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Could sun exposure improve melanoma survival?

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Abstract

Solar ultraviolet radiation (UVR) exposure is clearly associated with increased mortality from non-melanoma skin cancer – usually squamous cell carcinoma. However, the association with cutaneous melanoma is unclear from the evidence in ecologic studies, and the few analytic studies that have been published show that high levels of intermittent UV exposure prior to diagnosis are associated with improved survival from melanoma. We had previously noted that histologic evidence of solar elastosis was inversely associated with melanoma mortality in five-year follow up of a cohort of melanoma patients in Connecticut. Using data from this population-based study of cutaneous melanoma, we calculated the hazard ratio for melanoma-specific mortality, using a competing risk analysis, accounting for death due to other causes as a competing risk. Other potentially confounding covariates, such as other measures of solar exposure, surveillance measures and clinical prognostic factors, were evaluated and controlled in analyses. In a multivariate analysis, taking into account competing risks for mortality, awareness of skin, lesion thickness, anatomic site of melanoma and mitotic index, solar elastosis was positively and significantly associated with survival ($P < 0.01$; Hazard Ratio 0.5, 95% Confidence Interval 0.3, 0.8). These analyses suggest that some factor associated with sun exposure, particularly the more objective measure evaluated in the original lesion biopsy — solar elastosis — may play a more complex role in the progression of melanoma than previously thought. Further studies should focus on replicating these results and on understanding more thoroughly the biological relationship of solar exposure to progression in melanoma.

Introduction

Changes in melanoma incidence and mortality

In most developed countries throughout the world the incidence and mortality of melanoma have increased rather dramatically up to the year 2000, when the trends have flattened somewhat (1). Surprising to some is the fact that in most series that have measured Breslow thickness at diagnosis, the great majority of the increase is due to an increase in thin lesions, those less than 1 mm in Breslow thickness and thus have an excellent prognosis (2). Therefore, as one would anticipate, the mortality from melanoma has not changed significantly. It is disappointing, however, that the public health interventions that have been developed have not appeared to reduce morbidity.

As the very thin lesions have increased so dramatically, perhaps these are actually different from previous melanomas (3-6). In fact, it has been hypothesized that these lesions are actually the result of intense intermittent sun exposure in addition to increased diagnostic pressure and medical-legal considerations (5). An important suggestion from these authors is that these sun-induced melanomas could be more “indolent” than others.

Different etiologies for melanoma

Several authors have posited multiple etiologies for melanoma. It has long been thought that Lentigo maligna melanoma (LMM) is solely induced by long term sun exposure. In fact, one of the indications for diagnosis of LMM is the presence of solar damage, or solar elastosis, in the biopsy of the skin. However, we noted that there was a strong relationship between sun exposure and thin melanomas, many of them superficial spreading melanomas, even after deleting LMM from the analyses. This relationship could be due to multiple factors, such as those with higher social class having the dual characteristics of good health care and screening as well as the means to take holiday vacations where they would have the intense, intermittent sun exposure associated with the etiology of melanoma. Therefore, it is critical to account for social class, or educational level, and – more importantly – screening or detection pressure when evaluating the relationship between sun exposure and Breslow thickness in melanoma.

Long noted is the lack of a relationship between sun exposure and nodular melanoma (7), those melanomas that appear to be aggressive and in the vertical growth phase at diagnosis. Thus, one might prevent the slow-growing, more indolent sun-induced melanomas through sun protection measures, but based on current trends, it appears that the nodular melanomas remain unaffected by such measures. Whiteman posited a “divergent pathway” model for melanoma (8) that has captured the interest of many epidemiologists and pathologists. In this model, he has suggested that those individuals who are nevus-prone also tend to

develop melanomas on the trunk, while those individuals who are not nevus-prone tend to develop melanomas on their exposed skin and these are more likely to be sun-induced. While this model is attractive, it is still simplistic as our data from Connecticut show that solar damage, characterized as solar elastosis, occurs all over the body – on truncal areas as well as the extremities and the head and neck – in nevus-prone as well as sun-induced melanomas. Counterpoint to the suggestion that sun induced melanomas are more “indolent”, Lackiewicz et al. (9) have evaluated the SEER data in the United States and show a striking difference in survival in those melanomas on the face and neck with much poorer survival compared to those on the trunk and extremities. Thomas et al. (10) and Bastian’s group (11-12) have reported a different mutational profile in melanomas in chronically sun exposed areas compared to those in intermittently exposed areas, with *NRAS* mutations more common in sun exposed areas and among older individuals and *BRAF* (mostly V600E) mutations more common among “nevogenic” individuals, further supporting Whiteman’s hypothesis.

International data

Armstrong (13) has evaluated the 5-year survival from melanoma by country (with good records and more than 100 cases of melanoma annually), ranking 5-year survival by incidence. Strangely enough the higher the incidence, the better the survival, up to an incidence of approximately 25 per 100,000 with a survival rate of 90%. At the higher incidence rate, survival plateaus at the 90% level. While this observation might be due to better surveillance where there is a higher incidence, it could also be due to a higher incidence from sun-induced, and more slowly-growing, lesions which have a better survival (due to their indolent nature).

Connecticut data

In Connecticut, we were able to evaluate this suggestion as we had been investigating the role of surveillance (skin self-examination, physician skin examination) in relationship to mortality from melanoma (14). Thus, we were able to evaluate the relationship between sun exposure and mortality from melanoma, while controlling for surveillance and other important risk and prognostic factors (15). In this analysis the three major variables used to measure sun exposure – sunburn, intermittent sun exposure and solar elastosis – were each significantly associated with mortality from melanoma in univariate analyses (Hazard Ratio (HR) 0.5 -95% Confidence Interval (CI) 0.3-0.9, HR 0.6 – 95% CI 0.3-1.0, and HR 0.5 -95% CI 0.3-0.9, respectively). It should be noted that the most objective variable among these is “solar elastosis”. Thus, sun exposure *prior* to the diagnosis of melanoma was associated with better survival among those reporting higher levels of sun exposure or exhibiting more solar elastosis.

Solar elastosis

Solar elastosis consists of disorganized fibers made up of elastin that underly aging and/or sun-damaged skin. Little attention has been paid to solar elastosis, but in the two survival studies that have evaluated solar elastosis, an important inverse association between the presence of solar elastosis and survival from melanoma has been noted (16-17). Landi et al. (18) in an online supplement to a Science article have elaborated on the histological properties of solar elastosis. This work sets up a foundation for further biological and chemical elucidation of the properties of solar elastosis and how it might beneficially affect survival.

When sun exposure measures were appropriately controlled in multivariate survival analyses, solar elastosis in the Connecticut cohort was even more protective (HR 0.4, 95% CI 0.2-0.8) than other sun exposure measures and more significant than in univariate analyses. The data allowed for the control of skin surveillance and skin “awareness” was also found to be protective for survival (HR 0.5, 95% CI 0.3-0.9) while adjusting for the highly prognostic factors of Breslow thickness, anatomic site and mitoses.

Balance for solar elastosis in melanoma

Solar elastosis is an independent measure of solar exposure that likely accounts for host susceptibility factors as well as solar exposure. It is clear from the literature that continuous and high levels of solar exposure leads to the development of squamous cell carcinoma and that intermittent high doses of solar exposure are associated with basal cell carcinoma and cutaneous melanoma. Often sunburn is used as a measure for this blast of sun exposure, but it is likely that solar elastosis is more independently measured than sunburn. Whether solar elastosis itself is protective against survival is at this time unknown. There are other factors associated with sun exposure that solar elastosis may actually be measuring – such as improved DNA repair capacity, increased tanning with resultant “sun protection factor (SPF)”, thickened stratum corneum, or other yet to be understood factors.

Against these negative effects of sun exposure are placed the positive values of UV exposure, such as improvement in “seasonal affective disorder”, polymorphic light eruption, adaptation of DNA repair capacity, lower blood pressure, protection against some autoimmune diseases and, more recent evidence has implicated that the synthesis of vitamin D from UV exposure plays an important role in preventing some cancers – both incidence and potentially progression.

DNA repair capacity

Numerous studies have shown that repeated low doses of UV exposure induce DNA repair capacity and lead to adaptation. For example, de Winter et al. (19) showed a decrease in UV-induced dimer formation after repeated UV doses, and

that this was more effective among those with darker skin. Bataille et al. (20) reported photoadaptation after multiple low doses of UV exposure, such that the level of dimers was almost halved and this varied by skin type as well.

Vitamin D

Another explanation for the association with sun exposure and melanoma progression is that serum Vitamin D levels may not be adequate to prevent the development of melanoma, but that high levels in and around the time of diagnosis might prevent progression of melanoma (15, 21). Inadequate evidence exists to suggest that current vitamin D standards are too low, but it is likely that they could be and this could explain some of the conflicting results found in the literature in relationship to solar exposure (22-23).

Conclusion

Caution in the sun and with messages about the sun

In conclusion, the data are currently suggesting new directions for understanding the etiology and progression of melanoma. Although some of these directions are counter-intuitive, it would not be wise to ignore the suggestion that sun exposure is a two-edged sword: leading to the development of melanomas (possibly more indolent melanoma) but providing some protection against the progression of melanoma. How that mechanism may work is the subject of new investigations. The fact that the deeper melanomas have not changed their rate of incidence would suggest that we have not been successful in preventing them.

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