

## Commentary

# Is Sunlight Important to Melanoma Causation?

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Melanoma is considered an epidemic cancer in North America, Europe, and Australia over the past several decades. Incidence is still increasing in the United States, although the rate of increase is smaller than in previous years (1). To investigate this epidemic, etiologic studies have been conducted worldwide, yielding some understanding of melanoma risk factors and a greater appreciation for the complexity and heterogeneity of melanoma. Melanoma represents a paradigm for studying genetic and environmental determinants of cancer risk because both strong host risk factors (with some genes identified; refs. 2-5) and exposures (primarily UV radiation) have been identified in multiple populations. For several decades, different patterns of melanoma have been recognized. Subtypes of melanoma have been variously classified, including by histology (6), molecular profiles and UV exposure (7, 8), or by anatomic site as a surrogate of exposure (9, 10). One difficulty in conducting sufficiently powered studies to examine risk factors by melanoma subtype, however defined, is the need for careful phenotyping of study subjects. Most epidemiology studies have lacked power to separate adequately the risk factors for subtypes. Identified risk factors, therefore, are those of the more common subtypes.

Association between UV exposure and melanoma derives from several lines of evidence. Sun exposure is the dominant component of total UV dose in most humans, even in populations with substantial artificial-source UV exposure. Descriptive epidemiology of melanoma first revealed geographic variations in incidence, with generally higher rates of melanoma closer to the equator. More convincing were early case-control studies showing much lower risks of melanoma in individuals who migrated to very sunny areas after age 10 (11). Later case-control and cohort investigations have shown higher melanoma risk for individuals with greater sun exposure (12). Recently, tanning bed use, common among teenagers and young adults (13), has also been shown to confer increased risk of melanoma in case-control and prospective cohort studies (14, 15).

At least two issues complicate establishing solar UV exposure as a melanoma risk factor. First, measurements

of solar exposure are neither well codified nor precise. Second, exposure effects are highly modified by host factors and behaviors. Consistent UV measures across populations are particularly challenging, largely because UV intensity and sun-related behavior patterns vary so widely. Multiple components contribute to an individual's UV exposure at any given time, including cutaneous phenotype; extent of previous exposure (e.g., how tan at the time of exposure); type of clothing; extent of clothing; time of day; day of the year; latitude; elevation; cloud cover; air quality; extent of shade coverage; use of sunscreens (type of sunscreen, amount of application, time since application); activity; and posture (standing, sitting, prone, or supine). It is challenging to collect even part of this information with an activity diary and exposure meters (16).

Traditionally, exposure has been assessed primarily by questionnaires. In questionnaires, individuals are usually asked to recall usual exposures over various intervals at different ages. Their estimates are inevitably imprecise, and misclassification is a concern. Recall of adult exposures, however, seems to be more reproducible than that of childhood exposures, and total sun exposure (time spent outdoors) more reproducible than intermittent exposure (17). Questionnaire measures of cumulative exposures also correlate with solar damage assessed by histology (18). Despite the heterogeneity of exposure measures across populations, a recent meta-analysis still found that intermittent sun exposure, total sun exposure, and sunburns were all significantly associated with risk of melanoma (12).

In a collaborative case-control study (with University of California, San Francisco and University of Pennsylvania), we found that sun exposure patterns varied by gender and skin type; we therefore considered men and women separately. We used residential history as a surrogate of total lifetime UV exposure to try to minimize recall bias. We found that increasing individual risk was associated with higher average annual ambient UVB flux (measured UVB at ground level). For every 10% increase in UVB flux, melanoma risk was increased 19% for men and 16% for women (19). This residential measure worked in the highly mobile U.S. population, but did not discriminate exposures in Italian study subjects who mostly lived in the same geographic area for much of their lives (20). In the U.S. study, individual risk increased also with more adult time spent outdoors. Among both genders, individuals who tanned well spent much more time outdoors than those who did not. Even among those who tanned well, risk of melanoma increased with increasing adult sun exposure (19).

Solar exposure also importantly influences melanoma risk through interactions with host susceptibility factors

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that may result in identifiable phenotypes. Melanoma risk phenotypes strongly linked to UV exposure include dysplastic nevi, common acquired nevi, freckling, and history of sunburns (21), but the relationships seem to be complex. Prevalence of dysplastic nevi seems to be related to sun exposure (22). Several studies in children have shown that increased sun exposure leads to increased number of nevi (23-25). Within melanoma-prone families having dysplastic nevi, nevi tend to increase in number and morphologic atypia with higher sun exposure, and to involute and disappear over time when sun-protective measures are followed (26). These observations suggest that sun exposure influences both nevus induction and progression. Freckling and number of sunburns are also complex variables reflecting host susceptibility and UV exposure. Freckling is related to UV exposure in fair-skinned individuals and sometimes to polymorphisms in the melanocortin-1 receptor gene (27). Sunburns result not only from an extreme exposure for the cutaneous phenotype of an individual but also from acute inflammatory response to the burn. The same exposure in another deeply tanned or pigmented individual may evoke little measurable response because of the filtering effects of the pigmentation. The visible cumulative changes in the skin reflect not only the total UV exposure but also the resulting host-specific damage. Within our case-control study, therefore, we developed a parsimonious relative risk model using a few UV-related phenotypic markers visible on the back, gender, age, and, for men, history of sunburns. These relative risk models yielded an attributable risk for melanoma of 86% for men and 89% for women (28). These risks likely represent the interaction of host susceptibility and total UV exposure.

Although there are numerous questions remaining about melanoma risk and UV exposure, including exposure timing, age at exposure, behavioral components, modulating effects of host susceptibility factors on exposure, and the biological mechanisms of melanoma induction (29), the body of evidence implicates UV exposure as a major contributor to melanoma etiology.

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