Atrophic and hypertrophic photoaging: Clinical, histologic, and molecular features of 2 distinct phenotypes of photoaged skin

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Background: Exposure to the sun causes premature skin aging, known as photoaging. Clinical features of photoaging vary widely among individuals. In one form, skin appears thin with telangiectasia, and in another form, skin appears thickened with coarse wrinkles. Etiologic, clinical, and therapeutic distinctions among different forms of photoaging remain largely unknown.

Objective: To characterize the clinical, histologic, and molecular features of hypertrophic and atrophic photoaging.

Methods: In total, 53 individuals were clinically classified as having primarily atrophic or hypertrophic photoaging or neither (controls). Participants' demographic and sun exposure–related lifestyle data were captured by questionnaire. Fifteen clinical features of participants were qualitatively or quantitively scored. Facial biopsies were analyzed for gene expression and histologic characteristics.

Results: Actinic and seborrheic keratosis, telangiectasia, and prior incidence of skin cancers were statistically significantly greater and photoaging scale severity, coarse wrinkles, thickness, and sallowness were significantly reduced in atrophic versus hypertrophic groups. Histology also revealed significantly less elastotic material in atrophic photoaging. Gene expression of matrix metalloproteinases and collagens did not differ between the 2 forms of photoaging.

Limitations: The study was not designed to identify other possible subtypes of photoaging.

Conclusion: Systematic, categorical, and quantitative clinical and histologic assessments distinguish atrophic and hypertrophic photoaging. (J Am Acad Dermatol 2019;81:480-8.)

Key words: aging; elastosis; photoaging; skin cancer; telangiectasia; wrinkles.

Extrinsic skin aging, also known as photoaging, is skin aging due to external factors, the major one being ultraviolet (UV) irradiation from the sun.[1-4] Other extrinsic factors, such as tobacco smoke and ionizing radiation, likely contribute to this clinical phenotype.[5-8] Extrinsic skin aging is best observed on sun-exposed sites, such as the face, lateral neck, and extensor forearms. Photoaging is clinically characterized by uneven skin color manifested as erythema, telangiectasia, dyspigmentation, lentigines, and sometimes sallowness, a yellowish hue of the skin. Wrinkles might be pronounced in some cases and might be fine, coarse, or both. The extrinsic aging phenotype is associated with many

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cosmetic concerns, skin fragility, easy bruising, and skin barrier disruption. Extrinsic influences that lead to an accelerated form of skin aging are always superimposed on natural chronologic aging.

Importantly, numerous types of cutaneous malignancies might arise in extrinsically aged skin. This point has been well-illustrated in studies of automobile drivers who develop more photoaging and skin cancers on the sun-exposed portion of the face closest to the window.[9,10] We and others have noted variability in the clinical findings seen in extrinsically aged skin. Patients with coarse, heavy wrinkles seem to have fewer skin cancers and precancers than those with smoother skin and telangiectases. A clinical study reported an inverse relationship between the prevalence of basal cell carcinoma (BCC) and severity of wrinkles.[11]

CAPSULE SUMMARY

- Although clinical features of facial photoaging vary widely among individuals, we show that 2 broad categories, atrophic and hypertrophic, can be distinguished by clinical, histologic, and molecular characteristics.
- These clinically distinct forms of photoaging might benefit from specific types of therapies.

Gilchrest was among the early adopters of the terms hypertrophic photoaging (HP), skin characterized by deep, coarse wrinkles, homogeneity of skin color and few cancers, and atrophic photoaging (AP), skin characterized by fine wrinkling, a shiny appearance, erythema, telangiectasia, dyspigmentation, and a tendency to develop precancers and invasive skin cancers.[12,13] Little work, however, has been done to explore the basis for the differences that might account for these distinct clinical phenotypes.

How useful the terms hypertrophic and atrophic are for classifying and treating patients is also not clear. To begin addressing this question, we assessed and quantified multiple clinical features of individuals with evident photoaging. In parallel, skin biopsies were taken from sites with prominent features of photoaging to provide histologic and molecular evaluations of the skin. The results of this observational study are presented here.

MATERIALS AND METHODS

Study participants

The study protocol was approved by the University of Michigan Hospital and Health Systems Institutional Review Board. Study participants with clinical evidence of varying degrees of facial photoaging were identified and recruited from the clinics at Michigan Medicine Dermatology. Inclusion criteria encompassed persons of either sex, aged >49 years, and generally healthy. Persons who had undergone cosmetic procedures to improve aging skin were excluded.

Clinical assessments

Participants were evaluated by dermatologists using a published photonumeric scale for photoaging.[14] Fitzpatrick skin types were determined for each participant, as previously described.[15] Lesion counts of actinic keratoses (AKs), lentigines, sebaceous hyperplasia, and seborrheic keratoses were performed. Photoaging, fine wrinkling, coarse wrinkling, sallowness, thickness, telangiectases, dryness, and erythema were graded as mild, moderate, or severe. Fine and coarse wrinkling were described as being located in the periorbital region, perioral region, cheek, periorbital and perioral regions, periorbital region and cheek, perioral region and cheek, or at all 3 sites. Skin texture was graded as smooth, moderate, or rough. Chromameter measurements were made assessing for light, dark, and redness values (Minolta Chroma Meter CR400, Osaka, Japan). Dyspigmentation was assessed as absent, mild, moderate, or severe. Clinical findings of Poikiloderma of Civatte and Favre Racouchot were determined to be present or absent. The number of prior AK, BCC, squamous cell carcinoma (SCC), and melanoma skin cancers was assessed by patient history. A questionnaire (Appendix 1; available at https://data.mendeley.com/datasets/7w5k86xpyz/1) captured data relating to the participant's self-described demographic, lifestyle relevant to sun exposure or other sources of UV irradiation. Descriptive data obtained from this survey are presented in Appendix 2 (available at https://data.mendeley.com/datasets/7w5k86xpyz/1).

Histologic assessments

Punch biopsies (3-mm diameter) were obtained from facial sites of clinically evident photoaging (typically cheek). The biopsies were fixed overnight in 4% buffered formalin, embedded in paraffin, sectioned (5-μm thick), stained with hematoxylin and eosin, and examined by light microscopy. Collagen degradation was assessed semiquantitatively, as described previously,[16] by scoring for fiber length, fiber width, disorganization of the collagen bundles, and the depth to which disorganization was apparent. Telangiectasia was scored as mild,

Abbreviations used:

AK: actinic keratosis
AP: atrophic photoaging
BCC: basal cell carcinoma
ECM: extracellular matrix
HP: hypertrophic photoaging
MMP: matrix metalloproteinase
SCC: squamous cell carcinoma
SE: standard error
UV: ultraviolet

moderate, or severe as described.[17] Inflammation was scored as absent, detected, perifollicular, widespread, or extensive. The percentage of sebaceous gland surface area was estimated as none, 5%-10%, 10%-25%, 25%-50%, or >50%.

Elastotic material was assessed by Verhoeff Van Gieson staining of skin sections. Elastotic material in each section was qualitatively assessed as absent, mild, moderate, widespread, or extensive. After this assessment, sections were digitally imaged, and the percentage of the total area encompassed by elastotic material (black stain) was quantified. Both assessments yielded comparable results.

Gene expression analysis

A second biopsy of photoaged facial skin was embedded in optimal cutting temperature compound and frozen. Total RNA was isolated from cryostat sections and analyzed for gene expression by quantitative real-time PCR as described.[17]

Statistical methods

All clinical and laboratory assessments were summarized with standard descriptive statistics, including mean, standard error (SE), and range, for continuous variables. Categorical variables were summarized by frequency and percentage for each response category.

We used general linear models and 1-way analysis of variance to compare groups and determined false discovery rates for multiple comparison procedures. Statistical significance was determined using Kruskal-Wallis tests on nonnormal and ordinal data. Fisher's exact or χ^2 tests were used to assess group differences for categorical data. Wilcoxon-Mann-Whitney post hoc tests, with false discovery rates for multiple comparison adjustments, were run on each significant pair. An overall alpha-level of 0.05 was used to determine statistical significance and all tests were 2-sided. Data were analyzed by using SAS software v.9.3 (SAS Institute Inc, Cary, NC).

RESULTS

Clinical findings in atrophic and hypertrophic photoaging

Study participants lacking either pronounced wrinkles or pronounced erythema were categorized as control participants. Participants with prominent erythema without prominent coarse wrinkles were categorized in the AP group. Participants with prominent coarse wrinkles without prominent erythema were categorized in the HP group. AP and HP are 2 ends of a clinical spectrum, and both forms existed in many participants to differing degrees. Typical features of AP and HP are shown in the photographs in Fig 1. The characteristics of participants in the AP, HP, and control groups are depicted in Table I. Age and sex were not statistically significantly different among the groups. The control group was age- and sex-matched to the HP group. Tobacco use, Fitzpatrick phototype, and sun exposure history among the AP, HP, and control group participants were also similar (Supplemental Table I; available at https://data.mendeley.com/datasets/7w5k86xpyz/1).

Notable results of the clinical evaluators' assessments of participants are depicted in Fig 2. Global photoaging scale was lower ($P = .011$) in the AP group than the HP group. As expected, global photoaging scale was lowest in the control group (Fig 2, *A*). The distribution of coarse wrinkles among participants in the 3 groups is shown in Fig 2, *B*. Nearly all participants in the HP group had coarse wrinkling that was rated as moderate or severe, whereas less than half of the participants in AP group had coarse wrinkling rated as moderate and none had had coarse wrinkling rated as severe ($P < .0001$). No differences in the location of the wrinkles were noted among the groups.

Participants with HP tended to be rated with a mild degree of telangiectases (83%), whereas participants in the AP group more often had moderate (36%) or severe (32%) telangiectases ($P = .006$) (Fig 2, *B*). Not surprisingly, Chroma Meter measurements for redness were greater in the AP group (mean 15.3 ± SE 0.7) than the HP group (mean 11.8 ± SE 0.6) ($P = .003$) (data not shown). Skin thickness determined by visual assessment was noted to be more pronounced (moderate or severe) in the HP group (65% of participants) than the AP group (21% of participants) ($P = .037$) (Fig 2, *B*).

General sallowness was significantly greater in the HP group than the AP group ($P = .005$) and the control group ($P = .004$) (Fig 3, *A*). However, the degree of dyspigmentation (Fig 3, *A*) and number of

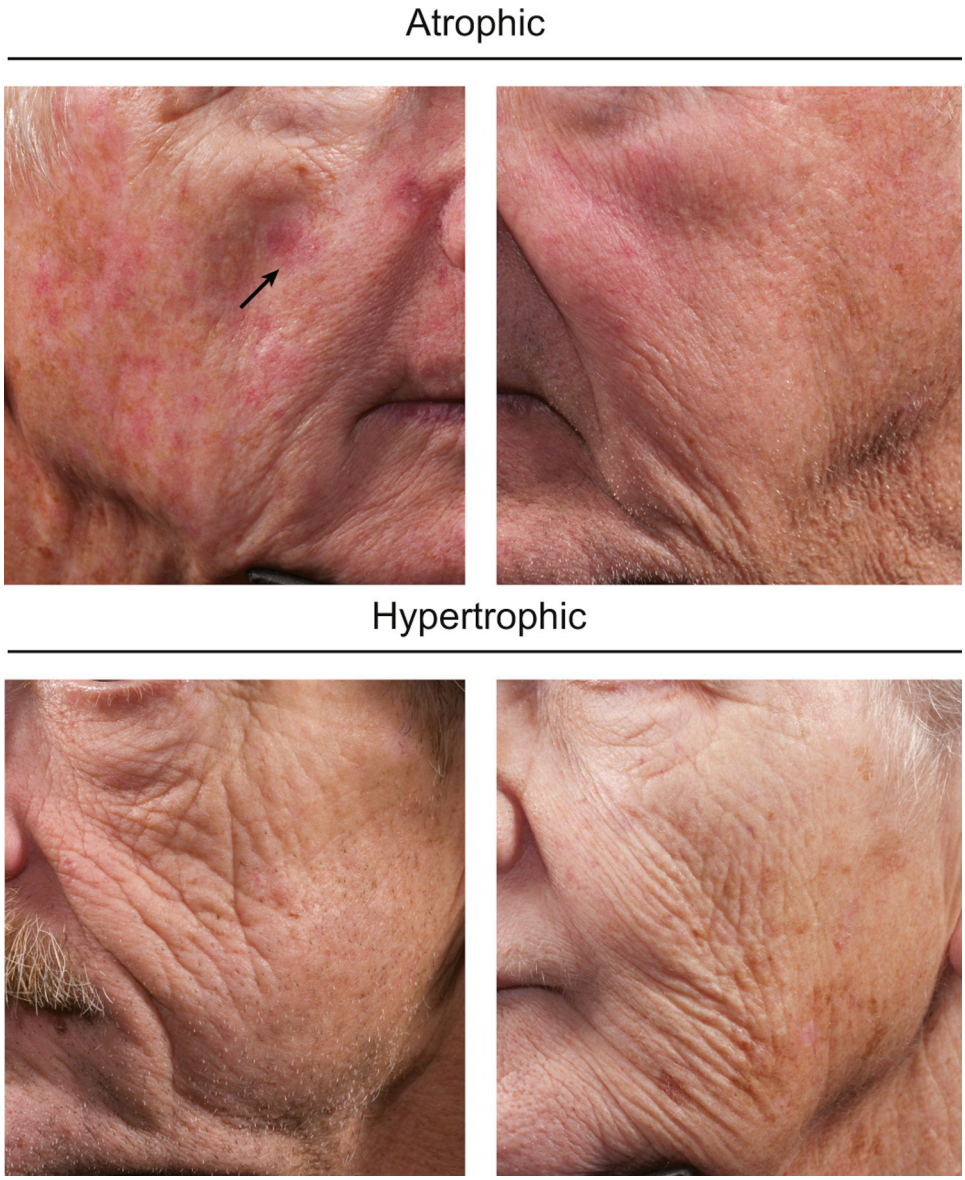

Fig 1. Representative photographs of participants with atrophic or hypertrophic photoaging. Top row, 2 participants with atrophic photoaging demonstrate salient features, including fine wrinkles inferior to the eye and around the mouth, the paucity of coarse wrinkles, patchy erythema, a slightly shiny quality to skin's appearance, and scattered light brown lentigines. An actinic keratosis is indicated (*arrow*). Bottom row, 2 participants with hypertrophic photoaging demonstrate deep, coarse wrinkling of the central cheek. The skin color is homogenous with a sallow hue, and there is minimal to absent erythema and telangiectasia.

lentigines (Fig 3, *B*) were not significantly different between the AP and HP groups. Thus, brown discolorations are not a distinguishing feature between the 2 groups.

Lesion counting revealed that the AP group (mean 8.8 ± SE 3.1 lesions) had more AK lesions than the HP group (mean 1.2 ± SE 0.5 lesions) and the control group (mean 0.7 ± SE 0.6 lesions) ($P = .001$) (Fig 4). Likewise, the AP group (mean 4.3 ± SE 1.0 lesions) had more seborrheic keratoses than the HP group (mean 1.6 ± SE 0.4 lesions) ($P = .025$) (Fig 4).

The incidence of keratinocyte cancers was significantly greater in the AP group than the HP group ($P = .002$). Approximately two-thirds (68%) of the AP participants reported a history of keratinocyte cancer (53% BCC, 37% SCC), while less than one-fifth (17%) of the HP participants reported a history (17% BCC, 4% SCC) (Fig 5). Three participants in

Table I. Age, sex, and ethnicity of all study participants and by group

Demographic	Photoaged participant, n = 53	Atrophic, n = 19	Hypertrophic, n = 23	Control, n = 11
Age at enrollment, y, mean (SE) [range]	69.4 (1.6) [49-90]	74.5 (1.8) [55-87]	68.2 (2.6) [50-90]	63.4 (3.3) [49-79]
Sex, n (%)				
M	30 (57)	14 (74)	10 (43)	6 (55)
F	23 (43)	5 (26)	13 (57)	5 (45)
Ethnicity, n (%)				
White	51 (96)	17 (89)	23 (100)	11 (100)
Other or multiple	2 (4)	2 (11)	0 (0)	0 (0)

SE, Standard error.

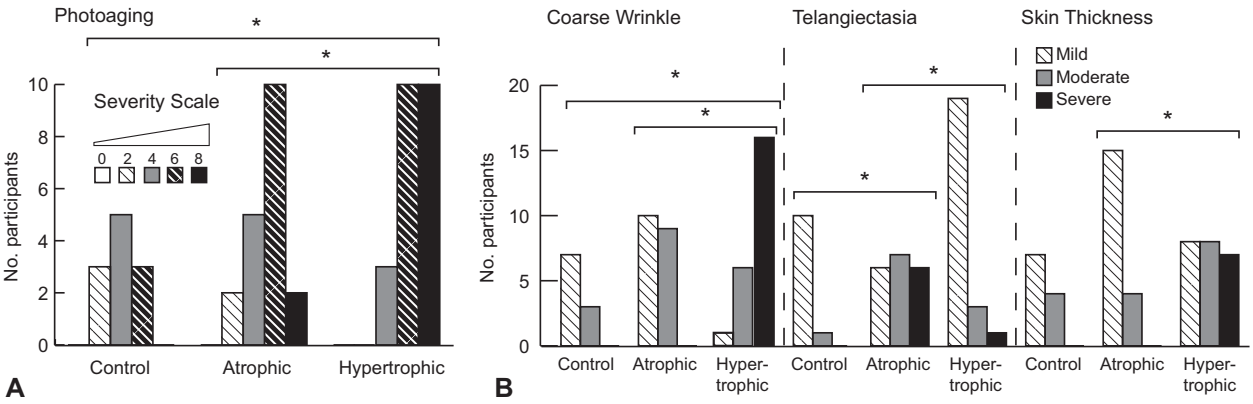

Fig 2. Assessment of photoaging severity, wrinkles, telangiectasia, and skin thickness in atrophic and hypertrophic photoaging. **A**, A global photoaging scale was used to assign the degree of photoaging of each participant. The scale ranges 0-8, where 0 represents absence of photoaging and 8 indicates severe photoaging. **B**, For each participant, coarse wrinkles, telangiectasia, and skin thickness were assessed as mild, moderate, or severe. The brackets indicate the comparison groups. *$P \leq .01$ for all comparisons, except the telangiectasia graph comparisons, which is $P \leq .04$.

the AP group reported a melanoma diagnosis, but none of the HP participants had a history of melanoma (data not shown).

Histologic and biochemical findings in AP and HP

A prominent feature of photoaged skin is fragmentation and reduced organization of collagen fibrils and elastin fibers, which comprise the bulk of the dermal extracellular matrix (ECM).[18,19] Degradation of the collagenous ECM in photoaged skin is mediated by a subset of matrix metalloproteinase (MMP) enzymes, which specifically cleave collagen and other ECM proteins. UV irradiation induces MMP-1, MMP-3, and MMP-9, which together have the capacity to degrade most of the proteins in the dermal ECM.[20,21] In addition, MMP-7 and MMP-12 have been reported to degrade elastin. Gene expression levels of these enzymes, as well as type I and type III collagens, were similar in the AP and HP groups (Supplemental Table II; available at https://data.mendeley.com/datasets/7w5k86xpyz/1). We also determined gene expression for versican (*VCAN*) and elastin-binding protein (also known as galactosidase beta 1, *GLB1*), which have been reported to be elevated in solar elastosis.[22] As shown in Supplemental Table III (available at https://data.mendeley.com/datasets/7w5k86xpyz/1), both genes were expressed at similar levels in AP and HP.

We next performed histologic assessments of photodamaged AP and HP skin compared with participant-matched sun-protected buttocks skin. As expected, photodamaged skin displayed significantly more elastotic damage, sebaceous gland prominence, dilated vessels, and inflammation (Supplemental Table IV; available at https://data.mendeley.com/datasets/7w5k86xpyz/1). We next histologically assessed collagen fibrils for thickness, organization, and density. No statistically significant differences between AP and HP were noted in these qualitative features of collagen fibrils. In contrast, the presence of aberrant elastic fibers (elastosis) localized in the upper dermis was

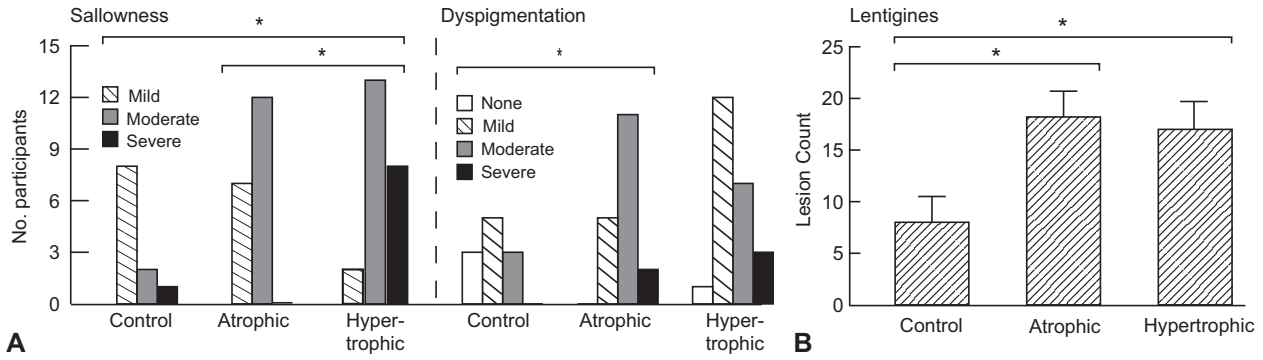

Fig 3. Assessment of skin coloration in atrophic and hypertrophic photoaging. For each participant, skin sallowness and dyspigmentation severity (**A**) and lentigines counts (**B**) were assessed. The brackets indicate the comparison groups. *$P < .05$ for all comparisons.

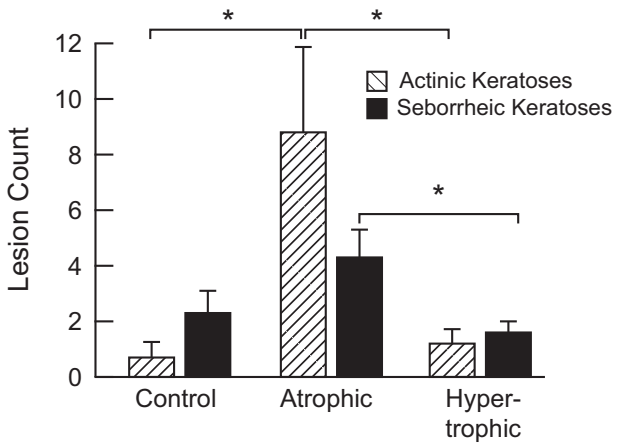

Fig 4. Greater incidence of actinic and seborrheic keratoses in atrophic than in hypertrophic photoaging. Actinic and seborrheic keratoses were numerically quantified by lesion count. The brackets indicate the comparison groups. *$P < .03$ for all comparisons.

significantly more prominent in the HP group than the AP group ($P = .009$). Qualitative grading of the degree of elastosis, rated as none, mild, moderate, widespread, or extensive, revealed that most HP participants (65%) had extensive elastosis, while the AP group (19%) infrequently had extensive elastosis (Fig 5, *A*). To further quantify elastosis, we stained skin sections using the Verhoeff Van Gieson method, which colors elastic fibers and elastotic material black and collagen fibrils red. Representative images of stained sections from control, AP, and HP skin are shown in Fig 5, *B*. The amount of elastotic material was quantified by computerized image analysis. The percentage of the total dermal area that was covered by elastotic material in the HP group (19.5 ± 2.0%) was nearly twice that of the AP group (11.5 ± 1.7%) ($P = .011$) (Fig 5, *B*).

DISCUSSION

HP and AP have been observed and discussed, but to date, no formal, direct evaluation of similarities and differences between these 2 clinical phenotypes has been undertaken. Our study was designed to include a diverse group of persons with lighter skin (Fitzpatrick skin phototypes I-III) with clinical photoaging. We categorized participants into photoaging phenotypes by the prevalence of erythema and coarse wrinkles on their skin, the hallmarks of AP and HP, respectively. In addition to abundant wrinkles, participants with HP tended to have increased skin thickness, more sallowness, a higher global photoaging score, and less erythema. In addition to erythema and telangiectases, participants with AP were noted to have more AKs and seborrheic keratoses and a history of skin cancer.

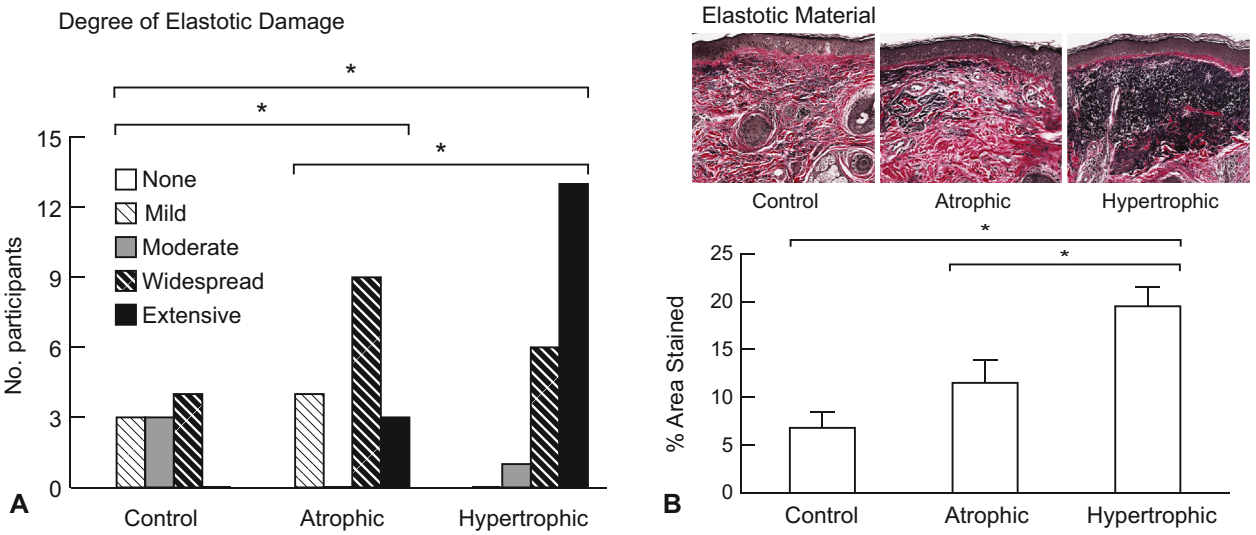

Fig 5. Greater elastotic material accumulation in hypertrophic than in atrophic photoaging. **A**, Hematoxylin-eosin–stained sections from participants in the control (n = 10), atrophic (n = 16), and hypertrophic (n = 20) groups were graded for the degree of elastotic damage by blinded dermatopathologists. Participants with hypertrophic photoaging were graded as having an extensive degree of elastotic damage more often than atrophic photoaging ($P = .009$) or control ($P < .001$) participants were. Also, the degree of elastotic damage was significantly greater in the atrophic group than the control group ($P < .05$). **B**, Representative images of Verhoeff Van Gieson staining of elastotic material. Skin from control participants revealed patchy staining of elastotic material in the upper dermis. Increased solar elastotic material was observed in atrophic photoaging participants, compared with age-matched controls. Dense and heavy staining of solar elastotic material, throughout the dermis, was present in participants with hypertrophic photoaging. Image analysis was used to quantify the area of solar elastotic material in Verhoeff Van Gieson–stained sections. Participants with hypertrophic photoaging had a significantly greater area of staining compared with atrophic photoaged ($P = .011$) or control ($P < .001$) participants.

The association of AK with AP and not HP corroborates previous work.[11] Clinicians should maintain a higher index of suspicion for precancers and invasive skin cancers in patients with the AP phenotype. As skin cancer screening continues to take considerable time and resources, it would be useful to educate primary care providers to recognize AP and HP phenotypes so that they are aware of the relative risks of the 2 populations. In addition, therapeutic and preventive strategies to combat skin cancer should be more strongly considered for persons who have the AP phenotype. Oral nicotinamide has recently been demonstrated to be safe and effective in reducing nonmelanoma skin cancers and AKs in high-risk populations,[23] and considering this vitamin preferentially for those with the AP phenotype might be worthwhile.

The most notable histologic difference between HP and AP was the degree of solar elastotic changes. The quantity of solar elastotic material in HP was significantly greater than in AP. Perhaps this disorganized elastotic material contributes to the clinical phenotype of coarse wrinkling seen in HP. Elastotic material resides in the upper dermis and might create a wrinkled appearance by virtue of nonuniform space-filling. The finding that the organization and density of collagen fibrils, which are much more abundant than elastin fibers and elastotic material, are similar in HP and AP lends some support to this possibility. Clearly, the role of elastotic material in wrinkle formation requires further investigation.

Emerging evidence highlights the importance of the dermal ECM microenvironment as an active participant in the formation of epithelial cancer.[24,25] One could speculate that the higher incidence of skin cancer in AP than HP could reflect differences in the composition and mechanical properties of the dermis. Keratinocyte skin cancers, such as BCC and SCC, need to be able to expand in the dermis, and this growth and expansion might be impaired by stiff elastotic material. Alternatively, perhaps accumulation of abundant solar elastotic material is a protective

response of skin to damage from solar UV radiation. The causes of higher incidence of BCC and SCC in AP versus HP remain elusive. Increased vascularity could contribute to tumor formation by providing an enriched microenvironment for tumor growth, as well as an altered cytokine milieu, which could alter immunoregulatory pathways to facilitate tumor development. Individuals who are genetically predisposed to develop HP might be protected from cancer, but the tradeoff is a deeply wrinkled clinical phenotype. Solar elastosis tends to confer a yellowish hue to the skin, and this discoloration might indeed explain the increase in sallowness observed in HP.

The telangiectases observed in the AP group might be the result of collagen fragmentation, leading to an altered dermal ECM in which blood vessels become more clinically apparent. Telangiectatic photoaging was reported to be a distinct clinical entity from erythematotelangiectatic rosacea.[17] In telangiectatic photoaging, erythema and telangiectases were noted to be laterally distributed, and there was less transient and nontransient erythema compared with erythematotelangiectatic rosacea. Immunohistochemical analyses revealed less neurogenic mast cell activation and MMP-mediated ECM remodeling compared with erythematotelangiectatic rosacea. Telangiectatic photoaging is perhaps a subtype of the AP variant described here.

Recently, a photonumeric scale for atrophic photoaging was published, which will be useful in both the clinical and research realms.[26] Many skin aging scales exist, but the validity and reliability of most scales are poor.[27] Distinct photonumeric photoaging scales for AP and HP would likely be useful both for research and clinical care purposes. Tools to distinguish between AP and HP could have widespread implications for how photoaging is addressed in the relevant populations and might help to address whether different anti-aging regimens should be recommended for the distinct phenotypes. It is possible that approaches taken to treat AP and HP might differ. It would be valuable to study the effects of known anti-aging therapies, such as lasers and retinoids, on AP and HP and to understand if the response to treatment varies by the subtype. It would also be interesting to investigate whether the impact of early interventions to prevent photoaging differs between AP and HP.

Our results quantify the observed clinical and histologic differences between HP and AP. The reasons for the differences between these 2 distinct clinical phenotypes of photoaged skin might ultimately reflect fundamental differences in the responses of skin to sun exposure.

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