Sex differences in the association of cutaneous melanoma incidence rates and geographic ultraviolet light exposure

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Background: Cutaneous melanoma (CM) incidence rates continue to increase, and the reasons are unknown. Previously, we reported a unique age-specific sex difference in melanoma that suggested additional causes other than solar ultraviolet (UV) radiation.

Objective: This study attempted to understand whether and how UV radiation differentially impacts the CM incidence in men and women.

Methods: CM data and daily UV index (UVI) from 31 cancer registries were collected for association analysis. A second dataset from 42 US states was used for validation.

Results: There was no association between log-transformed female CM rates and levels of UVI, but there was a significant association between male rates and UVI and a significant association between overall rates and UVI. The 5-year age-specific rate−UVI association levels (represented by Pearson's coefficient ρ) increased with age in men, but age-specific ρ levels remained low and unchanged in women. The significant rate−UVI association in men and nonassociation in women was validated in a population of white residents of the United States.

Limitations: Confounders, including temperature and latitude, are difficult to separate from UVI.

Conclusions: Ambient UVI appears to be associated with melanoma incidence in males but not in females. (J Am Acad Dermatol 2017;76:499-505.)

Key words: age-standardized rates; gender difference; melanoma; UV index; UVI; sex.

INTRODUCTION

Incidence rates of cutaneous melanoma (CM) have been increasing in the past few decades in the United States and in European countries.[1] The causation of melanomagenesis remains under debate,[2,3] especially the role of ultraviolet radiation (UVR), which is the major known environmental risk factor for CM and nonmelanoma skin cancer (NMSC). CMs frequently occur on the trunk, where UVR does not usually reach, while NMSCs are mostly

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found on sun-exposed body sites, such as the head, neck, and limbs.[4] Unlike NMSCs, CMs are not associated with cumulative ultraviolet (UV) exposure.[5] In addition, there are fewer UV signature mutations in patients with CMs than in those with NMSCs.[6] Therefore, in contrast to NMSC, the involvement and effect of UVR in CM is much more complex.[7] It is now generally accepted that CM is associated with intermittent UV exposure.[5] Based on this concept, the primary melanoma preventive measure is the application of sunscreen. The use of sunscreen began as early as the 1930s and has boomed since the 1950s, but the incidence of CM has continued to increase during this time period.[8]

CAPSULE SUMMARY

- The influence of sex on the association of melanoma incidence with ultraviolet light index is uncertain.
- Our study shows that melanoma rates are associated with ultraviolet light index in males but not in females.
- The differential effect on ultraviolet light index on melanoma incidence suggests the possibility of sex-specific prevention strategies.

Our previous publication indicated that women from the United States and from Nordic countries had higher CM incidence rates than men until 45 years of age, with a peak difference at 20 to 24 years of age.[9] There was no evidence of such a pattern for NMSC.[9] Basically, men and women were at equal risk of developing NMSC at a young age, although elderly men were at a higher risk, as was true for melanoma. Based on this comparison, we speculated that the etiology of melanoma in older age groups, as for NMSC,[9] was largely attributable to cumulative UV exposure, but causative factors in younger females required additional investigation.

The purpose of our current study is to understand the heterogeneous etiologic factors that may contribute to sex and age differences in CM. In this study, we collected cancer registry data for melanoma and computed daily average UV index (UVI) for that registry area. The association between UVI and sex- and age-specific rates was analyzed.

METHODS

Data collection, inclusion, and exclusion criteria

Melanoma tumor classification was based on the standard of the *International Classification of Diseases for Oncology* (ie, code C43). Cancer registries were selected primarily based on availability of data and majority of white populations, which include select European countries, the United States, Australia, and New Zealand. The data from the Northern Territory in Australia (which contains considerable population of indigenous Australians) were extracted to contain only nonindigenous populations. The European registry selection is mainly based on light eye color, as reported earlier.[10] Countries with >50% of population with light eye color were selected; therefore, France, Italy, and many southern European countries were excluded.

For primary analysis, US data were retrieved from the Surveillance, Epidemiology, and End Results (SEER) 18 database using 2013 data (including data from 1973-2011), with all cutaneous melanomas (site group: 7.1 melanoma; *International Classification of Diseases for Oncology, 3rd revision* behavior recode: 3; primary site C000-C809, histology types 8720-8723, 8726, 8728, 8730, 8740-8746, 8761, 8770-8774, and 8780). Only white (race = 1) data were included for analysis. Registries 27, 37, and 47 (ie, Atlanta metropolitan, rural Georgia, and Georgia excluding Atlanta/rural Georgia) were pooled as "Georgia," and registries 1 and 31 (ie, San Francisco—Oakland and San Jose—Monterey) were pooled as "SFSJ" because the UVI is the same for these areas. Therefore, US SEER data generated a total of 13 areas. The age-standardized incidence rates (ASRs) are calculated according to the world standardized population for 2000-2025 (National Cancer Institute SEER website).

For the validation dataset, information was extracted from International Agency for Research of Cancer (IARC) CI5 volume X, which contains data for 2003 to 2007 only. To ensure homogeneity of the data, only US data of the white population was used. This US dataset contained some overlapping period and regions from the SEER data entries; even within the same SEER region, the data collected in this set were limited to 2003 to 2007, which was different from the SEER dataset where data were collected since the establishment of the registry. The source of data is listed in Supplemental Table I (available at http://www.jaad.org).

UVI calculation and estimation

Daily average UVI was calculated based on records from July 1, 2002 to June 30, 2014 from a satellite database (available at: http://www.temis.nl/uvradiation/SCIA/stations_uv.html). For country UVI estimation, either the data obtained from the station in the center of the country was used or, when that was not possible, average data from stations on