Average Midrange Ultraviolet Radiation Flux and Time Outdoors Predict Melanoma Risk


Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Bethesda, Maryland 20892 [T. R. F., C. C. B., M. H. G., P. H., M. A. T.]; Pigmented Lesion Study Group, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104 [D. G., D. E. E., A. H.]; and Melanoma Clinic and Department of Epidemiology and Biostatistics, University of California, San Francisco, California 94143 [R. W. S., E. A. H.]

ABSTRACT

Sunlight is the major environmental risk factor for melanoma. Descriptive studies have shown latitudinal variation in population incidence and mortality rates [D. C. Whitteman and A. C. Green, Int. J. Dermatol., 38: 481–489, 1999, and B. K. Armstrong, Australian J. Dermatol., 38 (Suppl. 1): 51–56, 1997]. In analytic studies, individual exposure has been particularly difficult to quantify. Lifetime residential history was coupled with levels of midrange UV radiation (UVB flux) to provide a measure of individual exposure to sunlight thought to be less subject to misclassification and recall bias. Data were analyzed from 718 non-Hispanic white patients with invasive cutaneous melanoma from melanoma clinics in Philadelphia and San Francisco. Matched controls were 945 patients from outpatient clinics with similar catchment areas. The association of melanoma risk and history of UVB flux along with the usual outdoor exposure risk factors were studied. A 10% increase in the average annual UVB flux was associated with a 19% [95% confidence interval (CI), 5–35%] increase in individual odds for melanoma for men and 16% (95% CI, 2–32%) for women. In men, a 10% increase in hours outdoors was associated with a 2.8% (95% CI, 1.2–4.5%) increase in odds. Even in women who could develop a deep tan, a 10% increase in hours outdoors was associated with a 5.8% increase in odds (95% CI, 1.4–10.4%). The association between melanoma risk and average annual UVB flux was strong and consistent for men and for women. The association with total adult hours outdoors was notable for men of all skin types and women who develop a suntan.

INTRODUCTION

Sunlight is the major environmental risk factor for melanoma. However, estimates of melanoma risk from sun exposure have varied widely, likely because the methods for measuring this exposure were varied and often imprecise. In analytic studies, individual exposure has been particularly difficult to quantify, since both timing and magnitude are thought to be important, and neither is easily documented. Based on migrant studies, childhood exposure has been hypothesized to be a “critical period” for melanoma risk (1). Sun-related behavior is complex, and its reporting is subject to multiple biases. Individuals who burn rather than tan may be more likely to choose to spend much less time outdoors, particularly as adults. Intermittent high exposures at all ages may confer higher melanoma risk than total exposure (2). Confidence in this conclusion is tempered by the possibility of recall bias by the cases. Interview questions commonly used to measure sun exposure include number of sunburns, hours outdoors at various ages, and number of vacations in sunny places (1–3). All of these measures, especially those reflecting the exposures during childhood, embody attempts to recall rather ordinary events in the (distant) past, and are subject to both systematic recall bias and random misclassification.

In designing a case-control study for melanoma, we hypothesized that individual risk for melanoma is associated with lifetime residential history and the strength of the sunlight at those residences. Residential history should be a variable less subject to misclassification and differential recall bias than most measures of sun exposure. This paper reports on estimation of the association of melanoma risk and features of residential UVB2 history while also considering other risk factors such as time of outdoor exposure and skin response to sunlight.

MATERIALS AND METHODS

Participants. Patients, ages 20–79, with histologically confirmed invasive cutaneous melanomas, were recruited from those newly diagnosed in 1991–1992 at the Hospital of the University of Pennsylvania’s Pigmented Lesion Clinic in Philadelphia and the University of California’s Melanoma Clinic in San Francisco (4). Of the 768 eligible patients, 738 agreed to participate. Controls were from outpatient clinics with catchment areas similar to the two melanoma clinics (4) and were frequency matched to patients within strata defined by gender, age group, race, and study site. Of the 1228 randomly selected controls 1030 agreed to participate. Those presenting with dermatologic problems were excluded. The analysis was restricted to non-Hispanic whites because there were few subjects in other ethnic/race groups; hence, there were 718 cases and 945 controls.

Data Collected. Each participant was interviewed in person by trained interviewers to obtain individual characteristics including sunburn and suntan responses along with medical, occupation, residence, and outdoor exposure histories. Each participant was examined (4), and freckling pattern, skin color, solar damage, and counts of nevi ≥2 mm and dysplastic nevi were recorded. Extent of freckling and extent of solar damage were graded by comparison to a standard set of photos. Skin color was assessed by self-report and by examiner. Examiners (physicians and nurses) were uniformly trained and retrained every 6 months by the same instructor. Data were monitored weekly by the principal investigator. Dysplastic nevus status for each study subject was confirmed by an expert senior examiner (4, 5).

Residence, UVB Flux, and Outdoor Exposure History. The residence history was constructed in 6-month intervals beginning at date of birth and ending with date of interview, each rounded to January 1 or July 1. Each respondent reported locations of residence that lasted longer than 6 months, and the first year and duration of each. We defined the initial date for each location as July 1 of the first year of residence at that location.

Solar radiation between 280 and 330 nm (middle UV radiation or UVB) is of major concern for skin cancer risk (6). RB meters are used to measure radiant energy received per unit area. One RB count corresponds to ~0.068 mJ/cm2. The measured energy is a weighted average of wavelength-specific energy in the range 280–330 nm, with weight proportional to the biological activity of the wavelength. Our measure of UVB received at a location is RB counts received in 6 months, designated the UVB flux density or simply flux. A respondent was exposed to various fluxes as he or she moved from residence to residence. Summing assigned UVB values provided an estimate of the cumulative flux that could have been received. Dividing the cumulative flux by age in years provided an estimate of the average annual flux.

Regression equations for estimating flux at a location were derived from 11
years of ground level measurements from RB meters at more than 30 stations (6). Estimates of flux for locations in the continental United States were based on altitude, latitude, and daily sky cover. Estimates for other locations were based only on altitude and latitude. Six-month intervals with more than one residence were assigned the average flux of the associated residential locations. Time intervals not associated with a residential location were assigned fluxes using the observed mean imputation method (7).

Along with cumulative and average annual flux, we considered an estimate of the time spent outdoors. Respondents identified all of the outdoor jobs and all of the jobs held for 2 or more years. They estimated time outdoors on each job and the number of nonwork hours spent in the sunlight each day in the summer when UVB level is highest. The hours outdoors were comparable with other case-control studies, e.g., for the younger ages (8) and the adult ages (9). Responses were combined to estimate the hours spent outdoors in each 6-month interval of the individual’s residential history or the interval hours outdoors. Summing interval hours outdoors over age intervals provided an estimate of the cumulative hours outdoors, and dividing the cumulative hours outdoors by the appropriate number of years of age provided an estimate of the average annual hours outdoors.

Statistical Analysis. Standard statistical methods (10), including ANOVA and \( \chi^2 \) tests, were used to analyze flux and outdoor time variables. Conditional logistic regression was used to estimate ORs for melanoma and to test hypotheses (11). Likelihood ratio tests were used for several parameters and Wald tests for individual parameters. The statistical significance of a test statistic is given as a measure of the strength of evidence for an association in the study data. CIs have a nominal level 95%. All of the tests are two sided and \( P \) refers to \( P \leq 0.05 \). Subjects with unknown values for any analytic variable were excluded.

The exposure variables, flux, and outdoor time were analyzed on the natural logarithmic scale. The fit of models using log-transformed exposures was comparable with those using untransformed exposures, and the logarithmic exposure models provide easier interpretation. In particular, a 10% increase in an exposure variable is associated with the same increase in odds for melanoma for all of the referent exposure levels. This quantity will be denoted by OR10. An important advantage of this methodology is that the OR10 is independent of the scaling of the measurement instrument or the choice of measurement units.

RESULTS

Demographic data are summarized in Table 1. As would be expected from Surveillance, Epidemiology, and End Results data (12) more of the younger cases were women, and more of the older cases were men.

Table 1 Numbers and (percentage) of cases and controls by sex, study site and age group

<table>
<thead>
<tr>
<th>Age at interview</th>
<th>All respondents</th>
<th>Controls</th>
<th>Cases</th>
<th>Controls</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–29</td>
<td>518</td>
<td>400</td>
<td>427</td>
<td>318</td>
<td></td>
</tr>
<tr>
<td>30–39</td>
<td>91 (17.6)</td>
<td>62 (15.5)</td>
<td>89</td>
<td>71 (22.3)</td>
<td></td>
</tr>
<tr>
<td>40–49</td>
<td>119 (23.0)</td>
<td>102 (23.9)</td>
<td>102</td>
<td>93 (29.2)</td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>110 (21.2)</td>
<td>78 (18.3)</td>
<td>78</td>
<td>72 (23.1)</td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>95 (18.3)</td>
<td>87 (21.8)</td>
<td>64</td>
<td>47 (14.8)</td>
<td></td>
</tr>
<tr>
<td>70–79</td>
<td>69 (13.3)</td>
<td>50 (12.5)</td>
<td>42</td>
<td>25 (7.9)</td>
<td></td>
</tr>
</tbody>
</table>

Study site

Philadelphia 275 (53.1) 203 (50.8) 203 (47.5) 170 (53.5)

San Francisco 243 (46.9) 197 (49.3) 224 (52.5) 148 (46.5)

All respondents 518 400 427 318

Table 2 Means for cumulative UVB flux and average annual UVB flux for men and women by case-control status, age at interview, study site, and overall

<table>
<thead>
<tr>
<th>Study site</th>
<th>Cumulative flux UVB (10^-4 × RB units)</th>
<th>Average annual flux (10^-4 × RB units/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men Controls</td>
<td>Cases Controls</td>
</tr>
<tr>
<td>Philadelphia</td>
<td>5035 5316</td>
<td>4898 4985</td>
</tr>
<tr>
<td>San Francisco</td>
<td>6980 7390</td>
<td>6363 6677</td>
</tr>
<tr>
<td>All respondents</td>
<td>6589 6823</td>
<td>6160 6137</td>
</tr>
</tbody>
</table>

In Fig. 1, the average interval flux is plotted against age interval over both sexes by location. The average interval flux for each 6-month age interval was obtained using data from all of the respon-

If the coefficient for ln(exposure) is \( b \), then a 10% increase in the exposure is associated with relative odds of \( (1.1)^{b} \). The quantity \( (1.1)^{b} \) is the OR10 and depends only on the coefficient \( b \).
Cumulative flux was associated with an increase in risk for melanoma among men (OR10, 1.10; P = 0.054; CI, 1.00–1.22) and among women (OR10, 1.10; P = 0.076; CI, 0.99–1.22). In a model with the log of cumulative flux, the inclusion of the logarithm of age was important, significant for men (P = 0.032) but not women (P = 0.27).

Age was a significant risk factor for men despite the frequency matching on age group, because cases differed from controls within 10-year age groups. For both males and females, the estimated coefficient of log age was roughly the negative of the coefficient for the log of cumulative flux. This suggests that the log of average annual flux can be used instead of these two factors because the average annual flux is obtained by dividing the cumulative flux by age. Annual flux was strongly associated with the odds for melanoma in men. Annual flux can be used instead of these two factors because the average annual flux fit better than models that used average annual flux without a logarithmic transformation, and nearly as well as those that used both log age and log cumulative flux.

To check the impact of our method of imputing missing interval flux on the results, the 5% of respondents with >7.5% missing residence intervals were deleted. From this reduced data set, the estimates of the OR10s for annual flux and their significance levels were nearly unchanged.

To differentiate between age at exposure and amount of exposure, we divided residence history of each respondent into two groups of intervals: the intervals before age 20 years, the childhood years; and the intervals after age 19 years, the adult years. The average annual fluxes on a logarithmic scale were then included together in a logistic model. For males and females, respectively, the OR10s for ages 0–19 were 1.06 (CI, 0.97–1.16) and 1.07 (CI, 0.98–1.18) whereas for ages 20+ the OR10s were 1.13 (CI, 0.99–1.30) and 1.12 (CI, 0.95–1.30).

Although the OR10s for ages 0–19 are less than those for ages 20+, the differences between age group effects were not significant, and the fit of the model did not improve.

**Hours Outdoors.** For each respondent the cumulative number of hours outdoors and the average annual number of hours outdoors were calculated for ages 0–19 years and 20+ years. Means for each outdoor time variable are presented in Table 3 for cases and controls by sex, by age at interview, and by study site. During ages 0–19, the cumulative number of hours outdoors was greater for men than for women (P < 0.001), similar in Philadelphia and San Francisco (P = 0.68), and greater for those age 20–49 at interview (P < 0.001). The cumulative hours outdoors during these childhood ages were greater for controls than for the cases, significant for women (P = 0.008) but not for men (P = 0.42). Average annual hours outdoors for those >50 years of age was comparable with that of those with age at interview 20–49 (P < 0.16). For adult ages the cumulative hours outdoors and the average annual hours outdoors were greater for men than for women (P < 0.01). The average annual hours outdoors was less in Philadelphia than in San Francisco (P < 0.036). Both adult cumulative and average annual hours outdoors were greater for male cases than male controls (P < 0.001) but they were comparable for female cases and controls (P > 0.46).

For each age interval (Fig. 2), the average interval hours outdoors was calculated using data from respondents who were older than that age interval at the time of interview. The average hours outdoors was much greater for age intervals before age 20 than for in the later adult age intervals. The average number of hours outside in age intervals after age 19 years was greater for cases than controls for men but not for women and before age 20 usually greater for controls than for cases.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Means for cumulative hours outdoors and average annual hours outdoors during ages 0–19 and during adult ages, for men and women by case-control status, age at interview, study site, and overall</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Age at interview</th>
<th>Controls 20–49</th>
<th>Cases 20–49</th>
<th>Controls 50–79</th>
<th>Cases 50–79</th>
<th>Controls Adult Ages</th>
<th>Cases Adult Ages</th>
<th>Study site Philadelphia</th>
<th>Controls</th>
<th>Cases</th>
<th>Controls Adult Ages</th>
<th>Cases Adult Ages</th>
<th>Study site San Francisco</th>
<th>Controls</th>
<th>Cases</th>
<th>Controls Adult Ages</th>
<th>Cases Adult Ages</th>
<th>Study site All</th>
<th>Controls</th>
<th>Cases</th>
</tr>
</thead>
</table>

The conditional logistic regression analysis included terms on a logarithmic scale for average annual flux, cumulative hours outdoors during ages 0–19, and cumulative hours outdoors in the adult years 20+. The effect of annual flux was large and significant for both men and women. The effect of the cumulative hours outdoors during childhood years was negative but small and not significant for either men or women. The effect of cumulative hours outdoors as an adult was positive and significant for men, but the effect for women was small and not significant (results not shown).

**Other Risk Factors Affecting Hours Outdoors.** Some individual characteristics that are known to be associated with the risk for melanoma also may be associated with hours outdoors. If not accounted for, such variables could seriously bias estimates of the risk from hours outdoors. Using standard multivariate linear regression and the control data, among sunburn responses, suntan response, eye color, hair color, and the presence of small or large nevi, or dysplastic nevi, only suntan response after repeated and prolonged exposure to sunlight had an effect on cumulative hours outdoors as an adult for both men and women.

The mean average annual hours outdoors by sex, case or control status, and suntan response are given in Table 4. Only 17 respondents had unknown values for tan type. Average hours outdoors increased with greater tanning ability. Among men, the cases had greater average annual hours outdoors in every category of tanning ability, whereas among women, only the cases who could develop a deep tan had greater annual hours outdoors than their controls.

In separate conditional logistic regressions for males and for females, the initial model included average annual flux, cumulative hours outdoors in ages 0–19, and cumulative hours outdoors as an...
adult. For men, the categories of suntan response were important additional independent risk factors but significant only for those who could develop a deep tan ($P < 0.001$). The OR10s did not differ significantly ($P = 0.48$) by ability to tan. Table 5 summarizes results for men for the reduced model including average annual flux, hours outdoors at ages 0–19, and the ability to develop a deep tan. The OR10 for average annual flux was 1.16 ($P = 0.02$; CI, 1.02–1.32). The OR10 for total hours outdoors in ages 0–19 was 0.98 ($P = 0.17$; CI, 0.96–1.01). The OR10s for cumulative hours outdoors during the adult years were 1.01 ($P = 0.89$; CI, 0.99–1.01) for those who would develop moderate to no tan and 1.06 ($P = 0.011$; CI, 1.01–1.10) for those who would develop a deep tan. With the hours outdoors during adult ages set to the average for female controls, the OR for deep tan was 0.43 ($P < 0.001$; CI, 0.28–0.65).

The effects of including the individual characteristics that were not significantly associated with cumulative hours outdoors were studied. The estimated OR10s and significance of mean flux and hours outdoors both for ages 0–19 as well as adult ages were changed little by including other individual characteristics in the model, either one at a time, all in a single model, or by selecting the characteristics using standard step-down procedures (results not shown).

**DISCUSSION**

It has long been recognized that population incidence and mortality rates of melanoma increase with average latitude or annual flux. Here
we have shown that the individual risk for melanoma increases with the average annual flux received by an individual during a lifetime. This is the first time that individual risk has been associated with average annual flux and the first time that the OR10 for individual average annual flux has been estimated. We have estimated that a 10% increase in the average annual flux was associated with a 19% increase in the individual’s risk for melanoma in men and a 16% increase in women at any age. A difference in average annual flux >10% is actually common, e.g., RB meter measurements (6) showed that flux in New Orleans (1,860,000 RB units/year) is >20% higher than in Atlanta (1,530,000 RB units/year).

The residential mobility reported by the study respondents is noteworthy and may explain the apparent leveling in recent years of the relationship between melanoma mortality rates and latitude or UVB in descriptive studies (13, 14). Using residential history to estimate UVB exposure may be of particular importance in highly mobile populations in contrast to residentially stable groups (1–3, 15, 16).

Melanoma risk was more strongly associated with mean annual flux than with cumulative flux. The OR10s for ages 0–19 were slightly lower than for ages 20+, although not significantly so. This suggests that the effect of average flux may not depend on the age at which high flux is received.

An important part of this analysis has been the consideration of exposure patterns. It was clear that interval hours outdoors after the age of 20 were much smaller than those in younger ages. Previous reports of substantial childhood effect (1, 17) may simply reflect the cumulative hours outdoors during childhood rather than a “critical period” of exposure. However, there is evidence in mouse models that younger animals are more susceptible to UVB exposure than older animals (18).

It is surprising that the number of hours outdoors before the age of 20 was not associated with risk. The average hours outdoors during these ages was very high. It may be that for so many hours outdoors, flux is the major determinant for melanoma risk. Of course, it also may be that recall about hours outdoors in childhood was so poor and the error so large that definite conclusions cannot be made.

In our data, adult hours outdoors were strongly associated with the ability to develop a tan after repeated sun exposure. The risk for melanoma in men and in women decreased dramatically with the ability to tan. In men of all tan types and women who can develop a tan after repeated sun exposure, the risk for melanoma increases with increased time outdoors and, in particular, the risk increases even for those who can develop a deep tan. It is important that individuals of all suntan types avoid sun-seeking behavior.

The OR10s for variables measuring hours outdoors appear small, and it might be tempting to discount their importance. Note, however, that an average male with a light tan was outdoors only ~9.7 h/week (505 h/year in Table 4). If he worked outdoors and added only 3 h/day on weekdays, the total would increase by 155% increasing the OR to 1.3. Changes in behavior that appear to be minor may be associated with large relative changes in hours outdoors and, therefore, substantial changes in the risk for melanoma.

In this report we have considered the association of individual risk for melanoma and flux, and hours outdoors. Our novel measures of individual UVB received were obtained from a residence history. Answers to residence history questions are likely to be more accurate than answers to questions about past duration of exposure. The association between melanoma risk and average annual flux was strong and consistent. Questions dealing with hours outdoors require the respondent to summarize complex behavior. Nevertheless, we also have found an association for melanoma risk and total hours outdoors as an adult that was most notable for men of all skin types and women who develop a suntan. A more detailed consideration of age-specific hours outdoors and flux will be undertaken to examine the effects of intermittent exposure patterns and intermittent periods of high flux.

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