (38 men and 44 women; 11 aged 22-29 years, 32 aged 30-59 years, 27 aged 60-79 years, and 12 aged ≥80 years). Participants were recruited from the University of Michigan (Ann Arbor) general dermatology clinic. Potential participants
were chosen based on their age, sex, and willingness to participate in the study. All the participants signed an informed consent form approved by the University of Michigan institutional review board before entering the study.

**PHOTOGRAPHY**

A standardized photograph of each participant’s upper inner right arm was taken by a single professional photographer in the University of Michigan (Ann Arbor) Program for Clinical Research in Dermatology. We chose to photograph the upper inner arm because it is generally photoprotected and easy to photograph and because patients are generally more willing to have this site photographed rather than sites such as the buttocks. To ensure a consistent standardized photograph, we used a digital camera and macro flash unit (Nikon D1x; Nikon, Tokyo, Japan). Flash output and camera-to-arm distance were held constant for all photographs. For standardization, participants were asked to stand erect, to extend their arms 90° from the trunk laterally, and to gently place their hands (palms down) on a vertically placed pole. All the participants signed a photographic consent form approved by the University of Michigan institutional review board before being photographed.

**PHOTOGRAPHIC SCALE**

Five participant photographs were selected as standards representative of the degree of fine wrinkling and were assigned grades of 0, 2, 4, 6, and 8, thus creating a 9-point scale in which 0 represents no fine wrinkling and 8 represents severe fine wrinkling (Figure 1). The standards were selected for their ability to adequately portray nontactile and easily photographed features of photoprotected skin aging, namely, the degree of fine wrinkling. Only 5 standards were selected owing to the difficulty of capturing on film intermediate grades of difference, that is, grades 1, 3, 5, and 7. These 5 standard photographs were excluded from analysis of interobserver and intraobserver reliability, resulting in an effective sample size of 77 for these analyses.

**TESTING THE PHOTOGRAPHIC SCALE**

To test interobserver variability, 3 judges (2 residents in the Department of Dermatology, University of Michigan, and 1 medical student) were asked individually to grade 77 participant photographs using the photonumeric scale. Judges were blinded with respect to all aspects of participant history, including age, sex, and answers to health and lifestyle questions. Judges were instructed to focus on the central area of the upper arm, assessing only the degree of fine wrinkling and ignoring changes such as dryness and deep folds of the skin produced by excess weight or sagging skin. If the degree of fine wrinkling appeared to fall between 2 photographic standards, an intermediate grade (1, 3, 5, or 7) could be assigned to the photograph. None of the 5 standard photographs were graded by the judges.

One year later, the same 3 judges regraded the same set of photographs using the same photographic scale to assess fine wrinkling. Judges were blinded with respect to the first set of scores. These results were used to determine intraobserver reproducibility, or the ability of each observer to reproduce his or her score at a subsequent time, presumably having allowed enough time to pass that memory was not a factor.

**COLLECTING DATA ABOUT MULTIPLE HEALTH AND LIFESTYLE FACTORS**

We collected data by interviewing each participant. Participants answered questions regarding age, sex, ethnicity, history of cigarette smoking, use of nonsteroidal anti-inflammatory drugs, use of herbal or dietary supplements, sun exposure, sunscreen use, tanning bed use, and, for women, how many children they had birthed, use of hormone therapy, and oral contraceptive use. To determine race/ethnicity, participants classified themselves into 1 of 5 groups—white, African American, Asian, Hispanic, or American Indian.

Participants were asked how many years they had smoked and how many packs of cigarettes they smoked per day. We used this information to quantify smoking in pack-years (mean number of packs per day multiplied by years of smoking). Par-
participants were asked to estimate average hours of lifetime sun exposure per day; sun exposure was then categorized as minimal (<1 h/d), moderate (1-3 h/d), or severe (>3 h/d). Sunscreen use was measured in total lifetime years. Tanning bed exposure was quantified and categorized as none, minimal (<10 total lifetime visits), moderate (≥10 lifetime visits but <1 visit per day), or severe (≥1 visit per day). Hormone therapy and oral contraceptive use were measured in total lifetime years. Use of nonsteroidal anti-inflammatory drugs and herbal or dietary supplements were noted as either present or absent.

### STATISTICAL ANALYSIS

Descriptive statistics were generated for age, degree of photoprotected skin aging, years of hormone therapy or oral contraceptive use, number of children, total years of smoking, packs of cigarettes smoked per day, pack-years of smoking, hours of sun exposure per day, and years of sunscreen use. We performed the test to compare the degree of fine wrinkling in men and women, users and nonusers of nonsteroidal anti-inflammatory drugs, and users and nonusers of herbal or dietary supplements. One-way analysis of variance was applied to observe how the degree of fine wrinkling varied with race, sun exposure, and tanning bed use.

Correlation analyses were performed to determine significant predictors of the degree of fine wrinkling (Pearson correlations for continuous variables and Spearman correlations for categorical variables). We developed a multiple regression model controlling for confounding variables (age, years of hormone therapy, number of children, years of smoking, packs smoked per day, sun exposure, years of sunscreen use, and nonsteroidal anti-inflammatory drug use), with degree of fine wrinkling as the outcome. A forward selection linear regression method was used to create an optimal model for predicting the degree of photoprotected skin aging. All the statistics were generated using analytic software (SAS version 8.0; SAS Institute Inc, Cary, NC).

### USEFULNESS OF THE PHOTOGRAPHIC SCALE

An intuitive approach to assessing interobserver variability was to calculate a “maximum range of disagreement” score for each participant by taking the difference between the highest and lowest scores given by the 3 graders. This essentially represents a worst-case scenario in disagreement. The resulting maximum range of disagreement scores were then averaged across all 77 participants. The resulting mean ± SD maximum range of disagreement for the initial set of scores was 0.91 ± 0.08 (95% confidence interval, 0.76-1.06); therefore, the average maximum range of disagreement among the 3 graders was less than 1 unit on the photonumeric scale from 0 to 8. After 1 year the exercise was repeated and the mean ± SD maximum range of disagreement was found to be 1.01 ± 0.09, indicating slightly more disagreement among the graders after 1 year, although the difference was not significant (P = .30). To investigate the degree to which each grader could duplicate his or her scores 1 year after the initial grading, the absolute difference was determined between the first and second sets of grades for each participant. The resulting sets of absolute differences were then averaged (mean ± SD) across all 77 participants for each grader: grader 1, 0.30 ± 0.06; grader 2, 0.62 ± 0.08; and grader 3, 0.47 ± 0.10. Two of the 3 graders, on average, remained within approximately a half unit or less of their initial score for each participant. The number of exact matches was as follows: grader 1, 57 (74%); grader 2, 36 (47%); and grader 3, 59 (77%). Although grader 3 had more exact matches than grader 1, the mean difference was considerably higher. This seemed to be due to grader 3 using only the even integers (0, 2, 4, 6, 8) to score the participants’ degree of aging, thereby causing the mismatches to be of a greater magnitude (ie, ≥2).

### EFFECTS OF HEALTH AND LIFESTYLE FACTORS ON DEGREE OF FINE WRINKLING

The demographics of the study population are detailed in Table 1. We found a correlation between the degree of photoprotected skin aging and several factors: chrono-
logical age (r = 0.84; P < .001), years of smoking (r = 0.39; P < .001), packs smoked per day (r = 0.41; P < .001), pack-years of smoking (r = 0.41; P < .001), and, in women, the number of children to whom they had given birth (r = 0.46; P = .004) (Table 2).

We developed a multiple linear regression model to assist in predicting the mean degree of fine wrinkling of the skin while controlling for potentially confounding variables (chronological age, years of hormone therapy, years of smoking, hours of sun exposure, etc.). Based on the results of the forward linear regression method, the optimal model for predicting mean degree of photoprotected skin aging (R² = 0.754) includes 2 variables: chronological age (b₁ = +0.103; P < .001) and packs of cigarettes smoked per day (b₂ = +0.448; P = .04).

EFFECT OF SMOKING ON DEGREE OF PHOTOPROTECTED SKIN AGING

Forty-one participants (50%) gave a history of cigarette smoking at some point in their lives. Among former smokers, the number of packs smoked per day ranged from 0.25 to 4.00. When groups were stratified by age we found that in individuals 45 years and older, the degree of photoprotected skin aging was significantly greater in smokers than in nonsmokers (Figure 2).

We developed a photonumeric scale for the assessment of photoprotected skin aging as measured by the degree of fine wrinkling of the upper inner arm. Although many scales have been developed for the assessment of photaging, there is no published scale, to our knowledge, for the assessment of photoprotected skin aging. The present photonumeric scale proved to be a consistent and reproducible means of evaluating photoprotected skin aging. These results indicate that this scale is an uncomplicated evaluation system for the clinical investigator involved in the assessment and treatment of photoprotected aging skin.

Previously, Griffiths et al1 and Larnier et al3 developed 9- and 6-point photonumeric scales, respectively, for the assessment of photodamaged facial skin. Chung et al4 developed separate grading systems for photodamage based on facial wrinkling and pigmentary changes in Korean individuals. However, none of these photonumeric scales were designed to assess changes seen in photoprotected skin. Photodamaged skin is characterized by increased roughness, coarse wrinkles, and pigment irregularities, whereas sun-protected aged skin is predominantly characterized by fine wrinkling.6-9 We examined a largely photoprotected site and ignored changes associated with photodamage, such as pigment irregularities and coarse wrinkling, focusing instead on fine wrinkling of the skin to evaluate photoprotected skin aging.

As expected, we found that increasing age correlated strongly with the degree of chronological aging of the skin. The underlying mechanisms of photoprotected skin aging have not been elucidated as well as those of photaging. However, collagen synthesis is decreased and matrix metalloproteinase (MMP) levels are increased in the sun-protected skin of elderly individuals, findings similar to those seen in photoaged skin.8,10,11 These data suggest that there are similarities between the pathogenesis of natural skin aging and photaging. UV radiation is an oxidative stress. On exposure to UV radiation, reactive oxygen species such as hydrogen peroxide are generated.12 This eventually leads to increased MMP levels, decreased levels of procollagen I, and, finally, physical changes associated with photoaging.8 The etiology of photoprotected skin aging is far less clear. One theory proposes that aging is the end result of cumulative cellular damage caused by the generation of excess reactive oxygen species via oxidative metabolism.13,14 This theory would help explain the molecular similarities seen in photoaged and photoprotected skin.

Cigarette smoking has long been investigated as a risk factor for premature skin aging. Several studies1-5,7,16 have separately determined that cigarette smoking independently contributes to premature skin aging, as measured by the severity of facial wrinkling in white and Ko-

Table 2. Correlation Between Variables and Degree of Photoprotected Skin Aging

<table>
<thead>
<tr>
<th>Variable</th>
<th>Participants, No.</th>
<th>Strength of Correlation</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>82</td>
<td>0.84</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sunscreen use, y</td>
<td>81*</td>
<td>-0.13</td>
<td>.25</td>
</tr>
<tr>
<td>Estimated hours of sun exposure daily</td>
<td>81*</td>
<td>0.02</td>
<td>.87</td>
</tr>
<tr>
<td>No. of children birthed†</td>
<td>38</td>
<td>0.46</td>
<td>.004</td>
</tr>
<tr>
<td>Hormone therapy, ††</td>
<td>43</td>
<td>0.09</td>
<td>.55</td>
</tr>
<tr>
<td>Oral contraceptive use, ††</td>
<td>40</td>
<td>-0.26</td>
<td>.11</td>
</tr>
<tr>
<td>Years of smoking</td>
<td>82</td>
<td>0.39</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Packs smoked per day</td>
<td>82</td>
<td>0.41</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pack-years of smoking, y</td>
<td>82</td>
<td>0.41</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*One patient in each group could not quantify either years of sunscreen use or hours of sun exposure per day.
†For female participants only.

Figure 2. Mean degree of fine wrinkling by smoking status and age. The effect of smoking on the degree of photoprotected skin aging increases with increasing age. Error bars represent SD. *P = .05. †P = .004.
rean individuals. Several research groups\textsuperscript{2,10,17} found that the odds of facial wrinkling increased as the number of pack-years of smoking increased. Another study,\textsuperscript{15} however, found no strong or consistent dose-response gradient across age and sex groups between pack-years of smoking and wrinkle score.

In this study examining nonfacial, photoprotected skin, we found that the number of packs of cigarettes smoked per day, total years of smoking, and pack-years of smoking were correlated with the degree of skin aging. After controlling for participant age and other variables in a multiple regression model, we found that only packs of cigarettes smoked per day was a major predictor of the degree of photoprotected skin aging. This finding probably reflects the high degree of intercorrelation among the 2 independent variables assessing smoking history (packs per day and years of smoking). In participants older than 65 years, smokers had significantly more fine wrinkling than nonsmokers. Similar findings were seen in participants aged 45 to 65 years.

In a small study\textsuperscript{18} using image analysis, the sun-exposed skin of smokers was found to have more solar elastosis than the sun-exposed skin of nonsmokers. In another small study,\textsuperscript{19} biopsy samples taken from the upper inner arm of cigarette smokers showed increased relative area, number, and thickness of elastic fibers compared with controls. The ultrastructural alterations of the elastic fibers were thought to resemble changes seen in solar elastosis.\textsuperscript{19} However, a larger study\textsuperscript{20} found no significant difference in the amount and width of elastic fibers in the sun-protected skin of smokers compared with nonsmokers.

Yin et al\textsuperscript{27} found that tobacco smoke extracts induced expression of MMP-1 messenger RNA in vivo. In addition, his group found elevation of MMP-1 and MMP-3 messenger RNA levels and decreased production of procollagens I and III in cultured human fibroblasts after exposure to tobacco smoke.\textsuperscript{21} Again, these changes mirror those associated with UV light exposure, suggesting that the generation of reactive oxygen species after tobacco exposure leads to molecular changes (elevated MMP levels and decreased levels of procollagen) that eventually lead to wrinkling and other changes we tend to associate with age, in photoexposed and photoprotected sites.

In this study, we asked participants to categorize themselves into racial/ethnic groupings. There is a general perception that some ethnic groups age better or worse than others. In addition, it has been noted that there are differences in the manifestations of photoaging in the skin of white and Asian individuals; for that reason, a separate scale has been developed for the assessment of photoaging in Korean skin.\textsuperscript{1,2} The racial/ethnic differences in photoaged skin are most likely related to variability in innate melanin-related photoprotection. We suspect that there would not be differences in a photoprotected site, but in this study we did not have enough participants of nonwhite origin to detect a difference. A much larger study comparing larger ethnic groups would be helpful in determining whether this photonumeric scale can be used in individuals of color.

In conclusion, we created a reliable and reproducible photonumeric scale for the evaluation of photoprotected skin aging. Presumably its primary role would be in categorizing groups of individuals before treatment with agents aimed at reducing the degree of photoprotected skin aging or as a tool in pathophysiologic studies investigating photoprotected skin aging. This scale would allow greater reliability among centers involved in studies of photoprotected skin aging and enable independent evaluation of high-quality study photographs. In addition, we demonstrated that the degree of photoprotected skin aging correlates well with age and packs of cigarettes smoked per day. More studies are needed to continue to elucidate the independent risk factors for aging of photoprotected skin.

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Author Contributions: Dr Helfrich had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.


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REFERENCES


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**Call for Papers**

**On the Horizon**

On the Horizon is designed to showcase a recent finding in the scientific literature that is likely to have a significant impact on our understanding of skin disease pathogenesis and ultimately contribute to more effective disease management. While treatment is an obvious focal point of the section, other elements of improved disease management might include prevention, counseling, and public policy. The section is intended to have a concise, consistent structure. It begins with an abstract reprinted from the scientific literature that represents the focus of the article. This is followed by a short commentary of approximately 500 words and a few relevant references. If crucial to the message, 1 or 2 figures or tables might be included. The content should be focused and contained to a single page of the ARCHIVES.

To achieve our goal of making On the Horizon a monthly feature of the ARCHIVES, we need your help. We know that excitement about advances in dermatology is shared by many dermatologists in and out of academics, as well as fellows, residents, and students. We invite all kindred spirits to submit material to On the Horizon. This is an excellent opportunity for residency program directors and other faculty mentors to get their trainees involved in writing about, not just reading about, scientific advances relevant to dermatology. Submissions may go directly to Gary S. Wood, MD, the section editor, or through one of the assistant section editors.
Turk, Kilinc-Karaarslan, and Ozdemir. *Acquisition of data: Gencoglan, Gerceker-Turk, and Ozdemir. Analysis and interpretation of data: Gerceker-Turk, Akalin, and Ozdemir. Drafting of the manuscript: Gencoglan, Gerceker-Turk, Kilinc-Karaarslan, Akalin, and Ozdemir. Critical revision of the manuscript for important intellectual content: Ozdemir. Administrative, technical, and material support: Gerceker-Turk. Study supervision: Ozdemir.*

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REFERENCES


**Correction**

Error in Author Order. In the Evidence-Based Dermatology Study by Helfrich et al, published in the March issue of the *ARCHIVES* (2007;143:397-402), there was an error in the author order in the byline. The names should have appeared as follows: Yolanda R. Helfrich, MD; Le Yu, MD; Abena Olori, MD; Ted A. Hamilton, MS; Jennifer Lambert, MS; Anya King, MPH; John J. Voorhees, MD; Sewon Kang, MD. The online version of this article was corrected on March 15, 2007.