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Skin microtopography as a measure of photoaging and risk of squamous cell carcinoma of the skin in a US population

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Abstract

Background—Skin microtopography as a measure of photoaging is a non-invasive approach to measuring chronic ultraviolet radiation (UVR) exposure, and reflects the degree of dermal elastosis in populations of European descent in the subtropics. Less is known about the utility of this approach in populations at different latitudes, and whether it relates to skin cancer risk.

Methods—A population-based case-control study of 342 SCC cases and 331 age- and gender-matched controls were evaluated for histologic evidence of solar damage and severity of photoaging based on microtopography on a six-grade scale. Odds ratios for SCC associated with degree of photoaging were estimated using logistic regression analysis adjusted for potentially confounding factors.

Results—After adjustment for known risk factors, SCC was associated with increasing photoaging grade (OR = 1.7, 95% CI = 0.9–3.0 for severe photoaging; OR = 2.8, 95% CI = 1.6–5.0 for very severe photoaging). Associations remained among those with actinic keratosis (OR = 3.4, 95% CI = 0.9–12.4 for severe photoaging, OR = 5.7, 95% CI = 1.7–19.6 for very severe photoaging).

Limitations—There was limited statistical power, particularly for subgroup analyses.

Conclusion—Our findings provide further evidence of microtopography as an independent, objective indicator of risk of SCC.

Keywords

Microtopography; photoaging; squamous cell carcinoma; ultraviolet radiation

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Introduction

Photoaging is the damaging process by which ultraviolet radiation (UVR) alters the properties of the skin resulting in visually apparent changes including increased numbers of wrinkles and loss of elasticity. Histopathologic features include decreased epidermal thickness, alterations in the amount and type of dermal collagen, and disorganization of elastin fibers (elastosis). [1–3] In previous studies, extent of elastosis in normal skin has been related to amount of sun exposure over a person's lifetime on the head and neck.[4,5] Thus, while also influenced by skin color (extent of melanin in the skin), the accumulation of elastin is considered an objective measure of chronic sun exposure in populations of European descent. The clinical utility of this is as yet unclear. Various photoaging scales have been developed, although mostly for cosmetic applications.[6]

An objective measure of UVR exposure could be valuable for epidemiologic studies because there is often discordance between self-reported and actual UVR exposure as identified by histologic examination, and imperfect test-retest reliability of sun exposure questionnaires.[7,8] Yet, it is not typically possible to obtain and review skin biopsies from participants due to the invasive nature of the procedure and the requirement for trained medical personnel for both the collection and assessment of the samples. Moreover, potential subjects may be deterred from participating in studies involving normal skin biopsies, increasing the likelihood of incomplete data and the introduction of selection bias.

Skin surface microtopography is an alternative to histopathologic grading of dermal elastosis and comprises the fine, interwoven lines and ridges of the skin surface.[9,10] Predictable changes in the skin surface occur with chronic sun exposure including progressive loosening of the basket weave pattern and overall skin laxity.[6,11–14] Skin microtopography can be captured simply using silicon impressions, which viewed under a 10-power microscope and graded using a six-tiered system proposed by Beagley and Gibson.[15,16] This system has been validated in an Australian population-based cohort <70 years old.[13] Previous studies also from Australia found positive associations with higher cutaneous microtopography grade in relation to other objective measures of sun exposure, including clinical assessment of degree of solar elastosis and number of actinic keratoses.[16,17] Skin cancer risk has been less studied in relation to cutaneous microtopography. One Australian study reported an association with patient reported history of "nonmelanoma skin cancer"[16] and another study found an association with histologically confirmed BCC. An association with SCC was less clear in this study possibly due to the relatively small number of cases (n=45).[17]

Few studies on photoaging in populations further from the equator exist, leaving uncertainty as to whether findings apply to populations with lower ambient UVR levels. One study from England of women ages 18–46 found no relation between time spent abroad and degree of photoaging,[18] but, it did not evaluate others measures of UVR exposure nor associations with skin cancer occurrence. As part of a population-based case-control study of keratinocyte cancer, we sought to investigate the relation between skin surface microtopography and risk of cutaneous SCC in a U.S. population living at northern latitudes, away from the equator.

Materials and Methods

Histologically confirmed cases of newly diagnosed invasive SCC, among residents of New Hampshire aged 25 to 74 year old from July 2009–August 2011, were identified through a network of dermatology and dermatopathology practices in New Hampshire and surrounding regions.[19] Controls were chosen from either the Center for Medicare and Medicaid services (≥65 years old) or from driver's license records provided by the New Hampshire Department of Transportation (<65 years old). Controls were frequency matched by gender and age (25–35, 36–45, 46–50, 51–59, 60–64, 65–69, and 70–74 years) and assigned comparable reference dates and anatomic sites to the cases. For this study, we restricted our analysis to subjects between 25 and 69 years old as microtopography has only been validated in subjects up to age 70 and may not apply to older individuals.[13] To be eligible, participants were required to be English-speaking and with a working telephone number. Cases and controls were interviewed concurrently and interviewers were masked to the case-control status of study participants and study hypotheses. This study has been approved by the Committee for the Protection of Human Subjects at Dartmouth College, the authors' Institutional Review Board, and the Declaration of Helsinki protocols were followed. Informed consent was obtained in accordance to the Committee for the Protection of Human Subjects at Dartmouth College.

Detailed personal interviews were performed (usually at the participant's home) to ascertain information on demographic characteristics, skin sensitivity to the sun, lifetime sun exposure history, and medical history including prolonged use of non-steroidal anti-inflammatory drugs (NSAIDS) (use defined as 4 times a week for at least a month) and photosensitizing drugs (defined as use of known photosensitizing agents for at least a month) prior to the reference date.[20,21] For cases, we requested the original diagnostic pathology materials, which underwent standardized histopathologic re-review by a study board-certified dermatopathologist (AP).[5] The degree of solar elastosis of the dermis adjacent to the tumor was graded as follows: mild elastosis referred to single, scattered, blue-gray elastotic fibers; moderate elastosis, clumps of elastotic fibers with intervening normal papillary dermis; and severe elastosis, near or complete replacement of the papillary dermis by clumped elastotic fibers and/or amorphous masses of elastotic material. We also documented the presence of actinic keratosis in the skin adjacent to the tumor, a benign UVR-induced skin lesion, a proportion of which are SCC precursors. [21] An actinic keratosis was defined by the presence of cytologically atypical epithelial cells confined to the epidermis with dysplastic features limited to the lower epidermis.

During the interview, participants (cases and controls) were asked to hold a wooden cylinder (approximately 3 cm in diameter) while a silicon mold of the back of the left hand was taken (approximately 1 inch in diameter) avoiding cuts, scars, moles, major veins, or other raised areas of the skin, using CutterSil Light silicon mold solution (Heraeus Kulzer, South Bend, IN). There were no anatomic variations or skin grafts that required the use of the right hand. Molds were graded under 10 power magnification of the silicon mold impression using the Beagley and Gibson 6 grade system, where grade 1 (least photoaged) represented undamaged skin characterized by fine surface lines, evenly spaced, of uniform depth, and arranged in a two-directional network and grade 6 (most photoaged) was characterized by a

flattened surface, loss of vertical lines, and occasional horizontal lines that were significantly deepened.[15]

Severity of photoaging was defined using moderate (grades 3 and 4), severe (grades 5), and very severe (grade 6) categories due to the sparse number of participants in the lower grades (e.g., only one participant with grade 3, and none with grades 1 or 2). A single trained reader graded all molds. We computed odds ratios of SCC associated with skin grade overall using moderate photodamage as the reference group. We further computed odds ratios by severity of photoaging by strata of skin sensitivity to first solar exposure (tendency to tan or burn after one hour of sun exposure for the first time in summer), gender, use of NSAIDs, and previous use of photosensitizing medications (yes/no)[21] and by subgroups based on anatomic site of the tumor (head and neck or other), presence or absence of actinic keratosis and degree of histologic solar elastosis. We used logistic regression models adjusted for age, gender and skin type (unless stratified by these factors) in the statistical package SAS® v9.2.

Results

In the overall study (reference ages 25 –74 years old), a total of 698 cases and 763 controls were confirmed eligible for inclusion. Of those, 548 (78.7%) cases and 535 (70.1%) controls were interviewed. Of the cases, 465 (85%) consented for pathologic re-review and materials were requested from pathology laboratories; 393 (85%) were received. Sufficient diagnostic tissue for SCC confirmation was present in 387 (98%) cases and 367 (93%) had sufficient tissue adjacent to the tumor for evaluation for the actinic keratosis and solar elastosis. For the current study of subjects with reference age 25 to 69 years old, skin impressions were evaluated for microtopography in 346 subjects with histologically confirmed SCC and 331 age- and gender-matched controls. The younger age group for this study had more men (67.7% men ≥70 years old vs. 56.6% men 26–69 years old; p-value <0.001), but had no appreciable difference in the distribution of skin reaction to first sun exposure (tan, sunburn then tan, painful sunburn then peel, painful sunburn then blister) (data not shown). Ultimately, microtopographic scoring of photoaging with clear and readable silicone impressions were available on 333 SCC cases and 325 controls. In 13 SCC cases and 6 controls, smudging and other concerns about silicone impression quality affected the scoring, and these subjects were excluded from the analysis.

Cases and controls were similarly distributed across three age strata and between genders due to frequency matching (Table 1). Cases were more likely to have a skin type with a tendency to sunburn, and to have had more severe sunburns (Table 1). Cases were similar to controls with respect to previous NSAID or photosensitizing drug use overall (Table 1).

We found increasing odds ratios of SCC with increasing degree of photoaging (OR = 1.7, 95% CI = 0.9–3.0 for severe photoaging; OR = 2.8, 95% CI = 1.6–5.0 for very severe photoaging, with moderate photoaging as the referent category) after adjusting for reference age, gender, and skin response to first sun exposure (Table 2). We further analyzed the odds of SCC in stratified subsets according to skin type, gender, medication use, anatomic site, and amount of solar elastosis (Table 2). There were little to no differences in the odds ratios of SCC stratified by skin response to first sun exposure, anatomic site, or use of

photosensitizing medications (Table 2). The odds ratios of SCC related to photoaging were slightly higher among women and those who had a prior history of NSAID use (Table 2). Degree of photoaging was strongly related to SCC among cases with the presence of actinic keratosis or solar elastosis adjacent to their tumor compared to cases without histologic evidence of actinic keratosis or severe elastosis respectively (Table 2).

Discussion

Photoaging is a marker of prolonged and repeated UVR exposure, the primary risk factor in keratinocyte cancer pathogenesis. In our study, we found that higher grades of photoaging, as measured by cutaneous microtopography, were associated with increased odds ratios of squamous cell carcinoma (SCC) after adjustment for major risk factors, and specifically among those with histologic evidence of actinic damage. Despite the clear relationship between UVR damage and skin cancer, few studies have investigated observable skin changes in relation to histologically confirmed keratinocyte cancer, specifically SCC, and none have been performed in a North American population. Thus, our unique study of SCC, with a large number of newly diagnosed SCC cases, suggests that microtopography grade is an independent indicator of risk in a population living at northern latitudes.

An early study by Holman, et al. comparing two alternative measures of photoaging (cutaneous microtopography and paraocular photography) found that higher degrees of photoaging as measured by cutaneous microtopography were predictive of subject-reported history of “nonmelanoma skin cancer” with age-adjusted ORs of 3.9, 3.6, and 9.2 for grades 4, 5, and 6 respectively compared to grades 1–3 ($p_{trend} = 0.004$).[16] Unfortunately, this study lacked histologic confirmation of keratinocyte cancer and so was unable to assess risk of either SCC or basal cell carcinoma (BCC) separately. In a later case-control study from Australia, higher grades of cutaneous microtopography were confirmed to be strongly associated with BCC with odds ratios up to 3.25 among those with severe photodamage.[17] In this study, the association was weaker between photoaging score and SCC (OR = 1.84, 95% CI = 0.81 – 4.18, for grade 6 versus grades 1–3). However, the study had a limited number of SCC cases (n=45) compared to BCC cases (n=266), which reduced their statistical power to detect an association.[17] Melanoma also has been associated with more severe photoaging in Australia; the OR for all subtypes of melanoma was 2.68 for those with photoage grade 6 compared to those with grades 1–3.[22] Of interest, the relationship was stronger among histologic subtypes of melanoma considered related to actinic exposure as opposed inherent melanocytic proliferation. A Danish case-control study of melanoma found no association between malignant melanoma and microtopography[23] highlighting the need for further studies such as ours in populations further from the equator.

In stratified analyses, the association between grade of photoaging and SCC was present among both men and women and among those with and without sun sensitive phenotypes, suggesting that photoaging can be used to assess risk of SCC for all genders and skin types. We did not detect any clear evidence of effect modification by prior use of photosensitizing drugs or NSAIDs. Literature regarding the effects of NSAIDs on the risk of SCC has been inconsistent,[24–29] yet, a recent review and meta-analysis suggested an overall reduced risk of SCC among NSAID users.[30] Previous work has found an increased risk of SCC with use of

photosensitizing drugs.[20,31,32] While our results suggest that an association between photoaging and SCC among both users and non-users of photosensitizing medication and NSAIDs, lack of evidence of effect modification could at least in part be due to limited statistical power of our analyses, and thus, additional, larger studies are required.

As mentioned, the odd ratios of SCC related to photoaging were clearly evident among those with actinic keratosis and severe solar elastosis in the skin adjacent to the SCC than those without. This might be expected if microtopography represents chronic UVR exposure in the subgroup of SCC cases most strongly related to chronic UVR damage, and perhaps less so in cases involving other factors (i.e., inherited susceptibility and immunosuppression among others). Importantly, it suggests that degree of photoaging is a predictor of SCC risk even beyond other measures of extreme photoaging. Findings by anatomic site of the tumor did not markedly differ, implying that our measure taken from a single site on the back of the hand relates to risk of SCC regardless of anatomic location of the tumor.

Evidence suggests that chronic sun exposure leads to changes at the molecular level within the dermis, which over time likely contributes to progressive alterations in microtopographical appearance. UVR induces activation of matrix metalloproteinases, leading to enhanced degradation in extracellular collagen.[33] As the amount of intact collagen decreases, cell surface interactions with surrounding fibroblasts diminish, resulting in impaired fibroblast function and causing numerous downstream effects on chemical signaling and maintenance of the dermal microenvironment.[34,35] Given that fibroblasts are the primary cell responsible for maintaining dermal integrity, it follows that these changes in the microenvironment ultimately would be seen as ultrastructural changes on the skin surface. Our results provide evidence that a similar process may underlie both photoaging and carcinogenesis. In support of this, increased expression of certain metalloproteinases is seen in SCC as compared to other forms of keratinocyte cancer.[36] Further research is needed to better characterize the relationship between these biological processes and the pathogenesis of SCCs.

Although our study was appreciably larger than the one previous study of SCC from Australia, we also had limited statistical power particularly for the stratified analyses. Another constraint of our analyses was that biopsy specimens were not available to histologically evaluate solar elastosis or keratosis among controls for comparison. As with most case-control studies, there is the possibility of recall bias, for example in the reporting of sensitivity to the sun, NSAID use and photosensitizing drug use. Additionally, our study was limited to a population living in New Hampshire and therefore may not be generalizable to other regions of the US or elsewhere.

Our research has important implications both for clinical practice and large-scale population-based epidemiologic studies of skin malignancies. Evaluation of surface microtopography is a non-invasive alternative to skin biopsy to measure photoaging. In large-scale studies, it may be a useful objective measure of chronic UVR exposure and UVR-related cancer risk even in populations in regions with low ambient UVR. It also has potential clinical utility. While dermatologic examination alone is a sensitive tool for identifying incident skin cancer, [37] its predictive value and role in prevention is less

clear.[38,39] Therefore, microtopography grading could provide an additional predictor of skin cancer risk in the clinical setting although further studies are needed to establish this. In summary, our findings support skin microtopography as an objective method for assessing UVR related risk of SCC in populations residing in regions of lower ambient UVR.

Abbreviations

CI	Confidence interval
NSAID	Non steroidal anti-inflammatory drug
SCC	Squamous cell carcinoma
OR	Odds ratio
UVR	Ultraviolet radiation

References

1. Fisher GJ, Wang ZQ, Datta SC, et al. Pathophysiology of premature skin aging induced by ultraviolet light. N Engl J Med. 1997; 337:1419–28. [PubMed: 9358139]
2. Mera SL, Lovell CR, Jones RR, et al. Elastic fibres in normal and sun-damaged skin: an immunohistochemical study. Br J Dermatol. 1987; 117:21–7. [PubMed: 3651333]
3. El-Domyati M, Attia S, Saleh F, et al. Intrinsic vs. photoaging: a comparative histopathological, immunohistochemical, and ultrastructural study of skin. Exp Dermatol. 2002; 11:398–405. [PubMed: 12366692]
4. Bernstein EF, Underhill CB, Hahn PJ, et al. Chronic sun exposure alters both the content and distribution of dermal glycosaminoglycans. Br J Dermatol. 1996; 135:255–62. [PubMed: 8881669]
5. Karagas MR, Zens MS, Nelson HH, et al. Measures of cumulative exposure from a standardized sun exposure history questionnaire: a comparison with histologic assessment of solar skin damage. Am J Epidemiol. 2007; 165:719–26. [PubMed: 17204514]
6. Griffiths CE, Wang TS, Hamilton TA, et al. A photonumeric scale for the assessment of cutaneous photodamage. Arch Dermatol. 1992; 128:347–51. [PubMed: 1550366]
7. English DR, Armstrong BK, Kricker A, et al. Case-control study of sun exposure and squamous cell carcinoma of the skin. Int J Cancer. 1998; 77:347–53. [PubMed: 9663594]
8. Rosso S, Minarro R, Schraub S, et al. Reproducibility of skin characteristic measurements and reported sun exposure history. Int J Epidemiol. 2002; 31:439–46. [PubMed: 11980813]
9. Seddon JM, Egan KM, Zhang Y, et al. Evaluation of skin microtopography as a measure of ultraviolet exposure. Invest Ophthalmol Vis Sci. 1992; 33:1903–8. [PubMed: 1582796]
10. Weiler L, Knight JA, Vieth R, et al. Comparison of self-reported lifetime sun exposure with two methods of cutaneous microtopography. Am J Epidemiol. 2007; 165:222–30. [PubMed: 17101707]
11. Battistutta D, Pandeya N, Strutton GM, et al. Skin surface topography grading is a valid measure of skin photoaging. Photodermatol Photoimmunol Photomed. 2006; 22:39–45. [PubMed: 16436180]
12. Green AC, Hughes MC, McBride P, et al. Factors associated with premature skin aging (photoaging) before the age of 55: a population-based study. Dermatology. 2011; 222:74–80. [PubMed: 21196710]
13. Hughes MC, Strutton GM, Fourtanier A, et al. Validation of skin surface microtopography as a measure of skin photoaging in a subtropical population aged 40 and over. Photodermatol Photoimmunol Photomed. 2012; 28:153–8. [PubMed: 22548398]
14. Lucas RM, Ponsonby AL, Dear K, et al. Associations between silicone skin cast score, cumulative sun exposure, and other factors in the ausimmune study: a multicenter Australian study. Cancer

epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2009; 18:2887–94.

15. Beagley, J., Gibson, I. School of Biology. Western Australian Istitute of Technology; Perth: 1980. Changes in skin condition in relation to degree of exposure to ultraviolet light.
16. Holman CD, Armstrong BK, Evans PR, et al. Relationship of solar keratosis and history of skin cancer to objective measures of actinic skin damage. Br J Dermatol. 1984; 110:129–38. [PubMed: 6696833]
17. Kricker A, Armstrong BK, English DR, et al. Pigmentary and cutaneous risk factors for non-melanocytic skin cancer--a case-control study. Int J Cancer. 1991; 48:650–62. [PubMed: 2071226]
18. Silva Idos S, Higgins CD, Abramsky T, et al. Overseas sun exposure, nevus counts, and premature skin aging in young English women: a population-based survey. J Invest Dermatol. 2009; 129:50–9. [PubMed: 18615111]
19. Gilbert-Diamond D, Li Z, Perry AE, et al. A population-based case-control study of urinary arsenic species and squamous cell carcinoma in New Hampshire, USA. Environ Health Perspect. 2013; 121:1154–60. [PubMed: 23872349]
20. Robinson SN, Zens MS, Perry AE, et al. Photosensitizing agents and the risk of non-melanoma skin cancer: a population-based case-control study. J Invest Dermatol. 2013; 133:1950–5. [PubMed: 23344461]
21. Rigel DS, Stein Gold LF. The importance of early diagnosis and treatment of actinic keratosis. J Am Acad Dermatol. 2013; 68:S20–7. [PubMed: 23228303]
22. Holman CD, Armstrong BK. Cutaneous malignant melanoma and indicators of total accumulated exposure to the sun: an analysis separating histogenetic types. J Natl Cancer Inst. 1984; 73:75–82. [PubMed: 6588237]
23. Osterlind A, Tucker MA, Stone BJ, et al. The Danish case-control study of cutaneous malignant melanoma. II. Importance of UV-light exposure. Int J Cancer. 1988; 42:319–24. [PubMed: 3417359]
24. Asgari MM, Chren MM, Warton EM, et al. Association between nonsteroidal anti-inflammatory drug use and cutaneous squamous cell carcinoma. Arch Dermatol. 2010; 146:388–95. [PubMed: 20157019]
25. Butler GJ, Neale R, Green AC, et al. Nonsteroidal anti-inflammatory drugs and the risk of actinic keratoses and squamous cell cancers of the skin. J Am Acad Dermatol. 2005; 53:966–72. [PubMed: 16310056]
26. Elmets CA, Viner JL, Pentland AP, et al. Chemoprevention of nonmelanoma skin cancer with celecoxib: a randomized, double-blind, placebo-controlled trial. J Natl Cancer Inst. 2010; 102:1835–44. [PubMed: 21115882]
27. Johannesdottir SA, Chang ET, Mehnert F, et al. Nonsteroidal anti-inflammatory drugs and the risk of skin cancer: a population-based case-control study. Cancer. 2012; 118:4768–76. [PubMed: 22644960]
28. Torti DC, Christensen BC, Storm CA, et al. Analgesic and nonsteroidal anti-inflammatory use in relation to nonmelanoma skin cancer: a population-based case-control study. J Am Acad Dermatol. 2011; 65:304–12. [PubMed: 21529996]
29. Wysong A, Ally MS, Gamba CS, et al. Non-melanoma skin cancer and NSAID use in women with a history of skin cancer in the Women's Health Initiative. Prev Med. 2014; 69:8–12. [PubMed: 25150382]
30. Muranushi C, Olsen CM, Pandeya N, et al. Aspirin and nonsteroidal anti-inflammatory drugs can prevent cutaneous squamous cell carcinoma: a systematic review and meta-analysis. J Invest Dermatol. 2015; 135:975–83. [PubMed: 25521453]
31. Jensen AO, Thomsen HF, Engebjerg MC, et al. Use of photosensitising diuretics and risk of skin cancer: a population-based case-control study. Br J Cancer. 2008; 99:1522–8. [PubMed: 18813314]
32. Kaae J, Boyd HA, Hansen AV, et al. Photosensitizing medication use and risk of skin cancer. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2010; 19:2942–9.

33. Chung JH, Seo JY, Lee MK, et al. Elevated matrix metalloproteinases and collagen fragmentation in photodamaged human skin: impact of altered extracellular matrix microenvironment on dermal fibroblast function. J Invest Dermatol. 2013; 133:1362–6.

34. Fisher GJ, Shao Y, He T, et al. Reduction of fibroblast size/mechanical force down-regulates TFG-B type II receptor: implications for human skin aging. Aging Cell. 2016; 15:67–76. [PubMed: 26780887]

35. Varani J, Schuger L, Dame MK, et al. Reduced fibroblast interaction with intact collagen as a mechanism for depressed collagen synthesis in photodamaged skin. J Invest Dermatol. 2004; 122:1471–9. [PubMed: 15175039]

36. O'Grady A, Dunne C, O'Kelly P, et al. Differential expression of matrix metalloproteinase (MMP)-2, MMP-9, and tissue inhibitor of metalloproteinase (TIMP)-1 and TIMP-2 in non-melanoma skin cancer: implications for tumour progression. Histopathology. 2007; 51:793–804. [PubMed: 18042068]

37. Enamandram M, Duncan LM, Kimball AB. Delivering value in dermatology: insights from skin cancer detection in routine clinical visits. J Am Acad Dermatol. 2015; 72:310–3. [PubMed: 25484266]

38. Koh HK, Caruso A, Gage I, et al. Evaluation of melanoma/skin cancer screening in Massachusetts. Preliminary results. Cancer. 1990; 65:375–9. [PubMed: 2295061]

39. Wolff, T., Tai, E., Miller, T. Screening for Skin Cancer: An Update of the Evidence for the U.S. Preventive Services Task Force. Rockville (MD): Agency for Healthcare Research and Quality (US); 2009. U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews.

Summary

Previous research has found that higher grades of photoaging as measured by cutaneous microtopography are related to increased degree of dermal elastosis in populations near the equator. We investigated photoaging as part of a population based skin cancer case-control study in New Hampshire and found that higher grades of photoaging were associated with increased risk of cutaneous squamous cell carcinoma (SCC). Our results persisted after adjustment for known skin cancer risk factors, and the increased SCC risk was present even among those with histologic evidence of actinic keratosis in the skin adjacent to the tumor. Microtopography may be an independent indicator of skin cancer risk in the US.

Table 1

Selected Characteristics of Squamous Cell Carcinoma Cases and Controls in New Hampshire, USA, 2009–2011.

Characteristics	SCC Cases N (%)	Controls N (%)
Reference age		
24–59	122 (35)	122 (37)
60–64	112 (32)	92 (28)
65–69	112 (32)	117 (35)
Gender		
Male	198 (57)	185 (56)
Female	148 (43)	146 (44)
Skin sensitivity to first solar exposure[a]		
Tan	18 (5)	70 (21)
Mild burn then tan	165 (48)	162 (49)
Burn then peel	134 (39)	77 (23)
Burn then blister	27 (8)	22 (7)
Number of painful sunburns[a]		
None	50 (16)	69 (25)
1–2	52 (17)	61 (22)
≥ 3	212 (68)	142 (52)
NSAID medication use[a,b]		
Never	219 (44)	191 (41)
Ever	280 (56)	280 (60)
Photosensitizing medication use[a]		
Never	73 (23)	70 (23)
Ever	249 (77)	234 (77)

[a]Skin sensitivity missing from two SCC cases. Number of painful sunburns missing from 59 control and 32 SCC case subjects. NSAID medication use missing from one SCC case. Photosensitizing medication use is missing from 27 control and 24 SCC case subjects.

[b]NSAID use defined as use at least 4 times a week for at least a month

Table 2

Odds Ratios (95% confidence intervals) of Squamous Cell Carcinoma and Severity of Photoaging Overall and Stratified by Skin Sensitivity to First Sun Exposure, Actinic Keratoses, Solar Elastosis and NSAID Use, New Hampshire, USA, 2009–2011.

	Severity of photoaging	SCC Cases (%)	Controls (%)	OR (95% CI) [a]
Overall[b]				
	Moderate (3+4)	23 (6.9)	55 (16.9)	1.0 (ref)
	Severe (5)	66 (19.8)	88 (27.0)	1.7 (0.9–3.0)
	Very severe (6)	244 (73.2)	182 (56.0)	2.8 (1.6–5.0)
Skin sensitivity to first sun exposure				
Tan or mild sunburn then tan	Moderate (3+4)	17 (9.7)	44 (19.3)	1.0 (ref)
	Severe (5)	37 (21.1)	65 (28.5)	1.5 (0.7–3.1)
	Very severe (6)	121 (69.1)	119 (52.1)	3.0 (1.6–5.8)
Sunburn then peel or blister	Moderate (3+4)	6 (3.8)	11 (11.3)	1.0 (ref)
	Severe (5)	29 (18.5)	23 (23.7)	2.0 (0.6–6.4)
	Very severe (6)	121 (77.5)	63 (64.9)	3.0 (1.0–9.2)
Gender				
Men	Moderate (3+4)	9 (4.7)	21 (11.6)	1.0 (ref)
	Severe (5)	38 (20.1)	43 (23.8)	1.7 (0.6–4.3)
	Very severe (6)	142 (75.1)	116 (64.4)	2.4 (1.0–5.6)
Women	Moderate (3+4)	14 (9.7)	34 (23.4)	1.0 (ref)
	Severe (5)	28 (19.4)	45 (31.0)	1.5 (0.7–3.4)
	Very severe (6)	102 (70.8)	66 (45.5)	3.8 (1.8–8.0)
NSAID medication use[c]				
Never	Moderate (3+4)	17 (10.8)	28 (19.1)	1.0 (ref)
	Severe (5)	29 (18.4)	44 (30.1)	1.0 (0.4–2.3)
	Very severe (6)	111 (70.7)	74 (50.6)	2.3 (1.1–4.6)
Ever	Moderate (3+4)	6 (3.4)	27 (15.0)	1.0 (ref)
	Severe (5)	36 (20.5)	44 (24.5)	3.0 (1.1–8.2)
	Very severe (6)	133 (76.0)	108 (60.3)	4.2 (1.6–11.0)
Photosensitizing medication use				
Never	Moderate (3+4)	7 (10.1)	16 (23.5)	1.0 (ref)
	Severe (5)	19 (27.5)	18 (26.5)	2.5 (0.8–7.9)
	Very severe (6)	43 (62.3)	34 (50.0)	3.1 (1.1–9.1)
Ever	Moderate (3+4)	12 (5.0)	37 (16.0)	1.0 (ref)
	Severe (5)	46 (19.1)	61 (26.5)	2.1 (0.9–4.5)
	Very severe (6)	182 (75.8)	132 (57.3)	3.6 (1.8–7.5)
Anatomic site				
Head and neck	Moderate (3+4)	12 (7.7)	55 (16.9)	1.0 (ref)
	Severe (5)	29 (18.8)	88 (27.0)	1.3 (0.6–2.8)
	Very severe (6)	113 (73.3)	182 (56.0)	2.2 (1.1–4.5)
Other anatomic sites	Moderate (3+4)	11 (6.4)	55 (16.9)	1.0 (ref)

	Severity of photoaging	SCC Cases (%)	Controls (%)	OR (95% CI) [a]
	Severe (5)	37 (21.7)	88 (27.0)	2.1 (0.9–4.6)
	Very severe (6)	122 (71.7)	182 (56.0)	3.3 (1.6–6.9)
Actinic keratosis				
Absent	Moderate (3+4)	15 (10.0)	55 (16.9)	1.0 (ref)
	Severe (5)	35 (23.3)	88 (27.0)	1.4 (0.7–2.9)
	Very severe (6)	100 (66.6)	182 (56.0)	1.9 (1.0–3.7)
Present	Moderate (3+4)	3 (3.0)	55 (16.9)	1.0 (ref)
	Severe (5)	20 (20.4)	88 (27.0)	3.4 (0.9–12.4)
	Very severe (6)	75 (76.5)	182 (56.0)	5.7 (1.7–19.6)
Solar elastosis				
None – mild - moderate	Moderate (3+4)	9 (10.7)	55 (16.9)	1.0(ref)
	Severe (5)	22 (26.1)	88 (27.0)	1.5 (0.6–3.7)
	Very severe (6)	53 (63.1)	182 (56.0)	1.7 (0.7–4.0)
Severe	Moderate (3+4)	7 (5.4)	55 (16.9)	1.0 (ref)
	Severe (5)	29 (22.6)	88 (27.0)	2.1 (0.8–5.3)
	Very severe (6)	92 (71.8)	182 (56.0)	2.8 (1.2–6.7)

[a] Odds ratio and 95% confidence interval estimated from logistic regression models adjusted by age at diagnosis, sex (male, female) and skin response to first sun exposure (tan, mild sunburn then tan, painful sunburn and peel, sunburn and blister) unless stratified by one of these factors.

[b] Microtopographic grading was restricted to subjects with clear microtopography recorded in silicone mold material. 13 SCC cases and 6 controls were excluded due to smudging and other concerns about quality that affected the scoring.

[c] NSAID use defined as use at least 4 times a week for at least 1 month