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Brief Communication

Ambient Ultraviolet Radiation and Sebaceous Carcinoma Incidence in the United States, 2000–2016

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Abstract

Sebaceous carcinoma (SC) is an aggressive skin tumor. Although ultraviolet radiation (UVR) is an important risk factor for some skin cancer types, no population-level study has evaluated for an association between UVR and SC risk. Herein, we examined satellite-based ambient UVR in relation to SC incidence using Surveillance, Epidemiology, and End Results 18 cancer registry data (2000–2016). There were 3503 microscopically confirmed cases of SC diagnosed during the study period. For non-Hispanic whites, there was an association between increasing ambient UVR and SC risk (incidence rate ratio [per UVR quartile] = 1.15, 95% confidence interval = 1.11 to 1.19; two-sided $P < .001$) including among individuals with and without putative Muir-Torre syndrome. In contrast, there was no association between ambient UVR and SC risk for other race and ethnicities. Our findings support a role for UVR in SC tumorigenesis, which suggests that photoprotection may reduce SC risk, particularly for high-risk populations (eg, Muir-Torre syndrome).

Sebaceous carcinoma (SC) is an aggressive skin cancer with a 5-year mortality rate of 20%. SC risk factors include male sex, older age, Muir-Torre syndrome (MTS; OMIM 158320), and immune suppression (1–3). In contrast to many other cancer types, SC incidence in the United States has been increasing since 1973, when the Surveillance, Epidemiology, and End Results (SEER) database first began tracking cancer statistics (4,5). Therefore, it is important to identify exposures underlying these trends, which could assist with preventive efforts, screening, and early diagnosis of SC.

SC most commonly occurs on chronically sun-exposed skin of the head and neck in older, non-Hispanic white (NHW) patients suggesting that ultraviolet radiation (UVR) may contribute to SC development (2,5). However, population-based epidemiological data examining the association of UVR with SC are lacking.

In this study, we examined the association between ambient UVR and SC risk in the United States by linking satellite-based ambient UVR with SEER 18 cancer registry data (27.8% of US population) for the years 2000–2016 by county (6). UVR data were cloud-adjusted daily ambient irradiance (wavelength = 305 nm) on a 1-degree latitude × 1-degree longitude grid, which were derived from the National Aeronautics Space Administration's Total Ozone Mapping Spectrometer database (7). Because satellite-based estimates of UVR in the United States have varied little aside from relatively small fluctuations due to the 11-year solar cycle (8), in the present analysis, daily noontime estimates over the years 1982–1992 were averaged to represent a full solar cycle. SEER counties were assigned to UVR quartiles, low (Q1) to high (Q4), with cutoffs constructed to have similar person-years at risk across quartiles. We report age-adjusted cancer rates and incidence rate ratios (IRRs) for microscopically confirmed cases of SC (International Classification of Diseases for Oncology-3 code 8410/3) using the Tiwari method in SEER*stat 8.3.6 (9,10). Individuals were designated as having putative MTS, a phenotypic variant of Lynch syndrome (OMIM: 120435), if they had SC plus another Lynch syndrome cancer (3). Poisson models comparing SC incidence with UVR were adjusted for sex, age, diagnosis period, and registry volume to calculate IRRs. We report 95% confidence intervals (CIs) and two-sided P values for each IRR, and statistical significance was defined as a P value less than .05. Registry volume was categorized into tertiles using census-based population size to create three roughly equal

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Table 1. Incidence rates of sebaceous carcinoma by clinical characteristics

Characteristic	No. of cases (%)*	Rate per million persons (95% CI)†	IRR (95% CI)‡	P§
Total	3503 (100.0)	2.43 (2.35 to 2.52)	—	—
Tumor location				
Nonhead and neck	909 (25.9)	0.62 (0.58 to 0.66)	—	—
Head and neck	2566 (73.3)	1.80 (1.73 to 1.87)	—	—
Unknown	28 (0.8)	—		
Gender				
Female	1363 (38.9)	1.67 (1.58 to 1.76)	1.00 (Referent)	—
Male	2140 (61.1)	3.46 (3.31 to 3.61)	2.07 (1.94 to 2.22)	<.0001
Age, y				
<50	254 (7.3)	0.26 (0.23 to 0.30)	1.00 (Referent)	—
50–64	837 (23.9)	3.27 (3.05 to 3.50)	12.5 (10.9 to 14.5)	<.0001
65–79	1330 (38.0)	10.8 (10.2 to 11.4)	41.2 (36.0 to 47.3)	<.0001
≥80	1082 (30.9)	22.7 (21.4 to 24.1)	86.8 (75.6 to 99.9)	<.0001
Race/ethnicity				
Black	100 (2.9)	0.71 (0.57 to 0.87)	1.00 (Referent)	—
Asian or Pacific Islander	187 (5.3)	1.51 (1.30 to 1.75)	2.14 (1.66 to 2.77)	<.0001
American Indian or Alaskan Native	21 (0.6)	1.50 (0.90 to 2.33)	2.12 (1.22 to 3.47)	.009
Hispanic white	255 (7.3)	1.71 (1.50 to 1.95)	2.42 (1.90 to 3.10)	<.0001
Non-Hispanic white	2722 (77.7)	2.65 (2.55 to 2.75)	3.73 (3.05 to 4.64)	<.0001
Unknown	218 (6.2)	—	—	
Diagnosis period				
2000–2005	871 (24.9)	1.92 (1.80 to 2.06)	1.00 (Referent)	—
2006–2010	1030 (29.4)	2.48 (2.33 to 2.64)	1.29 (1.18 to 1.41)	<.0001
2011–2016	1602 (45.7)	2.82 (2.68 to 2.96)	1.46 (1.35 to 1.59)	<.0001

*Clinical characteristics of microscopically confirmed cases of sebaceous carcinoma (International Classification of Diseases for Oncology-3 code 8410/3) diagnosed in Surveillance, Epidemiology, and End Results (SEER) 18 database. Analysis includes cases from San Francisco–Oakland, Connecticut, Detroit (Metropolitan), Hawaii, Iowa, New Mexico, Seattle (Puget Sound), Utah, Atlanta (Metropolitan), San Jose-Monterey, Los Angeles, Alaska, rural Georgia, California (excluding San Francisco, San Jose-Monterey, and Los Angeles), Kentucky, Louisiana, New Jersey, and greater Georgia. There were 3503 sebaceous carcinomas diagnosed in 3352 persons between 2000 and 2016. Table values with no estimate are marked (—).

†Rates with 95% confidence intervals (CIs; Tiwari method) are age-adjusted to the 2000 US standard population (19 age groups, Census P25-1130).

‡Incidence rate ratios (IRRs) with 95% CIs comparing incidence rate to reference group were calculated in SEER*stat 8.3.6 using the Tiwari method.

§Two-sided *P* values for IRRs.

categories. There was no evidence of overdispersion in any of the Poisson models, and these analyses were performed using STATA 15.0 (College Station, TX).

There were 3503 SCs diagnosed in the study population with 287 tumors (8.2%) occurring in individuals with putative MTS. Individuals with SC were predominantly NHW (77.7%) and male (61.1%) (Table 1). The overall incidence was 2.43 cases (95% CI = 2.35 to 2.52) per million persons per year, and the incidence increased by 3.3% (95% CI = 2.2 to 4.5) per year between 2000 and 2016 (Table 1).

Among NHWs (n = 2667 cases), there was an association between ambient UVR quartile and SC risk (IRR [per UVR quartile] = 1.15, 95% CI = 1.11 to 1.19, $P < .001$) (Figure 1). This association was also observed for NHWs with (n = 222 cases; IRR [per UVR quartile] = 1.22, 95% CI = 1.08 to 1.39, $P = .002$) and without (n = 2445 cases; IRR [per UVR quartile] = 1.14, 95% CI = 1.09 to 1.19, $P < .001$) putative MTS (Figure 1) and for multiple age groups (50–64, 65–79, 80 years; $P < .05$, all analyses) and diagnosis periods (2000–2005, 2006–2010, 2011–2016; $P < .05$, all analyses) (Supplementary Table 1, available online).

In contrast to NHWs, there was no association between ambient UVR and SC risk among other race and ethnicities with increased skin pigmentation suggesting that melanin pigment, which absorbs UVR, is protective against SC tumorigenesis similar to other cutaneous malignancies (11). There were also differences in the effect size between NHW men (n = 1655 cases; IRR [per UVR quartile] = 1.20, 95% CI = 1.15 to 1.26; $P < .001$) and NHW women (n = 1012 cases; IRR [per UVR quartile] = 1.06, 95% CI = 1.00 to 1.13; $P = .05$), which may be partially explained by gender differences in sun-protective behavior and an increased likelihood for outdoor occupations among men (12–14) (Figure 1).

Because HIV infection is a risk factor for SC (1), we separately examined associations between ambient UVR and SC risk by county-level HIV prevalence [low prevalence counties: < 308.5 cases per 100 000 persons [2016 national average] (15)]. Among NHWs, there was a statistically significant association between ambient UVR quartile and SC risk for areas with low (n = 2158 cases; IRR [per UVR quartile] = 1.05, 95% CI = 1.01 to 1.09, $P = .02$) and high (n = 509 cases; IRR [per UVR quartile] = 1.73, 95% CI = 1.38 to 2.18, $P < .001$) HIV prevalence. The association was much stronger within high HIV–prevalence counties, suggesting that NHW patients with HIV in areas with high ambient UVR may be at particularly high risk for SC. Additional studies are necessary to confirm this finding given the limited number of cases and the absence of laboratory confirmation of patient HIV status (Supplementary Table 1, available online).

The association between ambient UVR and SC risk may be partially explained by UVR-induced mutagenesis. In support of this hypothesis, one prior study identified UVR-mutational signatures in one-third of SC tumors (16). UVR-induced immunosuppression in the skin may also be contributing to SC tumorigenesis (17–19). Immunosuppression is an important risk factor for several skin cancer types. Rates of melanoma and

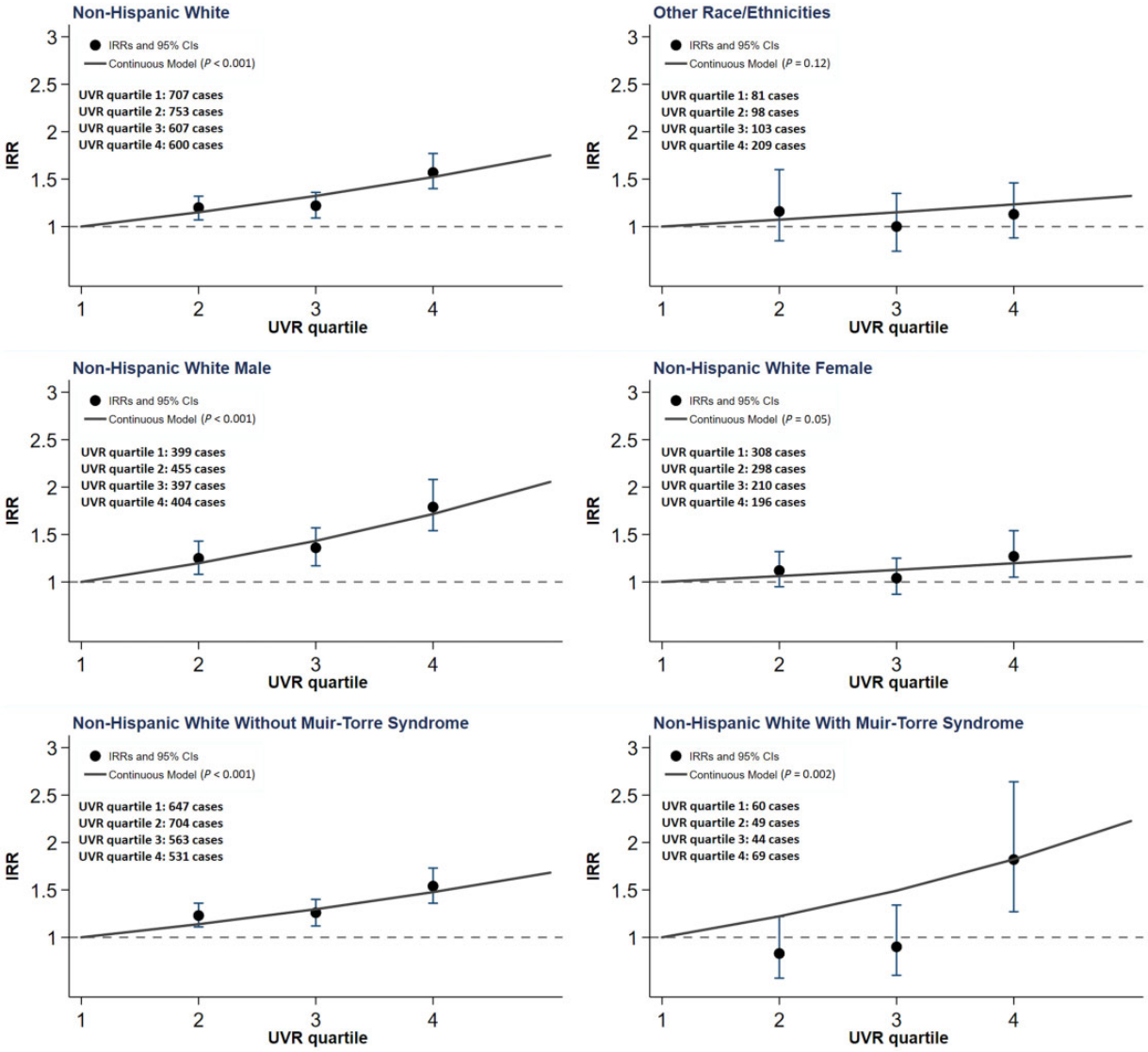

Figure 1. Ambient ultraviolet radiation (UVR) and incidence rate ratios for sebaceous carcinoma in select subgroups. Incidence rate ratios (IRR) with 95% confidence intervals (CIs) for microscopically confirmed cases of sebaceous carcinoma (International Classification of Diseases for Oncology-3 code 8410/3) diagnosed in Surveillance, Epidemiology, and End Results cancer registries (2000–2016) with increasing UVR. UVR data were cloud-adjusted daily ambient irradiance (wavelength = 305 nm). Analysis includes cases of sebaceous carcinoma from San Francisco–Oakland, Connecticut, Detroit (Metropolitan), Iowa, New Mexico, Seattle (Puget Sound), Utah, Atlanta (Metropolitan), San Jose-Monterey, Los Angeles, rural Georgia, California (excluding San Francisco, San Jose-Monterey, and Los Angeles), Kentucky, Louisiana, New Jersey, and greater Georgia. Cases from Hawaii and Alaska were excluded from the analysis because they were outliers for ambient UVR. Incidence for each UVR quartile was compared with UVR quartile 1 to calculate the IRR. Models are adjusted for sex, age (<50 , 50–64, 65–79, and 80 years and older), diagnosis period (2000–2005, 2006–2010, 2011–2016), and registry volume. Individuals were designated as having putative Muir-Torre syndrome, a phenotypic variant of Lynch syndrome (OMIM: 120435), if they had SC plus one of the following Lynch syndrome cancers: colon, rectum, stomach, liver, biliary tract, urinary bladder, renal pelvis, ureter, small intestine, pancreas, ovary, endometrial.

keratinocyte carcinomas are elevated for solid organ transplant recipients receiving immunosuppressant medications and individuals with HIV infection (1,20–23). Additionally, higher ambient UVR is associated with an increased risk for Kaposi sarcoma among HIV-infected patients, suggesting that UVR could be contributing to Kaposi sarcoma–associated herpes virus infection and subsequent tumor development through UVR-induced immunosuppression (24). Further studies are needed to determine whether UVR-induced immunosuppression contributes to SC development.

A limitation of this study is that ambient UVR data may not be representative of individual UVR exposure, which can be influenced by sun-seeking (leisure time outdoors, outdoor occupation) and sun-protective behavior (sunscreen, hats, etc.). Misclassification of exposure may also occur if individuals frequently migrate between areas with disparate ambient UVR. However, we identified associations between ambient UVR and SC risk for multiple subgroups, which strongly implicates UVR in SC tumorigenesis.

This is the first population-based epidemiological study to identify UVR as a risk factor for SC. Photoprotective measures should be advocated in high-risk populations to prevent this aggressive skin cancer. The biologic mechanisms underlying this association require further investigation.

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