Sun Exposure and Mortality From Melanoma

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Background: **Melanoma incidence and survival are positively associated, both geographically and temporally. Solar elastosis, a histologic indicator of cutaneous sun damage, has also been positively associated with melanoma survival. Although these observations raise the possibility that sun exposure increases melanoma survival, they could be explained by an association between incidence and early detection of melanoma. We therefore evaluated the association between measures of skin screening and death from cutaneous melanoma.** ***Methods:*** **Case subjects (n = 528) from a population-based study of cutaneous melanoma were followed for an average of more than 5 years. Data, including measures of intermittent sun exposure, perceived awareness of the skin, skin self-screening, and physician screening, were collected during in-person interviews and review of histopathology and histologic parameters (i.e., solar elastosis, Breslow thickness, and mitoses) for all of the lesions. Competing risk models were used to compute risk of death (hazard ratios [HRs], with 95% confidence intervals [CIs]) from melanoma. All statistical tests were two-sided.** ***Results:*** **Sunburn, high intermittent sun exposure, skin awareness histories, and solar elastosis were statistically significantly inversely associated with death from melanoma. Melanoma thickness, mitoses, ulceration, and anatomic location on the head and neck were statistically significantly positively associated with melanoma death. In a multivariable competing risk analysis, skin awareness (with versus without, HR = 0.5, 95% CI = 0.3 to 0.9, *P* = .022) and solar elastosis (present versus absent, HR = 0.4, 95% CI = 0.2 to 0.8, *P* = .009) were strongly and independently associated with melanoma death after adjusting for Breslow thickness, mitotic index, and head and neck location, which were also independently associated with death.** ***Conclusions:*** **Sun exposure is associated with increased survival from melanoma. [J Natl Cancer Inst 2005;97:195–9]**

Incidence rates for melanoma have increased in the last 50 years in all developed countries with large Caucasian populations, and mortality rates have increased as well, although less steeply. Sun exposure, particularly recreational or intermittent sun exposure, is the major known etiologic factor for melanoma, and it may interact with other important risk factors, such as nevi and tanning ability *(1)*. The consistent finding that intermittent sun exposure is associated with increased risk for melanoma has led to public health recommendations that excessive sun exposure should be avoided.

Sun exposure may be a determinant of either incidence or survival or both. Lemish et al. *(2)* noticed that survival increased with increasing melanoma incidence across several populations and suggested that melanoma might be biologically more benign if it occurs in association with high ambient sun exposure. Recent data from a larger number of different populations support the relationship observed by Lemish et al. *(2)*. In fact, melanoma incidence and survival are positively associated temporally and geographically *(3)*. At the individual level, two follow-up studies *(4,5)* have shown a possible association between survival from melanoma and solar elastosis, a histologic indicator of cutaneous sun damage.

Although these observations are consistent with a biologic effect of sun exposure on increased survival from melanoma, they could also be explained by increased early detection of melanoma, which is associated with increased incidence or increased sun exposure. To address the latter possibility, we have analyzed data on solar elastosis and melanoma survival from a population-based case–control study *(4,6),* considering the possible confounding effects of other variables, including physician skin examination, self-screening for melanoma, and perceived awareness of the skin.

Patients and Methods

Patients

We conducted a population-based case–control study of melanoma in Connecticut; the details of this study have been described previously *(6)*. In brief, case subjects were ascertained through the rapid case ascertainment mechanism of the Connecticut Tumor Registry, with a mean time of 3 months between pathologic diagnosis and interview (i.e., entry into the case–control study). All procedures were reviewed by the relevant institutional review boards, and all subjects provided written informed consent. In the original study, physician approval was given to contact 87% of eligible patients; 85% of these patients were interviewed, for an overall response rate of 75%. The original study enrolled 650 Caucasian residents of Connecticut diagnosed with invasive cutaneous melanoma from January 15, 1987, through May 15, 1989. For this analysis, we excluded 26 patients whose melanoma was diagnosed with lymph node or organ metastases. In addition, because lentigo maligna melanoma is closely related to solar elastosis, we excluded 95 patients who were diagnosed with lentigo maligna melanoma. We also excluded one patient who was missing follow-up status, leaving 528 patients in the database for the current analysis.

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Data Collection and Study Variables

Trained registered nurses conducted in-person interviews with all study participants. We designed a structured questionnaire to assess age at melanoma diagnosis, sex, level of education (high school or post–high school), history of severe sunburn with pain or blistering for 2 or more days (yes or no), intermittent sun exposure [categorized as low or high *(7)*], skin self-examination practices (yes or no), awareness of skin (yes or no), physician skin exam (yes or no), family history of melanoma (yes or no), site of melanoma (head and neck, trunk, or extremity), sunscreen use within last 10 years, sunscreen use before age 15 years, hair color (brunette or black, blond or brown, red or auburn), eye color (brown or light), and tanning ability (tans easily or poorly) *(6)*. A lifetime intermittent sun exposure index was created by summing recreational sun exposure histories before age 15 years and for the last 10 years [see references *(6)* and *(7)* for additional details] and then used to assign patients to either low or high intermittent sun exposure categories. A low level of intermittent sun exposure might be experienced by an individual who had never taken a sunny vacation, who spent less than 6 days per year in outdoor recreational activities, and who had never lived in a place that was at a latitude less than 32°N or S. A high level of intermittent sun exposure might be experienced by an individual who had taken more than 10 sunny vacations during his or her lifetime, spent more than 28 days per year in outdoor recreational activities, and had previously lived in a place at a latitude less than 32°N or S. Nurses trained in skin examination also counted nevi greater than 2 mm in largest diameter on the arms and backs of subjects (80%) who consented to undergo this procedure.

Yes/no information on skin self-examination practice, physician skin examination, and skin awareness were elicited by the following questions:

Skin self-examination. [Before your recent biopsy] did you ever (in your life) carefully examine your own skin? By this I mean actually check surfaces of your skin deliberately and purposely?

Physician examination. [Before your recent biopsy] did the doctor examine your skin during any of your visits?

Skin awareness. [Before your recent biopsy] did you ever think about your skin, how it looked, whether there were any changes, or whether there were any abnormal marks?

A single dermatopathologist (RB) conducted a standardized review of the histopathology of the primary melanoma for all of the 528 patients and recorded, among other things, solar elastosis (present or absent), thickness of lesion (according to the Breslow method), histologic subtype, ulceration (present or absent), mitoses (none or any).

Patients were actively followed-up over 5 years by biannual mail contact. Patients who did not reply to the mailing were contacted by telephone. For patients who could not be reached by telephone, we contacted their physicians. Vital status and date of death, if the patient was dead, were determined by physician interview or a spouse's report or from a death certificate. Cause of death was ascertained by death certificate and coded as "melanoma" when the first or underlying cause was listed as melanoma. Mean follow-up was 5.4 years for all patients. Eight percent of study participants had fewer than 4 full years of follow-up, 12% had complete follow-up between 4 and 5 years, and 80% were followed for 5 or more years.

Statistical Analysis

The primary endpoint for these analyses was death from melanoma. Risk of death from melanoma was estimated using a competing risk analysis *(8)*, accounting for death resulting from other causes as a competing risk. Time to death was calculated from the date of diagnosis of melanoma to death or last follow-up. The hazard ratios (HRs) of death were computed by means of competing risk regression and compared by means of a χ^2 test *(9)*. All statistical tests were two-sided. The competing risk package in R version 1.81, was used. This software is available free at http://www.fsf.org.

Results

Of the 528 patients in this analysis, 58 (11%) died of melanoma and 24 (5%) of other causes by the end of the study. The 2-, 3-, and 5-year cumulative incidence rates of death from melanoma were 3%, 6%, and 12% respectively. The median follow-up for patients who were alive was 5.4 years.

Evaluation of demographic and clinical variables showed the expected relationships with death from melanoma in univariate analyses (Table 1). For example, females had a slightly lower risk of death from melanoma than males (HR = 0.8, 95% CI = 0.5 to 1.3, $P = .33$). Although individuals who were older at diagnosis were more likely than those who were younger to die from melanoma (HR for every 10-year increase in age = 1.2, 95% CI = 1.0 to 1.4, $P = .08$), and more educated individuals were less likely than less educated individuals to die from melanoma (HR = 0.7, 95% CI = 0.4 to 1.1, $P = .11$), none of these associations was statistically significant. Furthermore, increasing Breslow thickness at diagnosis was strongly associated with increasing risk of death from melanoma (HR for each 1 mm increase in thickness = 1.4, 95% CI = 1.3 to 1.5, $P<.001$), as were anatomic site (patients with trunk and extremity melanomas were at a lower risk of death from melanoma than those with head and neck melanomas, HR = 0.4 and 0.3, respectively, $P = .001$), presence of ulceration (HR = 4.2, 95% CI = 2.4 to 7.2, $P<.001$), and presence of any mitoses (HR = 7.6, 95% CI 2.5 to 23.1, $P<.001$). Neither recent sunscreen use (HR = 0.6, 95% CI = 0.4 to 1.2, $P = .20$) nor childhood sunscreen use (HR = 0.5, 95% CI = 0.2 to 1.2, $P = .14$) were statistically significantly associated with the risk of death from melanoma. Nevus counts, for which we had data from only 80% of the patients, were not statistically significantly associated with death from melanoma (0–10 nevi, n = 194, HR = 1.0 [referent group] 11–30 nevi, n = 164, HR = 1.3, 95% CI = 0.7 to 2.5; >31 nevi, n = 84, HR = 2.1, 95% CI = 1.1 to 4.1, $P_{trend} = .10$).

Sun exposure was statistically significantly inversely associated with risk of death from melanoma, regardless of the measure used (Table 1). Individuals who had ever been severely sunburned (HR = 0.5, 95% CI = 0.3 to 0.9, $P = .02$) or who had high levels of intermittent sun exposure (HR = 0.6, 95% CI = 0.3 to 1.0, $P = .04$) were less likely to die from melanoma than individuals who had never been severely sunburned or who had low levels of intermittent sun exposure, respectively (Table 1).

The presence of solar elastosis was also inversely associated with death from melanoma (HR = 0.5, 95% CI = 0.3 to 0.9, $P = .02$). Although the prevalence of solar elastosis varied statistically significantly by site of melanoma, with 71% in melanomas on the head and neck, 59% in melanomas on the extremities, and 45% in melanomas on the trunk ($P<.001$), for

Table 1. Predictors of risk of death from melanoma in a population-based study of residents from Connecticut

Variable	Total no.*	No. of melanoma deaths	Hazard ratio (95% confidence interval)	*P* value
Demographic variables				
Sex				
Male	272	33	1.0 (referent)	.33
Female	256	25	0.8 (0.5 to 1.3)	
Age at diagnosis 10-year increase	528	58	1.2 (1.0 to 1.4)	.08
Education				
Up to high school	202	28	1.0 (referent)	.11
Greater than high school	326	30	0.7 (0.4 to 1.1)	
Sun exposure variables				
Ever severely sunburned				
No	173	27	1.0 (referent)	.02
Yes	353	31	0.5 (0.3 to 0.9)	
Intermittent sun exposure index				
Low	189	27	1.0 (referent)	.04
High	328	28	0.6 (0.3 to 1.0)	
Solar elastosis				
Absent	254	36	1.0 (referent)	.02
Present	268	21	0.5 (0.3 to 0.9)	
Screening variables				
Skin self-examination				
No	458	53	1.0 (referent)	.28
Yes	70	5	0.6 (0.2 to 1.5)	
Skin awareness				
No	225	37	1.0 (referent)	<.001
Yes	303	21	0.4 (0.2 to 0.7)	
Physician skin examination				
No	318	39	1.0 (referent)	.28
Yes	210	19	0.7 (0.4 to 1.3)	
Clinical variables				
Site of melanoma				
Head and neck	36	10	1.0 (referent)	.001
Trunk	284	30	0.4 (0.2 to 0.8)	
Extremity	208	15	0.3 (0.2 to 0.7)	
Breslow thickness 1-mm increase	528	58	1.4 (1.3 to 1.5)	<.001
Ulceration				
Absent	443	35	1.0 (referent)	<.001
Present	75	21	4.2 (2.4 to 7.2)	
Mitoses				
None	208	3	1.0 (referent)	<.001
Any	307	54	7.6 (2.5 to 23.1)	

*Numbers may vary because of missing data for some variables.

each melanoma site, patients with elastosis had better survival than those without. For melanomas of the head and neck, the hazard ratio of death for patients with solar elastosis compared with those without solar elastosis was 0.44 (95% CI = 0.12 to 1.65); for melanomas on the trunk, the hazard ratio was 0.34 (95% CI = 0.16 to 0.79); and for melanomas on the extremities, the hazard ratio was 0.64 (95% CI = 0.24 to 1.70).

We examined the association between screening and survival from melanoma. Screening for melanoma was inferred from skin awareness, skin self-examination, and physician skin examination. Compared with individuals who did not report skin awareness, individuals who did were at statistically significantly lower risk of death from melanoma (Table 1, $P<.001$). However, reported skin self-examination and physician skin examination were not statistically significantly associated with risk of death from melanoma ($P = .28$ for each).

When melanoma-specific mortality was analyzed in a multivariable setting, including all the variables from the univariate analysis and accounting for the competing risk of death from other causes, solar elastosis and skin awareness remained statistically significant predictors of survival, as did anatomic site, Breslow thickness, and mitotic index (Table 2). In addition, the point estimates of the hazard ratios in the multivariable model for intermittent sun exposure (HR = 0.6, 95% CI = 0.3 to 1.1) and ever severely sunburned (HR = 0.6, 95% CI = 0.4 to 1.1) changed little from their univariate values (Table 1), but the confidence intervals widened and *P* values rose, both to 0.12. In a multivariable model that included only the 80% of subjects for whom nevus counts were available and containing nevus count as a covariate, the hazard ratio of nevus count in association with death from the 95% confidence interval for melanoma increased slightly to 1.0 to 1.7 over its crude value. The point estimates of the hazard ratios for the other variables in this model were changed little from those shown in Table 2.

Discussion

The results of this population-based study of survival from melanoma suggest that some factors associated with high levels of sun exposure, such as solar elastosis and, to a lesser extent, sunburns and intermittent sun exposure, are inversely associated with death from melanoma. The association between survival and solar elastosis was not explained by confounding with early detection or screening behaviors, represented by skin awareness, skin self examination, and physician examination, or by confounding by social class, represented by educational level, all of which were also inversely associated with death from melanoma in univariate analyses. The inverse associations of solar elastosis and skin awareness with death from melanoma were also independent of its strong associations with melanoma site, lesion thickness, and mitoses.

One limitation of this study was the crude evaluation of sunscreen use. Moreover, the study was conducted during the 1980s, when few individuals would have used sunscreen regularly during most of their life. Thus, the weak and nonstatistically significant reductions in the risk of melanoma death may or may not be relevant to any contribution sunscreen use might make to an outcome of melanoma.

Our study was also limited by the use of the simple qualitative variables in a questionnaire assessment of early detection behaviors. Skin awareness, however, was a strong and independent predictor of survival of patients with melanoma and is a plausible indicator of likelihood of detecting melanoma early. Our study also lacked complete information on number of nevi, which could be confounded with sun exposure. However, analyses that included number of nevi as a covariate—based on the 80% data set that had nurse-assessed numbers of nevi—found no difference in point estimates of the solar exposure variables or other independent variables from those without adjustment of nevi from the full data set.

Table 2. Independent predictors of death from melanoma in a multivariable model*

Variable	Hazard ratio (95% confidence interval)	*P* value
Solar elastosis		
Absent	1.0 (referent)	.009
Present	0.4 (0.2 to 0.8)	
Skin awareness		
No	1.0 (referent)	.022
Yes	0.5 (0.3 to 0.9)	
Breslow thickness		
1 mm increase	1.3 (1.2 to 1.4)	<.001
Anatomic site		
Other	1.0 (referent)	.001
Head/Neck	3.0 (1.5 to 6.0)	
Mitoses		
None	1.0 (referent)	<.001
Any	7.6 (2.5 to 23.1)	

*This model was run with all the variables in Table 1. Only these variables remained statistically significant at a level <0.10 are shown.

Our study has several strengths. Because the original aim of this study was to evaluate the role of skin self-examination in preventing mortality from cutaneous melanoma, survival information was carefully collected. The approaches used to collect vital status data—i.e., phone calls to patients or spouses or physicians for those patients who did not respond to the mail follow-up questionnaire—avoided potential misclassification of cause of death, as could have occurred if we had relied solely on death certificates. Additionally, the association between sun exposure and death from melanoma could be adjusted for potential confounding by early detection because data on skin awareness, skin self-examination, and reported physician skin examination were available. Furthermore, early detection should not confound the associations found between solar elastosis and mortality. Although skin awareness was strongly associated with lesion thickness, the major prognostic factor for melanoma (P = .008), the relationship does not appear to be confounded by solar elastosis (OR = 1.3, 95% CI = 0.89 to 1.78, P = 0.19). Similarly, the relationship between solar elastosis and death from melanoma does not appear to be confounded by the association of solar elastosis with lesion thickness (P = 0.81). Thus, in our data, it seems as if solar elastosis is a clear independent prognostic factor for mortality from melanoma. Another strength of this analysis is that, although the sun exposure measures were qualitative, they showed strong associations with melanoma risk that were comparable with meta-analyses of the results from similar studies *(10,11)*. For example, Elwood and Jopson reported a relative risk estimate of 1.87 (95% CI = 1.67 to 2.09) from a meta-analysis of case–control studies, almost precisely the point estimate found in the case–control study *(6)* that contributed the patients to this study. The evaluation of solar elastosis by a single pathologist is an additional strength *(12)* because it avoids interobserver variation in diagnostic accuracy.

Is an effect of sun exposure on melanoma survival at all plausible biologically? Sun exposure is necessary for the synthesis of 25-hydroxy vitamin D_3 in the skin, which when converted to 1,25 $(OH)_2D_3$, the primary ligand for the vitamin D receptor, has antiproliferative and proapoptotic effects *(13,14)*. It would be reasonable to speculate, therefore, that the apparently beneficial relationship between sun exposure and survival from melanoma could be mediated by vitamin D. However, an alternative hypothesis is that sun exposure induces less aggressive melanomas by inducing melanization and increasing DNA repair capacity, both of which might reduce further mutational changes in a melanoma *(15,16)*. Which, if either, hypothesis is more plausible remains to be determined.

In summary, we found that intermittent sun exposure may increase survival from melanoma. If these results are confirmed, our findings have the potential to lead to interventions, such as stimulation of the vitamin D pathway or DNA repair capacity, that would increase survival from melanoma and, perhaps, from other cancers.

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