Research Article

Associations of Cumulative Sun Exposure and Phenotypic Characteristics with Histologic Solar Elastosis

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Abstract

Background: Solar elastosis adjacent to melanomas in histologic sections is regarded as an indicator of sun exposure, although the associations of UV exposure and phenotype with solar elastosis are yet to be fully explored.

Methods: The study included 2,589 incident primary melanoma patients with assessment of histologic solar elastosis in the population-based Genes, Environment, and Melanoma study. Ambient erythemal UV (UVE) at places of residence and sun exposure hours, including body site–specific exposure, were collected. We examined the association of cumulative site-specific and non–site-specific sun exposure hours and ambient UVE with solar elastosis in multivariable models adjusted for age, sex, center, pigmentary characteristics, nevi, and, where relevant, body site.

Results: Solar elastosis was associated most strongly with site-specific UVE [odds ratio (OR) for top exposure quartile, 5.20; 95% confidence interval (95% CI), 3.40-7.96; *P* for trend <0.001] and also with site-specific sun exposure (OR for top quartile, 5.12; 95% CI, 3.35-7.83; *P* for trend <0.001). Older age (OR at >70 years, 7.69; 95% CI, 5.14-11.52; *P* for trend < 0.001) and having more than 10 back nevi (OR, 0.77; 95% CI, 0.61-0.97; *P* = 0.03) were independently associated with solar elastosis.

Conclusion: Solar elastosis had a strong association with higher site-specific UVE dose, older age, and fewer nevi.

Impact: Solar elastosis could be a useful biomarker of lifetime site-specific UV. Future research is needed to explore whether age represents more than simple accumulation of sun exposure and to determine why people with more nevi may be less prone to solar elastosis. *Cancer Epidemiol Biomarkers Prev; 19(11); 2932–41. ©2010 AACR.*

Introduction

Melanoma risk is positively associated with intermittent sun exposure and may be modestly inversely associated with a high continuous pattern of sun exposure (1). Solar elastosis, which is generally considered to be a biomarker for cumulative sun exposure, is frequently found adjacent to melanoma in histologic sections and is available for assessment by pathologists. The distinguishing feature of histologic solar elastosis is accumulation of abnormal elastotic fibers in the upper and middle dermis, which may be related to activation of the human elastin promoter by UV radiation (2) or elastin degradation due to an influx of neutrophils that diffuse to the dermis in response to cytokine production after UVB exposure (3). In albino hairless mice, the UV erythema spectrum was the most predictive for elastosis quantified by computerized image analysis (4). The importance of understanding of the relationship of age, sun exposure behavior, and patient phenotype with solar elastosis among melanoma and other skin cancer patients is underscored by the use of solar elastosis as a biomarker in investigations of melanoma etiology (5-8) and outcome (9-13).

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Recent epidemiologic studies have explored environmental and personal determinants of skin damage, including whether there are separate effects of chronological aging and cumulative sun damage. These studies included people with basal cell carcinoma (BCC), squamous cell carcinoma (SCC) (14), or melanoma (5), or those who were drawn from the general population (15) and examined for either histologic solar elastosis (5, 14) or silicone cast score (5). Although severe solar elastosis was found to occur more frequently on sites that are more heavily exposed to the sun, no particular phenotypic determinant was identified in association with sun damage. Only one study sought to identify the most predictive measure of sun exposure (14).

The Genes, Environment, and Melanoma (GEM) study was able to estimate cumulative UV dose at the site of the melanoma for all participants by integrating reported site-specific sun exposure behavior with estimated ambient UV irradiance at residential locations throughout life. In addition to the personal sun exposure histories, a range of pigmentary characteristics for patients and pathology information for the melanomas was available. In this article, we aim to identify one or more measurements of sun exposure and the phenotypic or other personal characteristics that best predict histologic solar elastosis adjacent to the melanoma in incident primary cutaneous melanoma patients.

Materials and Methods

The participants in this study were patients with incident first or subsequent primary cutaneous melanoma diagnosed from 1998 through 2003 in the GEM study (16-18). GEM participants were ascertained from eight population-based cancer registries: two in Australia (New South Wales, Tasmania), two in Canada (British Columbia, Ontario), one in Italy (Torino), and three in the United States (Orange and San Diego Counties in California, New Jersey, and North Carolina).

The study protocol was approved by the institutional review board at the coordinating center, Memorial Sloan-Kettering Cancer Center, as well as the institutional review boards at each of the participating institutions. Physician approval was sought before contacting eligible participants, and all study participants provided informed consent. A total of 3,289 patients with incident primary cutaneous melanoma were enrolled from the eight centers. The participation rate was 53%, and participants tended to be slightly younger and were more likely to be female compared with the entire ascertained population (17).

Each participant provided informed consent to obtain diagnostic slides of their melanoma for a standardized pathology review. Expert dermatopathologists scored adjacent solar elastosis on the same slides as the melanomas by using a grading system (absent, mild/moderate, or severe) that correlated approximately to the chronic sun damage levels proposed by Landi et al. (8). The κ statistic, using the three categories, was 0.64 for scoring solar elastosis in a test set of 19 sections by three dermatopathologists who individually scored 70%, 20%, and 10% of the total slide collection. For the analyses in this report, solar elastosis was grouped as two categories, present (mild, moderate, severe elastosis) versus absent.

Phenotypic variables were assessed by items in a self-administered questionnaire for participant's natural hair color as a teenager, eye color, and skin color on the inside of the upper arm (16), and instructions for a count of nevi (moles) on the back, which, for analysis, were categorized as 0 to 10 and more than 10. Questions in a telephone interview asked for propensity to burn on first exposure to sunlight in summer in four categories as "no sunburn," "mild burn then peel," "painful burn then peel," "severe burn with blistering," and ability to tan on repeated exposure to sunlight in four categories as "go very brown and deeply tanned" to "get no suntan or get freckled only." Questions asked the number of each of painful and blistering sunburns at each decade of age in each of the warmer and cooler months and whether the melanoma site was usually burnt on these occasions; for analysis, these were dichotomized as any versus none.

UV measures

Each participant was asked in the telephone interview for his or her sun exposure hours in the warmer and cooler months of each decade of life (ages 10, 20, 30, and so on) up to his or her last completed decade of age. The warmer months in the Northern hemisphere were from April to September and the cooler months from October to March, and the opposite is true for the Southern hemisphere. To estimate total exposure hours for a typical week, the hours were summed for outdoor hours reported between 9 a.m. and 5 p.m. on work or school days and on nonworking days across warmer and cooler months. Additional questions at each decade of age asked for the frequency of clothing coverage of the melanoma site and frequency of wearing sunscreen on the site when outdoors in the warmer and cooler months. The interview also sought a lifetime history from age 15 years of hours spent in beach and water activities, which were known to be strongly associated with melanoma risk (16). Exposure hours were summed for each age interval, and appropriate hours were assigned to each decade of age. To estimate site-specific total sun exposure hours at each decade of age, we multiplied reported outdoor hours by the frequency of clothing coverage as follows: 0 (always or almost always covered), 0.25 (not always but more than half the time), 0.50 (about half the time), 0.75 (less than half the time), or 1.00 (never or hardly ever). Total site-specific sun exposure hours were summed from age 5 years and analyzed in categories defined by quartiles of subjects ranked in order by exposure. A measure of sunscreen use to the site was simply dichotomized as ever use or never use.

Using residential locations for each participant, ambient UV irradiance values were calculated for the warmer and cooler months at each decade of age. Erythemal UV
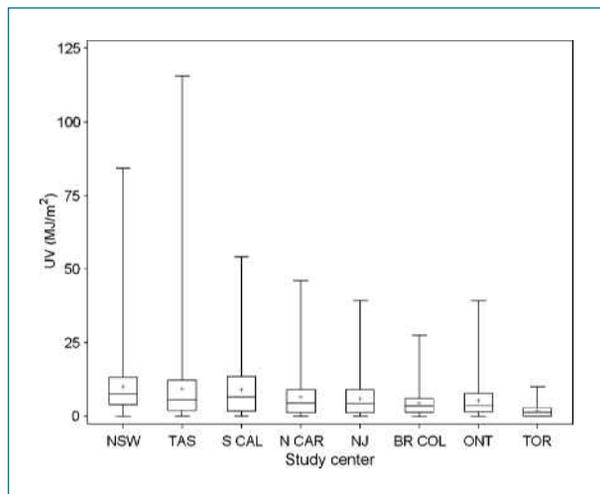
Figure 1. Cumulative site-specific UVE dose in MJ/m^2: mean, median, and interquartile range experienced at the body site by participants in GEM centers (NSW, New South Wales; TAS, Tasmania, Australia; S CAL, Southern California; N CAR, North Carolina; NJ, New Jersey, BR COL, British Columbia, Canada; ONT, Ontario, Canada; TOR, Torino, Italy). Site-specific UVE dose was calculated as total ambient UVE (estimated by the National Center for Atmospheric Research (NCAR) for each participant's place of residence at each decade of age) for an assumed average 8 hours a day multiplied by the proportion of total sun exposure hours that the site was exposed for each participant. This sun exposure measure takes into account both site-specific sun exposure behavior and ambient UV irradiance.

(UVE) irradiances were calculated as wavelength integrated spectral irradiance between 250 and 400 nm, weighted by the Commission Internationale de l'Eclairage erythemal sensitivity function (19), which gives greater weight to shorter wavelengths. The tropospheric UV-visible model "TUV" (20) was used to calculate daily, location-specific irradiances as a function of solar zenith angle, ozone column, and surface elevation, as described by Lee-Taylor et al. (21). The model used a discrete ordinates method (22) and a pseudospherical correction (23). Corrections for variations in the Earth-Sun distance and for cloud cover (24) were applied. Ozone column and cloud reflectivity data were obtained from the satellite-borne Total Ozone Mapping Spectrometer (25-27) version 7, for November 1978 to June 2000. Location-specific UVE, UVA (320-400 nm unweighted), and UVB (280-320 nm unweighted) irradiance estimates from the 1978 to 1989 climatology were applied to all participant exposure dates before 1990, and values from the 1990 to 2000 climatology were applied to exposure dates from 1990 onward.
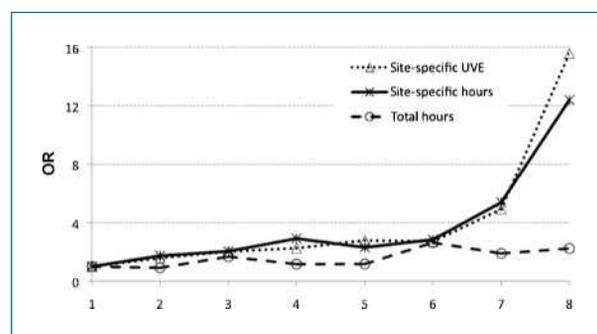
We estimated a cumulative site-specific UV dose for each of UVE, UVA, and UVB as the total ambient UV for an assumed average 8 hours a day multiplied by the proportion of total sun exposure hours for which each participant reported exposure of the site. The seasonal values for warmer months and cooler months were combined for an annual dose and totaled over a lifetime from age 5 years. UVE, UVA, and UVB were all highly correlated ($R^2 > 0.99$), although ambient UVB irradiance is more sensitive to the slant ozone column amount than ambient UVA. Thus, in this report, we present the analyses for UVE alone. The median and interquartile range for cumulative site-specific UVE in participants in each GEM center is presented in Fig. 1. Site-specific beach and water UVE dose was calculated in a similar fashion to total dose, substituting beach and water hours for total outdoor hours.

Statistical analysis

Age in these analyses was the patient's age at diagnosis of the melanoma for which the dermatopathologist scored solar elastosis in adjacent skin. GEM-wide quantiles were used in these analyses to categorize sun exposure variables into quarters of exposure for presentation in the tables and into eighths for presentation in Fig. 2, using cut points based on the exposure distribution in all participants. We examined the association of demographic, phenotypic, and sun exposure variables with solar elastosis and estimated odds ratios (OR) and 95% confidence intervals (95% CI) for the presence of solar elastosis with reference to none, calculated in logistic regression models adjusted for age as a continuous variable, sex, and study center, which was included as a covariate to adjust for differences in reviewing pathologists and percentages of diagnostic slides available in different centers. Tests for linear trend used the Wald test and modeled each covariate as a single continuous variable. All significance tests were two-sided. SAS (SAS Institute) version 9.2 was used for all analyses.

We assessed the strength of the association between solar elastosis and total reported hours of sun exposure, total site-specific hours (when the body site was exposed), ambient UVE at residential locations, total site-specific UVE (that is, integrating reported sun exposure behavior

Figure 2. ORs for solar elastosis on all body sites in 2,304 GEM participants: cumulative sun exposure measures in eight ordered categories containing equal numbers of participants in models adjusted for age, sex, center, pigmentary characteristics, and nevi. Site-specific exposure was also adjusted for body site (head and neck, trunk, arms, legs). Total hours and site-specific hours of sun exposure were reported by participants; site-specific UVE was calculated as total ambient UVE for an assumed average 8 hours a day multiplied by the proportion of the total sun exposure hours that the site was exposed for each participant.

and UVE), each in quartiles with the lowest quartile as the reference, and site-specific beach and water UVE in exposure tertiles with no exposure as the reference. Site-specific hours and UVE were also modeled as continuous variables, and we present the odds per 1,000 hours and per megajoule per square meter (MJ/m^2) of exposure, respectively. The effect of age was examined in separate analyses as a categorical and a continuous variable. Before modeling with the continuous variables, we confirmed that there was a linear relationship with solar elastosis by plotting each variable in turn against the log odds of solar elastosis (25). The approach to assessing sun exposure effects was to model each sun exposure variable with adjustment for age, sex, and center, and to include as covariates the phenotypic characteristics back nevi, hair, eye and skin color, ability to tan, and propensity to burn. Models for site-specific sun exposure also included a four-category variable for body site of the melanoma as head and neck, arms, legs, and trunk. To explore the extent to which age was an independent correlate of solar elastosis, we compared the estimates for age adjusted only for sex and center and when included in the multivariable model of sun exposure and phenotypic characteristics.

In addition to examining the size of any change in odds for solar elastosis and its statistical significance, we used the Akaike information criterion (AIC) to compare models and select the best-fitting model to explain the observed data, given the candidate set of models (28). We calculated the corrected AIC (AIC_c) values, which include a bias adjustment for the number of parameters relative to the sample size, and considered the best model as the one with the smallest AIC_c.

Results

Of the 3,289 participants with incident primary melanomas in the GEM study, 2,746 (83.5%) had slides available for review. After pathology slide review, participants were excluded if solar elastosis was not scored due to insufficient adjacent tissue ($n = 95$) or if the lesion was judged not to be melanoma by the reviewing pathologist ($n = 62$). The 2,589 (94.3% of 2,746) melanomas included had histologic solar elastosis adjacent to their melanoma scored as absent, mild-moderate, or severe; 1,805 (69.7%) had solar elastosis present. The mean age of these 2,589 participants was 58.9 years, and 56.4% were male. Most sites of melanoma were on the trunk (43.0%), whereas the lower extremities (19.8%), upper extremities (18.5%), and head and neck (18.1%) had approximately equal proportions; site was unknown for 0.6%.

Risk of solar elastosis increased substantially with age to OR 11.91 at 70+ years, with reference to 11 to 40 years (Table 1). The OR for each year of age was 1.05 (95% CI, 1.04-1.06). More men than women had solar elastosis (59.6% versus 49.0%) although the OR for solar elastosis in men, relative to women, was close to 1.0 when adjusted for age and study center. The odds for solar elastosis

by tertile of age were reasonably similar for men and women together and separately, although the increase with age was steeper in women than in men (Table 1; P for interaction = 0.05). Solar elastosis was more common on the head and neck and arms than the trunk or legs ($P < 0.001$; Table 1).

Dark hair (OR, 1.38; 95% CI, 1.08-1.77) and light eye color (OR, 1.37; 95% CI, 1.04-1.80) showed the strongest evidence of a positive association with solar elastosis when all phenotypic variables were fitted together in one model adjusted for age, sex, and center. There was weaker evidence that odds of solar elastosis increased with red hair (OR, 1.21) and skin that sunburned with blistering (OR, 1.47; Table 2). When site-specific UVE dose was also included in the multivariable model, the effects of hair and eye color weakened. Moreover, there was evidence of a stronger trend in the odds for solar elastosis as tanning ability decreased or sunburning increased (Table 2). The effects of the pigmentary variables were substantially similar when examined in a multivariable model of all pigmentary variables (as in Table 2) and when each variable was examined separately adjusted only for age, sex, and center (results not shown).

Having >10 nevi on the back, relative to <10, reduced the odds of solar elastosis (OR, 0.80; 95% CI, 0.65-0.98; $P = 0.03$) and was little changed when adjusted for pigmentary variables, except that the P value was 0.07 (data not shown). Addition of site-specific UVE dose caused the effect of back nevi to slightly increase to OR 0.77 (95% CI, 0.61-0.97) for >10 nevi ($P = 0.03$). In additional analyses, we found that the reduced odds for solar elastosis associated with the nevus propensity was mainly present for the trunk, arms, and legs (OR, 0.75; 95% CI, 0.59-0.96; $P = 0.02$) and was not at all evident for the head and neck (OR, 1.12; 95% CI, 0.36-3.49; $P = 0.84$), but the P value for interaction was 0.61.

Age was strongly and independently associated with elastosis in a model including site-specific UVE, phenotypic variables, and back nevi. The addition of these variables, however, reduced the odds for age by 1% for each year of age from OR 1.06 to 1.05 (95% CI 1.04-1.06) and by 35% at 70 years and older from OR 11.91 to 7.69 (95% CI 5.14-11.52), relative to 11 to 40 years, for men and women together and somewhat more in women (−40%) than men (−25%) of this age.

Solar elastosis was associated most strongly with estimates of cumulative sun exposure to the body site. Site-specific sun exposure hours increased the odds for solar elastosis to an OR of 5.12 for the top exposure quartile (Q4; P for trend <0.001; Table 3), and the OR for the continuous measure was 1.05 (95% CI, 1.03-1.06; $P < 0.001$) for each 1,000 site-specific hours. Inclusion of ambient UVE in this measure to give site-specific UVE dose increased the OR to 5.20 for Q4 (Table 3), and the OR for the continuous measure was 1.11 (95% CI, 1.08-1.14; $P < 0.001$) per MJ/m^2. Total outdoor hours without consideration of exposure of the body site or UVE increased the odds for solar elastosis to an OR of 2.13 for Q4 (P for

Table 1. Age, sex, and body site in relationship to histologic solar elastosis in participants in the GEM study (N = 2,589)

Characteristic	Solar elastosis		Present vs absent solar elastosis	P
	Absent n = 785	Present n = 1,804	OR* (95% CI)	
Sex				
Female	400	728	1.00	
Male	385	1,076	0.99 (0.81-1.21)	0.93
Age (y)				
11-40	216	162	1.00	
41-50	185	210	1.78 (1.30-2.43)	
51-60	181	355	3.50 (2.58-4.76)	
61-70	102	434	8.18 (5.84-11.45)	
71-97	101	643	11.91 (8.55-16.59)	<0.001
Age (y) by sex				
Male				
11-50	141	151	1.00	
51-70	172	490	3.32 (2.43-4.55)	
71-97	72	435	7.16 (4.96-10.34)	<0.001
Female				
11-50	260	221	1.00	
51-70	111	299	4.10 (2.97-5.65)	
71-97	29	208	11.50 (7.18-18.42)	<0.001
Body site				
Trunk/pelvis	449	665	1.00	
Head/neck	30	438	9.26 (6.08-14.11)	
Arms	71	409	5.32 (3.84-7.35)	
Legs	229	283	0.99 (0.76-1.29)	<0.001

*OR for sex adjusted for age (continuous) and study center; ORs for age adjusted for sex and center; ORs for age by sex adjusted for center. ORs for body site adjusted for age (continuous), sex, and study center.

trend < 0.001), whereas cumulative ambient UVE, as a nonspecific measure based only on places of residence, had no evident association with solar elastosis (OR, 1.29 for Q4; P for trend = 0.49) although the inclusion of center as a covariate to account for different pathology reviewers in different centers would have substantially limited between-subject variation in UVE in this analysis. We also examined site-specific UV dose for hours spent in beach and water activities as a measure of recreational sun exposure. The odds for the highest exposure tertile, with reference to no beach and water activities, was OR 2.37 (95% CI, 1.70-3.30; P for trend <0.001). All sun exposure models were adjusted for age, sex, center, and all phenotypic variables; site-specific measures were also adjusted for body site.

Site-specific UVE seems to be the best predictor of solar elastosis in these data. For exposure in quartiles (Table 3), the AIC$_c$ was lowest for site-specific UVE (AIC$_c$ = 2,006), although only slightly different to the value for site-specific sun exposure hours (AIC$_c$ = 2,007). Total sun exposure hours without site specificity did not fit the data well (AIC$_c$ = 2,279). The evidence that site-specific

UVE was the best measure of UV exposure was stronger when exposure measures were modeled as continuous variables (AIC$_c$ = 1,994 for site-specific UVE, 1,999 for site-specific exposure hours, and 2,278 for total exposure hours only). This hierarchy of cumulative sun exposure measures is clearly evident when ORs for exposure in eight categories are plotted graphically for all body sites together (Fig. 2).

In separate analyses by body site, the odds for solar elastosis were high for site-specific UVE to the head and neck (OR, 1.70; 95% CI, 0.26-11.13 for Q2; OR, 4.13; 95% CI, 0.71-24.14 for Q3; OR, 17.95; 95% CI, 2.52-128.15 for Q4; P = 0.002) whereas the odds for the trunk, arms, and legs were overall similar to the estimates in all participants (OR, 1.70; 95% CI, 1.26-2.30 for Q2; OR, 2.24; 95% CI, 1.60-3.12 for Q3; OR, 4.88; 95% CI, 3.13-7.62 for Q4; P < 0.001). The P for interaction by body site was 0.23. Almost all lesions on the head and neck (94%) were positive for solar elastosis, and most (59%) were rated as severe. After excluding head and neck lesions, the estimates for exposure categorized in eighths were very similar to those presented for all lesions in Fig. 2.

All models were adjusted for age, sex, center, and phenotypic characteristics.

Sunburn history showed no evidence of an association with solar elastosis in separate analyses of any site-specific painful sunburn (OR, 1.02; 95% CI, 0.79-1.32; $P = 0.88$) or blistering sunburn (OR, 0.95; 95% CI, 0.70-1.31; $P = 0.77$) relative to none in each case. Site-specific sunscreen use similarly had no apparent association with solar elastosis (OR for ever use, 1.18; 95% CI, 0.94-1.48; $P = 0.15$). In separate analyses of site-specific UVE in users and nonusers of sunscreen on the site, ORs in users were lower (OR, 1.32; 95% CI, 0.89-1.98 for Q2; OR, 2.22; 95% CI, 1.40-3.53 for Q3; OR, 4.53; 95% CI, 2.40-8.53 for Q4; P for trend < 0.001) than in nonusers for each exposure category, especially Q4 (OR, 2.06; 95% CI, 1.21-3.50 for Q2; OR, 2.81; 95% CI, 1.64-4.83 for Q3; OR, 8.47; 95% CI, 4.16-17.23 for Q4; P for trend < 0.001; P for interaction = 0.09). All analyses were adjusted for age, sex, center,

and phenotypic variables; the model for sunburn also included site-specific UVE and body site, and the model examining site-specific UVE by sunscreen use also included body site.

Discussion

We found that cumulative site-specific UVE dose had a strong positive dose-response relationship with histologic solar elastosis adjacent to melanomas. Additionally, site-specific UVE dose was the best of a number of sun exposure measurements in accounting for solar elastosis, judging by the AIC statistic. We also found that solar elastosis had a strong positive association with age even after adjusting for cumulative site-specific UVE dose, and that elastosis occurred more frequently in skin on the sun-exposed head and neck and the arms than on the lesser exposed trunk and legs. Having more than 10 nevi

Table 2. Pigmentary characteristics as correlates of histologic solar elastosis in participants in the GEM study ($n = 2,434$)

Characteristic	Solar elastosis		Present vs absent solar elastosis	P	Present vs absent solar elastosis	P
	Absent	Present				
	$n = 740$	$n = 1,694$	OR* (95% CI)		OR† (95% CI)	
Hair color						
Light hair (light brown, blonde)	480	1,011	1.0		1.0	
Dark hair (dark brown/black)	192	508	1.38 (1.08-1.77)		1.32 (1.00-1.73)	
Red	68	175	1.29 (0.90-1.85)	0.02	1.25 (0.83-1.87)	0.11
Eye color						
Dark eyes (brown, black)	153	282	1.0		1.00	
Light eyes (blue, gray, green, hazel)	587	1,412	1.37 (1.04-1.80)	0.02	1.20 (0.89-1.64)	0.24
Skin color						
Brown/dark olive/light olive	94	194	1.0		1.00	
Fair	503	1,162	1.17 (0.83-1.65)		1.10 (0.76-1.61)	
Very fair	143	338	1.08 (0.71-1.64)	0.56	0.82 (0.52-1.30)	0.14
Ability to tan						
Deep tan	125	257	1.0		1.00	
Moderate tan	321	666	0.97 (0.71-1.32)		1.11 (0.79-1.57)	
Mild or occasional tan	218	519	1.11 (0.79-1.57)		1.24 (0.85-1.82)	
No suntan at all or freckle only	76	252	1.15 (0.73-1.80)	0.70	1.64 (0.99-2.71)	0.26
Propensity to burn						
No sunburn	53	126	1.0		1.00	
Mild burn followed by some tanning	346	754	1.05 (0.69-1.59)		1.43 (0.90-2.28)	
Have a painful sunburn with peeling	293	645	1.12 (0.72-1.73)		1.70 (1.04-2.77)	
Get a severe sunburn with blistering	48	169	1.47 (0.83-2.58)	0.47	1.97 (1.05-3.68)	0.12

*Adjusted for age (continuous), sex, study center, and all variables in the table.
†Adjusted for age (continuous), sex, study center, and all other variables in the table, including site-specific sun exposure; also adjusted for body site; includes only participants with sun exposure information.

Table 3. The relationships between solar elastosis and lifetime cumulative sun exposure measures in participants in the GEM study (n = 2,304)

| Cumulative sun exposure | Solar elastosis | | Present vs absent solar elastosis | |
| | Absent n = 697 | Present n = 1,607 | Adjusted for pigmentary characteristics and nevi | |
			No OR* (95% CI)	Yes OR† (95% CI)
Site-specific measurement‡				
Site-specific sun exposure hours				
Quartile 1	262	302	1.00	1.00
Quartile 2	215	365	1.66 (1.24-2.21)	1.80 (1.34-2.41)
Quartile 3	171	406	1.69 (1.24-2.31)	1.86 (1.35-2.56)
Quartile 4	49	534	4.33 (2.87-6.53)	5.12 (3.35-7.83)
P for trend			<0.001	<0.001
Site-specific beach and water UVE dose				
None	258	464	1.00	1.00
Tertile 1	208	328	1.24 (0.93-1.66)	1.32 (0.99-1.78)
Tertile 2	138	393	1.66 (1.23-2.26)	1.85 (1.35-2.53)
Tertile 3	104	443	2.06 (1.50-2.83)	2.37 (1.70-3.30)
P for trend			<0.001	<0.001
Site-specific UVE dose				
Quartile 1	265	292	1.00	1.00
Quartile 2	232	348	1.53 (1.15-2.04)	1.66 (1.24-2.23)
Quartile 3	154	427	1.91 (1.40-2.61)	2.11 (1.53-2.91)
Quartile 4	46	540	4.41 (2.91-6.69)	5.20 (3.40-7.96)
P for trend			<0.001	<0.001
Non–site-specific measurement				
Total sun exposure hours				
Quartile 1	276	284	1.00	1.00
Quartile 2	187	386	1.41 (1.05-1.88)	1.47 (1.10-1.98)
Quartile 3	143	456	1.66 (1.20-2.29)	1.75 (1.26-2.43)
Quartile 4	91	481	1.96 (1.34-2.86)	2.13 (1.45-3.12)
P for trend			<0.001	<0.001
Ambient UVE				
Quartile 1	322	235	1.00	1.00
Quartile 2	186	365	1.05 (0.72-1.54)	1.07 (0.73-1.58)
Quartile 3	120	471	1.12 (0.65-1.93)	1.16 (0.67-2.01)
Quartile 4	69	536	1.23 (0.59-2.55)	1.29 (0.61-2.70)
P for trend			0.56	0.49

*Adjusted for age (continuous) sex, and center.
†Adjusted for age (continuous), sex, center, pigmentary characteristics (hair, eye and skin color, ability to tan, propensity to burn), and back nevi.
‡Site-specific sun exposure measures also adjusted for body site of melanoma.

on the back reduced the overall chance of solar elastosis. In addition to high cumulative sun exposure, our results indicate that older age and a tendency to fewer nevi were the personal characteristics that increased the chance of solar elastosis.

The strong positive association of histologic solar elastosis with cumulative sun exposure in GEM supports similar findings in previous studies that examined histologic solar elastosis in skin cancer patients (5, 14) or photoaging ratings in silicone skin casts in the general population (15). The link to cumulative exposure was consistent across sunlight environments from high levels of Queensland sun (5) to low levels in New Hampshire (14), across a wide latitude range at 27°S to 43°S (15), and now internationally in our study. All studies measured sun exposure behavior individually in participants, but only GEM and the New Hampshire study (14) used site-specific measurements; others used a composite of weekend outdoor hours and residential UVE (15) or broad categories of cumulative exposure (5). Rates of

sun damage were high, with moderate or severe elastosis in 70% of Queensland (5) and GEM melanoma patients, and 90% or more of New Hampshire BCC and SCC patients (14). Australian residents also had high skin damage scores (3.9 and 4.9 for each hand on a scale of 6; ref. 15). The finding in GEM that high levels of sun exposure increased the chance of solar elastosis more on the head and neck than at other body sites was in agreement with studies that directly measured sun exposure (5, 14) or examined tissue (5, 12, 29) at different body sites. Unlike the very strong and consistent association with cumulative sun exposure, site-specific lifetime recreational sun exposure increased the odds for solar elastosis but not strongly in our study, and only for intermediate exposure levels in the New Hampshire study (14) or not significantly in Queensland patients (5).

Karagas et al. (14) were the first to report the strong association of solar elastosis with cumulative sun exposure to the site, but did not present results for nonspecific measures and did not incorporate ambient UV as we did. The strong associations we observed in GEM for site-specific exposure can be ascribed to reducing exposure misclassification and giving weight to the environment by incorporating ambient UV and site-specific exposure hours into a single measure. We have shown that adding environmental UVE to self-reported sun exposure hours can improve site-specific sun exposure measurement. The results of our study support the use of solar elastosis as a biomarker of cumulative sun exposure in epidemiologic studies that collect skin tissue.

The positive correlation of age with solar elastosis agrees with the greater prevalence at older ages in New Hampshire, especially in women (14), and in Australia (5, 15, 30). Both age and cumulative sun exposure were independently associated with solar elastosis in our study and potentially also in the United States and Australian studies, which both mention that adjusting for age did not weaken the relationship with cumulative sun exposure. They do not, however, report estimates for age when adjusted for sun exposure (14, 15). The strong association with age may be due to a contribution of intrinsic aging to solar elastosis or to the accumulation of UV exposure with age that is not fully addressed by adjusting for sun exposure in the epidemiologic studies or to other unmeasured variables. We expect that future studies, perhaps incorporating site-specific UVE measurements, will attempt to disentangle the contributions of aging and sun exposure in causing sun-related conditions such as solar elastosis or skin cancer.

Our observation that a high nevus count on the back in the GEM study reduced the odds of solar elastosis by 20% is consistent with the Queensland study in which there was some evidence that greater numbers of nevi may have reduced the odds for solar elastosis, based on patient numbers (5), and the Australian general population study in which having any nevi reduced the odds of sun damage to 0.39 (95% CI, 0.23-0.66; ref. 15).

Sun exposure is positively associated with both nevus count (31) and the presence of solar elastosis. Thus, we could reasonably expect the nevus propensity to be associated with a greater likelihood of solar elastosis. Instead, the available evidence indicates that solar elastosis was less likely in the presence of a higher nevus count (5) even after controlling for sun exposure and sun sensitivity (see Table 3; ref. 15). Because nevi are genetically determined (32-34), there may be a genetic component to the resistance to solar elastosis. In our study, the reduced OR for solar elastosis associated with the nevus propensity was due mainly to solar elastosis on the trunk, arms, and legs. We suggest that being less prone to solar elastosis and possibly other forms of sun damage such as solar keratoses (14) may be another element in the dual pathway hypothesis under which a person predisposed to nevi requires less sun exposure to develop melanoma (35, 36). The hypothesis does not currently specify an element of resistance to sun damage in this pathway.

Our results for phenotype are moderately supportive of the importance of a sun-sensitive phenotype for solar elastosis (15). Reduced tanning ability and a severe sunburn response to unprotected exposure were each associated with solar elastosis in our study and strengthened on adjustment for sun exposure, although not significantly so; however, there was no strong and consistent effect of skin or hair color. Similarly, tanning and skin color (assessed by colorimeter) had no evident effect either way on solar elastosis in BCC and SCC patients (14), whereas the Queensland study did not report on pigmentary characteristics (5). There may not yet be sufficient evidence for the role of host phenotype in the development of skin damage. The lack of prominence for phenotype, especially fair skin, in association with solar elastosis in studies of normal skin in skin cancer patients may be due to most patients having fair skin (88% had fair or very fair skin in GEM).

Sunburn is considered to be a measure of intermittent sun exposure. Unlike the strong relationship with cumulative site-specific UVE, sunburn had no evident association with solar elastosis in our study or the New Hampshire study (14). A possible explanation is that people who burn readily may accumulate less time in the sun and thus are less likely to experience marked solar elastosis. Having sunburns or blistering sunburns, however, had a 2-fold or more increased odds of sun damage after adjusting for cumulative whole-body sun exposure, but not pigmentary characteristics, in the Australian general population study (15). There is no ready explanation for this inconsistency. Possibilities include differences in the nature of skin damage when measured by skin cast or histologic assessment, differences due to the body site examined because the back of the hand is less susceptible to skin cancer, or the possibility of confounding with an underlying genetic component (37) that is more common in people with skin cancer than in the general population. Another possibility is that

the high UV environment of the Australian population offered a greater opportunity to experience sunburn (87% reported any sunburn, 66% blistering sunburn; ref. 15) than in GEM (64% any sunburn, 45% blistering sunburn) or New Hampshire (57% painful sunburn; ref. 14). We interpret the lack of an effect of sunburn on solar elastosis in the skin cancer studies as further support for the contribution of cumulative sun exposure, and not intermittent sun exposure, to solar elastosis.

Our finding that the risk of solar elastosis was higher for site-specific UVE in people who reported no sunscreen use on the body site than in users is the first report of an apparently protective effect of sunscreens against this type of sun damage. It is, however, consistent with a strong inverse dose-response relationship between amount of sunscreen used regularly and development of new solar keratoses and remission of existing ones (38), and with prevention of SCC, but not BCC, by recent use of sunscreens (39).

Among the advantages of this report are the standardized histopathology review by expert pathologists of all melanoma slides, including the scoring of solar elastosis; the study's large international population base, accounting for potential confounding by phenotype; and the detailed sun exposure measurements integrating behavior with objective ambient UV measurements and restricting exposure to times when the site was exposed to the sun. All participants had melanoma and were unlikely to be aware of whether they had solar elastosis or not, thus minimizing the potential for recall bias.

The measures incorporating behavior, however, may have inaccuracies due to error in self-reported exposure hours over a lifetime. Our site-specific UVE dose may have other sources of error because it included only exposure hours between 9 a.m. and 5 p.m. (up to 15% of ambient UVE falls outside of 9 a.m.–5 p.m.; see ref. 40) and could make no allowance for variation in ambient UVE irradiance between 9 a.m. and 5 p.m.

Variables used in the modeling were not predictive of missing data for solar elastosis, except for center location, which was mainly due to the different percentages of participants with diagnostic slides available for review. Although all study participants had melanoma and thus our results might be considered not to apply more widely, the consistency of our results with the strong association of cumulative UVR dose and skin damage reported in the general population (15) supports their wider applicability.

We found that solar elastosis was strongly associated with cumulative lifetime site-specific UV dose. This relationship is biologically plausible. Our study was the first to show the extent of the improvement gained in evaluating the relationship between sun exposure and solar elastosis by using site-specific measurements and, additionally, the stronger effect estimates that resulted from accounting for ambient UV. We conclude that solar elastosis could be a useful biomarker of cumulative sun exposure in epidemiologic studies that collect skin biopsies. The strong relationship of solar elastosis with age could indicate the possibility of an explanation other than a simple accumulation of sun exposure over time. Finally, the inverse, independent relationship with number of nevi may suggest that people with a genetic predisposition to nevi may be less prone to sun damage. Future studies would usefully include possible genetic markers of relevance, including any that may be related to solar elastosis.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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