CORRESPONDENCE

Re: Sun Exposure and Mortality From Melanoma

The relationship between sun exposure and melanoma mortality and risk of lymphoma was explored in two recent articles and a related editorial (1–3). Unfortunately, the discussion in the related editorial (1) was not supported by the data presented.

The study by Berwick et al. (2) demonstrated, within the limits of a retrospective study, that patients with melanoma have a better prognosis if they had previous extensive sun exposure. The indices of sun exposure reflected many years of exposure dating to youth and did not relate to exposure in the interval after diagnosis of melanoma. No data on vitamin D levels were provided. The data strongly suggested that melanomas induced by intense sun exposure have a more benign behavior than those not induced by intense sun exposure. This is the most direct explanation for increased survival from melanomas arising in patients with a history of intense sun exposure and is analogous to experience with other sun-induced cancers. Squamous cell carcinomas of the skin induced by sun have a much better prognosis than squamous cell cancers arising in scars. This relationship between melanoma survival and sun exposure may explain the stable melanoma mortality rate despite an increase in incidence in sun–induced melanoma and has consequences for public health.

Data in the article by Smedby et al. (3) suggest that participants who had extensive sun exposure had a decreased lymphoma risk compared with participants with less sun exposure. However, there was an exception for patients with a prior history of skin cancer. Thus, lymphoma risk was elevated in patients with skin cancer plus extensive sun exposure and decreased in patients with extensive sun exposure without skin cancer. This difference in risk cannot be explained by vitamin D levels because vitamin D levels should also be elevated in patients with extensive sun exposure and skin cancer. The data suggest that sun-induced skin cancer is simply a marker for a decreased ability to handle carcinogenic insult. The skin cancer data conflict with a direct link between sun exposure and lymphoma risk or a role for vitamin D. This problem with the analysis, which attributed the results to vitamin D levels, is not without consequences because it would lead to the recommendation that people increase their exposure to a carcinogen.

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Berwick et al. (1) describe a statistically significant positive association between melanoma survival and solar elastosis and conclude that sun exposure is positively associated with melanoma survival. Two hypotheses are offered as possible explanations for these results: 1) vitamin D synthesized by sun exposure might inhibit melanoma progression, and 2) chronic sun exposure induces melanization and increases DNA repair capacity that might result in less aggressive melanomas and better outcomes (1,2).

We suggest a third hypothesis: the results might reflect a mixed population composed of individuals who develop a less aggressive “environmental” variant of melanoma as a result of sun exposure and individuals who develop “genetic” melanoma, a more aggressive variant resulting from a genetic predisposition independent of sun exposure. Such a dichotomous population might be revealed epidemiologically by differing associations with melanoma family history, a variable not controlled for in the study’s reported multivariable analysis. Moreover, family history was ascertained using a self-administered questionnaire, a method previously associated with melanoma overreporting by up to 40% (3). It has been estimated that only 5%–10% of melanoma patients have a medically verifiable family history (4,5). Although a verified family history has not been shown to predict rate of survival in those with metastatic disease (3), rates of metastasis and overall melanoma survival in those with and without a family history of melanoma have not been extensively examined.

Examination of potentially different distributions of molecular markers in environmental and genetic melanomas could provide additional insight. For example, those with UV-induced melanomas might be expected to have a different vitamin D receptor status than those with melanoma resulting from genetics. A statistically significant association between variant vitamin D receptor alleles and Breslow thickness, a highly predictive prognostic indicator, has been previously demonstrated (6), but association with a family history of melanoma is not yet known.

Before the boldest clinicians start sending melanoma patients to tanning salons, family history and genetic characterization of melanoma patients in this and other survival study cohorts will be needed to correctly interpret results associating UV radiation exposure with increased melanoma survival.

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The study by Berwick et al. (1) suggests that high sun exposure is associated with increased survival of patients with cutaneous melanoma, independent of prognostic factors, such as Breslow thickness or anatomic location. The presence of solar elastosis in the skin specimen harboring the melanoma was the sun exposure indicator that was mainly associated with increased survival. Similar to solar keratoses, solar elastosis is more prevalent on chronically sun-exposed skin, and it increases sharply after age 50 years (2).

Sun exposure is recognized as the main environmental cause of the melanoma epidemic that has stricken white populations since 1950. Melanomas in body sites chronically exposed to the sun (e.g., head and neck) are the most prevalent at older ages, whereas melanomas in body sites exposed to intermittent sun exposure are the most prevalent melanomas in people younger than 50 years (3). This suggests that intermittent sun exposure has a greater potential to cause melanomas at younger ages than chronic sun exposure. There is now evidence that skin normally covered by clothing is more sensitive to solar radiation than skin normally exposed to the sun (4) and that melanoma may arise from different biologic pathways (5,6). These elements prompt us to hypothesize that some melanomas could be associated with intermittent sun exposure and with the numbers and size of acquired nevi that develop during childhood and adolescence and would mainly occur on covered skin areas (e.g., the trunk). Other melanomas could be associated with chronic sun exposure and thus also with solar keratoses and solar elastosis and would mainly occur on uncovered body sites (e.g., the head). The results of Berwick et al. (1) suggest that tumors that arise more as a consequence of chronic sun exposure have a less aggressive phenotype than tumors that arise more as a consequence of intermittent sun exposure.

This suggestion is supported by the observation that lentigo melanoma (excluded in the study by Berwick et al.) is often associated with squamous cell skin cancer, solar keratosis, and chronic sun exposure. Lentigo melanoma has a less aggressive clinical course than nodular and superficial spreading melanoma. To test the possible effect of type of sun exposure (chronic versus intermittent) on survival of melanoma patients, it would be important to know whether indicators of intermittent sun exposure were associated with survival (with and without including solar elastosis in the model). It would also be important to know the age and body site distribution of melanomas separately for melanomas with and without signs of solar elastosis and whether solar elastosis was associated with indicators of intermittent sun exposure.

From a public health point of view, however, the findings of Berwick et al. do not bring any motive for changing the prevention messages aiming to control the incidence of cutaneous melanoma through reductions in sun exposure.

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RESPONSES

We welcome the three letters responding to our article “Sun Exposure and Mortality From Melanoma” (1). Kalish suggests that “…melanomas induced by intense sun exposure have a more benign behavior than those not induced by intense sun exposure.” We agree that this is a possibility; and one of us suggested it, somewhat cautiously, over 20 years ago “…melanoma might be biologically more benign if it occurs in association with high ambient sun exposure” (2). It is not the only possibility, though, for the point in the development
of melanoma at which sun exposure might exert its effect on survival is still not known. For example, at present we cannot distinguish between the effects of sun exposure at the time melanoma is initiated, during the course of its preclinical development, or after it has been diagnosed and treated. The last is, perhaps, unlikely because our sun exposure measures were directed to past rather than present exposure; but it cannot be excluded entirely.

Dellavalle and Johnson advance the hypothesis that melanoma largely due to sun exposure is less aggressive than melanoma largely due to genetic predisposition. This is certainly a possibility and is consistent with the dual pathway hypothesis for melanoma; one pathway is characterized by the presence of p53 staining and indicators of high sun exposure, and the other is characterized by the absence of p53 staining, high nevus density, and a higher prevalence of nevus remnants in the lesions (3). We have found evidence supporting this hypothesis in a subset of subjects in a different study (4).

Dellavalle and Johnson make the interesting suggestion that family history might be useful in distinguishing more aggressive from less aggressive melanomas. However, in what is apparently the only relevant study published to date, there was no statistically significant difference in survival time between 26 patients with metastatic melanoma who were members of families with multiple melanomas (median survival = 57.4 months) and 78 closely matched patients with metastatic melanoma from families with no previous melanoma history (median survival = 50.0 months; \( P = .99 \)) (5).

Autier and colleagues have written for vitamin D “conflicts with a direct link between sun exposure, an established skin cancer carcinogen, and malignant lymphomas (1)” are unclear and that the discussion of alternative scenarios is warranted in light of the novelty of the findings (2). However, we do not believe that our simultaneous and confirmatory finding of a positive association between skin cancer history and lymphoma risk, according to Dr. Kalish, “conflicts with a direct link between sun exposure and lymphoma risk or a role for vitamin D” (3).

We agree with Dr. Kalish that the biologic mechanisms of an inverse association between sun exposure, an established skin cancer carcinogen, and malignant lymphomas (1) are unclear and that the discussion of alternative scenarios is warranted in light of the novelty of the findings (2). However, we do not believe that our simultaneous and confirmatory finding of a positive association between skin cancer history and lymphoma risk, according to Dr. Kalish, “conflicts with a direct link between sun exposure and lymphoma risk or a role for vitamin D” (3).

We agree with Dr. Kalish that the biologic mechanisms of an inverse association between sun exposure, an established skin cancer carcinogen, and malignant lymphomas (1) are unclear and that the discussion of alternative scenarios is warranted in light of the novelty of the findings (2). However, we do not believe that our simultaneous and confirmatory finding of a positive association between skin cancer history and lymphoma risk, according to Dr. Kalish, “conflicts with a direct link between sun exposure and lymphoma risk or a role for vitamin D” (3).

In our report (1), we noted that frequent sunbathing and sunburns were associated with increased risk of skin
with non-Hodgkin lymphoma risk, abroad were also inversely associated different ages in Denmark, Sweden, and patients, frequent suntan habits at presented (Table 1). Relative risks for non-Hodgkin lymphoma after frequent sunburns were more difficult to interpret owing to even smaller numbers and very unstable estimates in categories of high exposure (data not shown). Thus, there was little to suggest that frequent sun exposure would be associated with an increased rather than a decreased lymphoma risk among skin cancer patients. We conclude that our overall findings appear to be independent of skin cancer history and that our concomitant observation of a positive association between skin cancer and lymphoma therefore does not contradict vitamin D as a plausible candidate factor, among other factors, for the observed overall inverse association. With respect to the intriguing link between skin cancer and lymphoma, we agree with Dr. Kalish that our results support the notion that skin cancer could be a marker for other deficiencies, such as deficiencies of immune function or DNA repair.

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Our editorial raised the question of whether vitamin D might account for findings in two reports published in the Journal (1,2) that suggested a beneficial impact of sun exposure on the incidence of malignant lymphoma, and outcome of skin melanoma (3). The authors of
both manuscripts, and of a third study that we cited, which had similar findings for non-Hodgkin lymphoma (4), all raised the question of whether vitamin D could account for the apparent salutary influence of sunlight. In his letter, Dr. Kalish indicated some legitimate questions regarding that interpretation, as did we in our editorial. We pointed out that the findings of Berwick et al. (1) applied to sun exposures predating the melanoma diagnosis, and we, like Kalish, suggested that the finding could be due to a more benign behavior of melanomas arising on chronically sun-exposed skin.

In support of the “most direct” explanation for the findings by Berwick et al., Dr. Kalish speculates that “…This relationship between melanoma survival and sun exposure may explain the stable melanoma mortality rate despite an increase in incidence in sun-induced melanoma.” Although this may be one explanation for the stable mortality rate, it is more likely a product of increased awareness and earlier detection. In the last several decades in the United States, an increasing proportion of melanomas have been diagnosed at a localized stage or as thin lesions, whereas the diagnosis of ulcerated poor-prognosis melanomas has declined (5). Corresponding with these trends, 5-year survival rates in melanoma statistically significantly improved from 1975 to 2000 (6).

Kalish cites the result in the article by Smedby et al. (2) that a history of non-melanoma skin cancer was associated with an increased risk of lymphoma as evidence against a hypothesis related to vitamin D. The results of Smedby et al. (2) indicated an inverse association with lymphoma for sunbathing, sunburns, and sunny vacations, and a positive association for nonmelanoma skin cancer. Clearly, these results are difficult to reconcile by one common mechanism. Considering this evidence, it seems likely that lymphomas—like melanomas—may arise through several pathways. Risk associated with a past history of skin cancer (reported by 4% of the case patients) is consistent with a role for a genetic variation in DNA repair efficiency or the immunosuppressive properties of UV radiation as discussed by Smedby et al. (2) and Hughes et al. (4). The observation in two recent reports (2, 4) of an inverse association related to periodic sun exposure suggests at least one additional mechanism through which sunlight might act. Whether this mechanism is related to vitamin D or some other correlate of sun exposure must still be sorted out.

No one, including the authors of the two reports, is suggesting that sunbathing is the route to cancer avoidance or to a better cancer outcome. However, the hypothesis that vitamin D—which can be obtained in supplement pills and diet, as well as through sun exposure—may act to prevent some forms of human cancer, is plausible and deserves additional study.

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