The impact of environmental ultraviolet exposure on the clinical course of mycosis fungoides

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Background: As phototherapy plays an important role in the treatment of early-stage mycosis fungoides (MF), it is possible that environmental ultraviolet (UV) exposure affects the natural history of the disease.

Objective: To assess the impact of environmental UV exposure on the clinical course of MF.

Methods: The National Solar Radiation Database was used to identify the top and bottom registries for UV exposure from the Surveillance, Epidemiology, and End Results−18 database. Incidence and survival were determined.

Results: The high-UV cohort had a 30% lower risk of developing MF than did the low-UV cohort (hazard ratio, 1.3; 95% confidence interval, 1.20-1.41; $P < .001$). When stratified by stage and race, this difference was appreciable only among those with early-stage disease and white race. There was no difference in survival between the high- and low-UV cohorts ($P = .098$); however, a small difference was observed among those with early-stage disease and white race, favoring high UV exposure.

Limitations: Retrospective design, use of the National Solar Radiation Database as a surrogate for individual sunlight exposure.

Conclusion: It is possible that environmental solar UV exposure may play a role in controlling early-stage MF among patients with photosensitive features. (J Am Acad Dermatol 2019;81:1074-7.)

Key words: mycosis fungoides; phototherapy; ultraviolet light.

The cornerstone of treatment for early-stage mycosis fungoides (MF) is skin-directed therapy, which includes ultraviolet (UV) light treatment such as psoralen plus UVA light photochemotherapy (PUVA) and narrowband UVB (nb-UVB). UV light therapy controls MF by inducing lymphotoxicity within the dermis and epidermis, decreasing circulating malignant CD4 lymphocytes, suppressing antigen-presenting Langerhans cells, and suppressing local type 2 helper T-cell cytokine production.[1] Sunlight has been associated with disease control in psoriasis, which is another light-responsive disease, and accordingly, it is possible that exposure to solar UV light, which is 95% UVA and 5% UVB, may provide disease control for early-stage MF.[2,3] The National Solar Radiation Database, which provides global data on annual cumulative solar irradiation as measured in watt-hours per square meter, and the Surveillance, Epidemiology, and End Result (SEER)18 database, which contains 18 diverse registries that encompass 28% of the US population, were used to test this hypothesis.

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Abbreviations used:

MF: mycosis fungoides
nb-UVB: narrowband ultraviolet B
NSRB: National Solar Radiation Database
PUVA: psoralen plus ultraviolet A
SEER: Surveillance, Epidemiology, and End Result
SS: Sézary syndrome
UV: ultraviolet
UVA: ultraviolet A
UVB: ultraviolet B

METHODS

From the SEER-18 database, adults aged 20 and older with MF and/or Sézary syndrome (SS) (International Classification of Diseases for Oncology codes 9700/3 and 9701/3) were analyzed over a 10-year span from January 2005 through December 2014. The NSRDB was used to quantify solar UV exposure among the 18 SEER registries. The top and bottom 4 registries for annual UV exposure were identified as New Mexico, Los Angeles, Hawaii, and Utah (high-UV cohort) and Seattle, Detroit, Connecticut, and New Jersey (low-UV cohort), respectively. Age-adjusted incidence and 10-year relative survival were determined for the high- and low-UV cohorts.

As UV light therapy is most efficacious in patch/plaque disease, the cohorts were stratified by early-stage disease (stages IA-IIA) and advanced-stage disease (stages IIB-IVB) as per the sixth and seventh editions of the American Joint Committee on Cancer stage groups.[4-6] Owing to differences in response to light therapy by skin tone, the cohorts were also stratified by white and black race.[4,7,8] To account for possible confounding variables, access to care and county-level socioeconomic factors were assessed. Notably, data on insurance status became available from 2007 onward. Categoric variables were compared by using the chi-square test and Fisher exact test. Continuous variables were compared by using the *t* test and

CAPSULE SUMMARY

- To our knowledge, this is the first report demonstrating a relationship between sun exposure and the clinical course of mycosis fungoides.

Table I. Baseline demographics

Characteristic	High-UV cohort (n = 607)	Low-UV cohort (n = 991)	*P* value
Mean age ± SD, y	56 (±16)	57 (±16)	.080
Sex, n (%)			.180
Male	317 (52%)	553 (56%)	
Female	290 (48%)	438 (44%)	
Race, n (%)			<.001
White	435 (72%)	720 (73%)	
Black	70 (11%)	170 (17%)	
American Indian/Alaska Native, Asian/Pacific Islander	58 (10%)	42 (4%)	
Unknown	44 (7%)	59 (6%)	
Stage, n (%)			.734
Early	364 (61%)	582 (60%)	
Advanced	76 (13%)	130 (13%)	
Unknown	152 (26%)	266 (27%)	
Insurance status, n (%)			.081
Insured	370 (61%)	656 (66%)	
Uninsured	13 (2%)	14 (1%)	
Unknown	224 (37%)	321 (33%)	
Chemotherapy, n (%)			.873
Yes	113 (19%)	189 (19%)	
No/unknown	494 (81%)	802 (81%)	
Rural-urban continuum, n (%)			.002
<250,000 people	58 (10%)	53 (5%)	
≥250,000 people	549 (90%)	938 (95%)	
County level data			
Mean % of families below the poverty line ± SD	13.2% (±5%)	9.1% (±5%)	<.001
Mean % with at least a bachelor's degree ± SD	30.5% (±11%)	35.7% (±9%)	<.001
Mean % with less than a high school education ± SD	18.6% (±8%)	10.5% (±3%)	<.001
Median household income	$56,884.35	$67,930.67	<.001

SD, Standard deviation; *UV*, ultraviolet.

analysis of variance. The Wilcoxon rank sum test and Kruskal-Wallis tests were used for variables with non-normal distributions. Survival analyses are presented with Kaplan-Meier curves, and comparisons were conducted using the Peto and Peto modification of the Gehan-Wilcoxon test.

RESULTS

Patient demographics are presented in Table I. There were 607 and 991 patients in the high- and low-UV cohorts, respectively. The cohorts were well balanced with regard to age, sex, stage, insurance status, and receipt of systemic treatment. The low-UV cohort had slightly more black patients and patients from metropolitan areas. The high-UV cohort included more patients from rural counties with higher levels of poverty, lower education, and lower income.

Age-adjusted incidence

The high-UV cohort had a significantly lower age-adjusted incidence of MF and/or SS than the low-UV group: 0.542 versus 0.705 per 100,000 persons (hazard ratio [HR], 1.3; 95% confidence interval [CI], 1.20-1.41; $P < .001$). When assessed by stage, this difference was appreciable only among those with early-stage disease (0.372 vs 0.439 per 100,000 persons [HR, 1.18; 95% CI, 1.04-1.34; $P = .010$]) and not advanced-stage disease (0.106 vs 0.114 per 100,000 persons [HR, 1.07; 95% CI, 0.85-1.35; $P = .561$]). When stratified by race, this difference was appreciable only among white patients (0.494 vs 0.657 per 100,000 persons [HR, 1.32; 95% CI, 1.20-1.46; $P < .001$]) and not black patients (0.766 vs 0.897 per 100,000 persons [HR, 1.17; 95% CI, 0.92-1.48; $P = .192$]).

Ten-year relative survival

There was no difference in survival between the high- and low-UV cohorts ($P = .098$). When stratified by stage, those with early-stage disease in the high-UV cohort had a more favorable survival than did those in the low-UV cohort, as depicted in Figs 1 and 2. Further stratification by race demonstrated a survival difference by UV exposure among white patients with early-stage disease but among not black patients, favoring high UV exposure (Figs 3 and 4).

DISCUSSION

The present analysis of the SEER-18 database demonstrates a relationship of annual cumulative environmental UV solar irradiation with incidence and survival in MF and/or SS. Therapeutic UV light (nb-UVB and PUVA) is an efficacious frontline treatment for patch/plaque disease. We postulated that people living in high−UV exposure regions may have better control of early-stage disease owing to

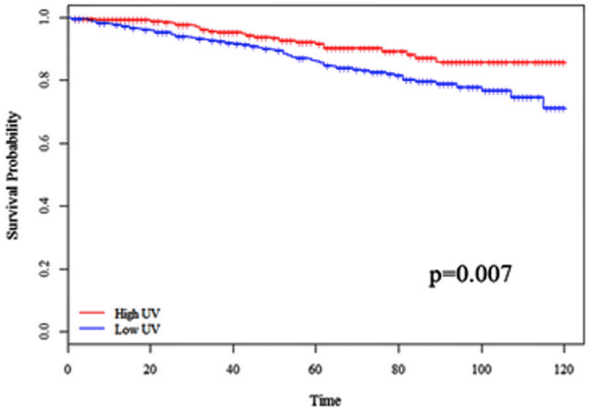

Fig 1. Ten-year survival: early-stage disease. *UV*, Ultraviolet.

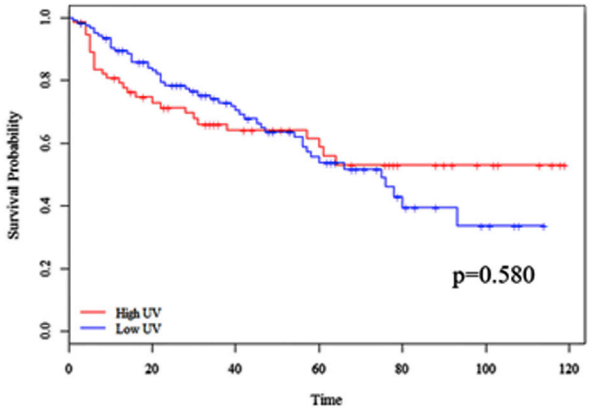

Fig 2. Ten-year survival: advanced-stage disease. *UV*, Ultraviolet.

prolonged exposure to ambient UV light. Indeed, residence in high−UV exposure areas was associated with up to a 30% lower incidence of disease, despite this cohort having more adverse socioeconomic demographics. Patients with fairer skin tones such as white patients (Fitzpatrick skin types I-IV) appear to be more responsive to PUVA than are those with darker skin tones, such as black patients (Fitzpatrick skin types V or VI) for the treatment of MF and psoriasis, which is another light-responsive disease.[4,7,8] In our analysis, white patients with early-stage disease benefited the most from high UV exposure, mirroring the pattern seen with therapeutic UV light. Likewise, high UV exposure did not affect the incidence of MF and/or SS in black patients.

In this analysis, there were more patients from urban areas in the low-UV group, with an absolute difference of 5%. Although it is known that the incidence of MF is higher in metropolitan areas, the low-UV cohort also had a higher representation of black patients, a population known to have a higher incidence of disease and greater mortality from MF and/or SS.[9-11] Therefore, it is unlikely that the differences in clinical course between the 2 cohorts,

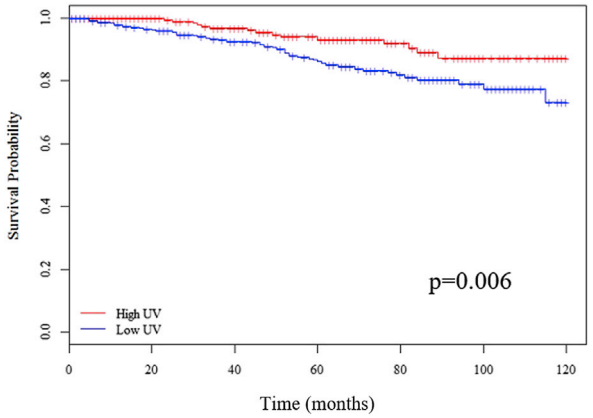

Fig 3. Ten-year survival: early-stage disease and white race. *UV*, Ultraviolet.

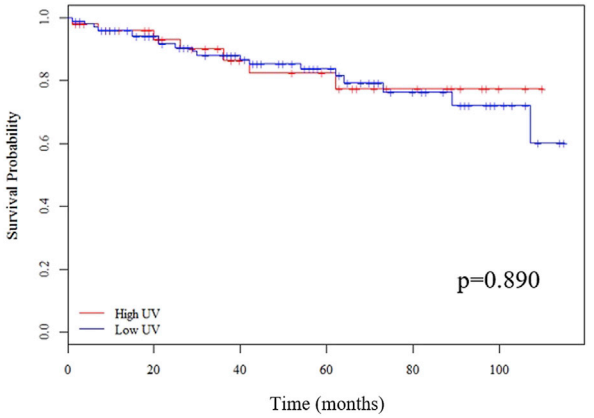

Fig 4. Ten-year survival: early-stage disease and black race. *UV*, Ultraviolet.

which were most pronounced among white patients with early-stage disease, are attributable to differences in the rural-urban continuum.

In the more advanced stages of disease, malignant T cells lose epidermotropism and involve deeper layers of the dermis and blood.[4,5] Therapeutic UV light is not able to penetrate the deeper parts of the dermis and therefore does not work well in advanced disease. Therefore, ambient light would not be expected to affect the course of patients with advanced disease. In this review of the SEER and NSRDB data, ambient UV exposure did not affect the clinical course of advanced-stage disease.

Although the majority of patients with early-stage disease do have a good prognosis, up to one-third do progress to advanced stages of disease and have a poor prognosis.[12] It is interesting that patients with early-stage disease in high—UV exposure areas seem to have a better survival than do patients in low—UV exposure areas, and it is possible that the ambient light is helping to control disease by decreasing progression. This possibility needs to be studied prospectively, as PUVA and nb-UVB have not been shown to prolong the survival of early-stage MF and/or SS.

To our knowledge, this is the first report demonstrating the impact of environmental solar UV exposure on the clinical course of MF and/or SS. Although the findings of this study are intriguing, it has several limitations, including retrospective design, use of the NSRDB as a surrogate for individual sunlight exposure, and possible coding inaccuracies or missing data in the SEER database. Our study is by no means a call for patients to move to high—UV exposure areas or even endeavor to expose themselves to more daytime sun in their current environments. Sun exposure does increase the risk of nonmelanoma skin cancer and malignant melanoma.[13] Until more data are available, any potential benefit of seeking active environmental UV exposure needs to be carefully balanced against harm.

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