Uveal Melanoma in Relation to Ultraviolet Light Exposure and Host Factors

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ABSTRACT

We conducted a case-control interview study among 1277 subjects (407 patients, 870 controls selected by using random digit dial) in 11 western United States to determine whether uveal melanoma and cutaneous melanoma shared common risk factors. After adjustment for other factors, the risk of uveal melanoma was increased for those with green, gray, or hazel eyes (relative risk (RR) = 2.5, P < 0.001) or blue eyes (RR = 2.2, P < 0.001) when compared to brown. A tendency to sunburn after 0.5 h midday summer sun exposure increased risk for uveal melanoma (burn with tanning RR = 1.5, P = 0.02; burn with little tanning RR = 1.8, P < 0.001; burn with no tanning RR = 1.7, P = 0.002); as did exposure to UV or black lights (RR = 3.7, P = 0.003); and welding burn, sunburn of the eye, or snow blindness (RR = 7.2, P < 0.001). An association with uveal melanoma was also noted with an increasing number of large nevi (P = 0.04 for trend), although the individual risk estimates were not remarkably different. These data suggest that host factors and exposure to UV light are risk factors for uveal melanoma.

INTRODUCTION

Melanoma of the uveal tract is the most common primary intraocular malignancy in adults (1), yet few risk factors have been identified. (2, 3) Individuals with light-colored eyes have been found to be at greater risk than those with brown eyes in both reports that have been published to date (2, 3), while those with red or blond hair were found to be at greater risk in one study (2). The lack of eye protection while in the sun was also noted (3). The incidence of uveal melanoma in whites, at 6/ million/year, is eight times the incidence in blacks (1, 4). We conducted a case-control study to determine risk factors for uveal tract melanoma. We also were interested in the similarity between risk factors for uveal melanoma and cutaneous melanoma.

SUBJECTS AND METHODS

Cases. Patients were diagnosed between January 1978 and February 1987 with uveal melanoma at the Ocular Oncology Unit at the University of California San Francisco (a major west coast referral center). We selected all white patients between 20 and 74 years of age at diagnosis who resided in the 11 western United States (Washington, Oregon, California, Idaho, Nevada, Utah, Arizona, Montana, Wyoming, Colorado, and New Mexico). The tumors in these patients involved the choroid (79%), mixed tumors (15%), ciliary body (4%), and iris (2%).

Diagnosis of uveal melanoma in the 439 eligible patients was established by one of us (D. H. C.) using multimodality noninvasive techniques (5). Where the diagnosis was uncertain, fine needle aspiration biopsy was performed. Patients were treated with radiation or surgery, with diagnosis histopathologically confirmed for all surgical patients. Ninety-three % (407) of the 439 eligible patients were interviewed. Five eligible subjects were deceased, 4 were too ill to participate, 6 refused to be interviewed, and 17 could not be located.

Controls. Random-digit dial telephone methods were used to select a sample of 870 white control subjects from the 11 western states where the patients resided (6). The area code and first three digits of the patients' telephone numbers were used to obtain control subjects who lived in the same geographic areas as the patients. To locate controls, we telephoned potential subjects up to 10 times at different times of the day, in the evenings, and on weekends. We attempted to locate two control subjects of the same sex within the same 5-year age group of each patient at diagnosis. Seventy-seven % of eligible control subjects completed interviews.

Interviews. Professional interviewers who were unaware of study hypotheses, administered structured questionnaires by telephone. The interview included demographic characteristics such as age, education and family income, whether they lived in urban or rural areas, tendency of the subjects' skin to tan or sunburn, host characteristics, including eye and hair color, number of large nevi, presence of freckles, medical history, including use of corrective lenses and reproductive history for women, exposure to UV or black lights (sunlight was excluded), and vacation and leisure-time activities. Among other factors, we also included questions about use of cigarettes, coffee, tea, and alcohol, service in the military, and whether the subjects were more likely to be automobile drivers or passengers. Hair and eye color were assessed by asking subjects what their natural hair color was at age 20, and whether they had blue, green, gray, hazel, or brown eyes. Numbers of large nevi were assessed by asking subjects "how many moles the diameter of a pencil eraser..." they had on their entire body including any that may have been removed. Eye diseases were assessed by asking subjects "Before the diagnosis of your eye tumor, were you ever treated by a physician for..." followed by the various conditions of interest such as "an injury that penetrated your eye, an injury or blow to your eye that did not penetrate, a sty infection, an infection in your eye other than a sty, glaucoma, uveitis" or, "Were you ever diagnosed with any other condition that affected your eyes?" Answers were coded by each type of condition, e.g., retinal detachment, welding burn, iritis, and then grouped when appropriate. Fifty-nine % of the interviews were conducted within 1 year of diagnosis of uveal melanoma, 82% within 2 years, and 98% within 4 years of diagnosis.

Analysis. Unconditional logistic regression analyses were used to estimate odds ratios (hereafter called relative risks) for host and environmental factors individually and in combination. A linear relationship was assumed for age. Ninety-five % confidence intervals for relative risks, tests for trend, and 2-tailed P values were computed according to the methods described by Breslow and Day (7) and were implemented using BMDP software (8). We first estimated unadjusted relative risks separately for women (186 patients, 423 controls) and men (221 patients, 447 controls). Multivariate unconditional logistic regression analyses also were run separately by sex. Because risk estimates and 95% confidence limits were similar for all but one factor in men and women, results are presented together. Only red hair color was significantly different between men and women and these results are presented below. When appropriate, we calculated the P value for linear trend for multiple levels of exposure. We used the stepwise logistic regression program to select significant variables for the models based on a priori study hypotheses. All variables that were significant at P < 0.10 in the univariate analysis were considered for the final multivariate models.
**UVEAL MELANOMA, UV, AND HOST FACTORS**

### Table 1 Descriptive and host factors, unadjusted and adjusted RR and 95% CI for ocular melanoma patients and control subjects

<table>
<thead>
<tr>
<th>Eye color</th>
<th>Patients N = 407 (%)</th>
<th>Control subjects N = 870 (%)</th>
<th>Unadjusted RR 95% CI</th>
<th>Adjusted a RR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown</td>
<td>69 (17)</td>
<td>292 (34)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Green, gray, hazel</td>
<td>154 (38)</td>
<td>251 (29)</td>
<td>2.59</td>
<td>1.84–3.66</td>
</tr>
<tr>
<td>Blue</td>
<td>184 (45)</td>
<td>327 (37)</td>
<td>2.38</td>
<td>1.71–3.32</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Natural hair color at age 20</th>
<th>Patients N = 399 (%)</th>
<th>Control subjects N = 785 (%)</th>
<th>Unadjusted RR 95% CI</th>
<th>Adjusted a RR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black, brown</td>
<td>218 (53)</td>
<td>494 (57)</td>
<td>1.0</td>
<td>1.0 b</td>
</tr>
<tr>
<td>Light brown</td>
<td>88 (22)</td>
<td>164 (19)</td>
<td>1.22</td>
<td>0.89–1.67</td>
</tr>
<tr>
<td>Blond</td>
<td>80 (20)</td>
<td>169 (19)</td>
<td>1.07</td>
<td>0.78–1.48</td>
</tr>
<tr>
<td>Red</td>
<td>21 (5)</td>
<td>43 (5)</td>
<td>1.11</td>
<td>0.62–1.97</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Freckles</th>
<th>Patients N = 407 (%)</th>
<th>Control subjects N = 870 (%)</th>
<th>Unadjusted RR 95% CI</th>
<th>Adjusted a RR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>284 (70)</td>
<td>621 (70)</td>
<td>1.0</td>
<td>1.0 b</td>
</tr>
<tr>
<td>Yes</td>
<td>111 (30)</td>
<td>222 (30)</td>
<td>1.09</td>
<td>0.83–1.44</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. of large nevi</th>
<th>Patients N = 399 (%)</th>
<th>Control subjects N = 785 (%)</th>
<th>Unadjusted RR 95% CI</th>
<th>Adjusted a RR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>200 (49)</td>
<td>476 (55)</td>
<td>1.0 c</td>
<td>1.0 a</td>
</tr>
<tr>
<td>1</td>
<td>68 (17)</td>
<td>153 (18)</td>
<td>1.06</td>
<td>0.75–1.49</td>
</tr>
<tr>
<td>2-3</td>
<td>71 (17)</td>
<td>133 (15)</td>
<td>1.27</td>
<td>0.90–1.79</td>
</tr>
<tr>
<td>4+</td>
<td>61 (15)</td>
<td>104 (12)</td>
<td>1.40</td>
<td>0.96–2.02</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Coffee, cups/day</th>
<th>Patients N = 399 (%)</th>
<th>Control subjects N = 785 (%)</th>
<th>Unadjusted RR 95% CI</th>
<th>Adjusted a RR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>65 (16)</td>
<td>217 (25)</td>
<td>1.0 d</td>
<td>1.0 e</td>
</tr>
<tr>
<td>1</td>
<td>45 (11)</td>
<td>102 (12)</td>
<td>1.47</td>
<td>0.92–2.36</td>
</tr>
<tr>
<td>2</td>
<td>75 (18)</td>
<td>166 (19)</td>
<td>1.51</td>
<td>1.00–2.27</td>
</tr>
<tr>
<td>3</td>
<td>64 (16)</td>
<td>131 (15)</td>
<td>1.63</td>
<td>1.06–2.50</td>
</tr>
<tr>
<td>4-5</td>
<td>75 (18)</td>
<td>137 (16)</td>
<td>1.83</td>
<td>1.21–2.77</td>
</tr>
<tr>
<td>6+</td>
<td>80 (20)</td>
<td>116 (13)</td>
<td>2.30</td>
<td>1.52–3.50</td>
</tr>
</tbody>
</table>

* The variables in the logistic regression model included eye color, coffee, 0.5 h sun exposure, leisure time, exposure to UV or black lights, snow blindness and eye burns, and age.

* This variable was adjusted for those in footnote a.

* P for trend < 0.05.

* P for trend = 0.05.

* P for trend > 0.005.

### RESULTS

Descriptive. Average age for the patients and control subjects were 54.9 years in each group, while the average education was 13.5 years for each group. The mean values for height and weight by sex were nearly identical for patients and control subjects, as were number of cigarettes smoked per day and number of alcoholic drinks consumed per week (data not presented).

Coffee consumption was not statistically significantly different between men and women, although women patients than their control subjects had red hair (RR = 0.45, 95% CI = 0.19–1.0). However, hair color was not associated with risk for uveal melanoma in sex-specific, nor combined analyses adjusted for other significant factors. An association with uveal melanoma was also noted with an increasing number of large nevi (P = 0.04 for trend), although the individual risk estimates were not remarkable. No assessment was made of iris nevi.

Sun or Light-related Factors. Table 2 shows sun or light-related factors in relation to uveal melanoma risk. A greater proportion of patients than control subjects sunburned when exposed to summer midday sun for 0.5 h, with an increase in risk with greater tendency to burn (P < 0.001 for trend). Two measures of sunlight dose were examined separately (vacations in sunny climates, and summer leisure time outdoors). Neither of these measures showed an increased risk for uveal melanoma for those who had spent more time in the sun. Having spent about one-half of summer leisure time outdoors conveyed a decreased risk for uveal melanoma (P = 0.01), although there was no consistent evidence of decreased risk with increased frequency of summer leisure time outdoors. A larger proportion of patients than control subjects had been exposed to UV (not including sunlight exposure) or black lights with number of years exposed supporting this association (RR = 2.9 for 1–5 years, and RR = 3.8 for 6 or more years).

Medical and Other Factors. Subjects were asked for a detailed history of eye conditions and other diseases. A greater proportion of patients than control subjects reported severe burns to the eyes for welding, the sun, or from episodes of snow blindness (Table 2). The average age at diagnosis of uveal melanoma patients who had had eye burns in the past was 60 years, with a 30-year lag between the eye burn and the tumor diagnosis. The average age of controls who had had eye burns, however,
was 51 years with only a 20-year lag between the eye burn and the interview. There were no differences between patients and controls for other eye pathology, whether blows to the eye, penetrations of the eye, glaucoma, cataracts, ocular infections, chalazia (sties), or use of eye medications. There also were no controls for other eye pathology, whether blows to the eye, was 51 years with only a 20-year lag between the eye burn and the interview. There were no differences between patients and controls for any other diseases at any age. The same proportion of patients and controls wore contact lenses or glasses, and had had previous X-rays to the eyes was reached in a case-control study of 497 uveal melanoma patients and light eyes in uveal melanoma patients.

**DISCUSSION**

We found an increased risk of uveal melanoma for the apparent effects of UV exposure (having had a severe eye burn or exposure to UV or black lights) and for host factors that may be affected by UV (propensity to burn rather than tan when exposed to the sun, light eye color, having numerous large nevi). A similar conclusion regarding intense UV light exposure to the eyes was reached in a case-control study of 497 uveal melanoma patients and 501 patients with detached retinas who served as the comparison group (3).

There are parallels between cutaneous and uveal melanoma. UV and host-related factors are found in both, e.g., sunburns of the skin in cutaneous melanoma patients and burns of the eyes in uveal melanoma patients; and, light skin in cutaneous melanoma patients and light eyes in uveal melanoma patients. The question of number of nevi in relation to uveal melanoma remains to be explored more fully in future studies.

Although the lens and cornea absorb UV light and protect the uveal tract from most UVB in adults, in children there is substantial transmission of UVA and UVB that decreases slowly with age (9). Even in adults, relatively low levels of visible light and UV radiation can damage the human retina (10). However, it is believed that the choroid and ciliary body are protected from this UV exposure and also from a large portion of the more energetic wavelengths of the visible spectrum by the tissues overlying them (11). Nevertheless, until the etiology of uveal melanoma is better understood, future studies of this tumor should investigate intense light exposures over the entire life span. It is also possible that the use of photosensitizing drugs may enhance ocular toxicity and tumor formation (12), although in this study, we found no difference between the patients and control subjects in use of medications of any type. However, we did not ask specifically about all photosensitizing drugs.

A lack of an association in the present study between uveal melanoma and wearing of contact lenses or glasses may have been related to the variability among types of lenses. It may also have depended on the age when the subjects started to wear glasses and whether they were worn all the time or part time. In work to evaluate the effect of prescription eyewear and sunglasses on attenuating ocular exposure to UV radiation (13, 14), Rosenthal et al. concluded that the protection provided against UV exposure by corrective lenses is highly variable and depends on the size of the glasses, their composition (plastic or glass), and wearing position (13). Although sunglasses attenuated ocular exposure slightly more effectively than untinted prescriptive glasses, their effectiveness was also subject to the same constraints of corrective glasses (14). The amount of UV radiation passing through spectacle lenses was similar whether facing away from or toward the sun. Another study examined the effects of wearing sunglasses, hats, or visors during sun exposure and found that rare use while in the sun was a risk factor for uveal melanoma although no consistent risk was noted with different frequencies of eye protection (3). When
The use of corrective lenses was examined, the estimated risk was 0.8 but this slight protective effect could have been due to chance (95% CI = 0.5–1.2) (3). Several studies have assessed the effects of UV radiation on the immune system (15–19). While sunscreen prevents sunburn, it does not prevent depression of natural killer cell activity and changes in the T-cell population (17). Further work is needed to determine whether people are more likely to have their immune systems compromised by UV radiation if they have light skin, light eyes, and a tendency to sunburn.

Eye color was also found to be a risk factor in two other studies of uveal melanoma (2, 3). The color of the iris is determined by degree of pigmentation, with relatively little melanin pigment producing a blue or gray iris and considerably more, a brown iris (9). Melanin in the iris can absorb UV as well as visible light (9). The protective effect of brown eyes may result from the ability of brown eyes to filter more UV light than light-colored eyes. In Canada, an index was used that combined eye and hair color to determine risks for uveal melanoma. They found risk estimates that ranged between 12 and 18 for the lightest eye-color hair combinations (2). Using the same categories, we found no additional risk for hair color; the combined eye-hair color estimates of relative risks for uveal melanoma remained the same as those for eye color alone. Although some early work found eye color to be a risk factor for cutaneous melanoma, studies with adjustment made for other potentially confounding variables, such as complexion and hair color, showed no statistically significantly increased risk for eye color (20–23).

Tendency to sunburn in intense sunlight also has been associated with cutaneous melanoma, (21, 23, 24) and freckles, used as an indirect measure of skin sensitivity, were shown to be related to uveal melanoma (RR = 1.4, 95% CI = 1.04–2.0), while no association was noted for use of sunlamps or for sunbathing (3). Neither tendency to sunburn nor the number of freckles in childhood were associated with uveal melanoma in Canada (2).

A large number of total body nevi counted by dermatologists (25, 26) and many nevi on the arms increase risk of cutaneous melanoma (22, 24, 27, 28). We did not ask subjects to distinguish between normal nevi and those with irregularities. Clinically dysplastic nevi have been identified in 4.5% of 41 patients with uveal melanoma (29). Counts of nevi on the arms and counts of total body nevi are highly correlated (30). Nevi on the arms should be counted in future studies of uveal melanoma.

We believe coffee drinking is not etiologically related to uveal melanoma for four reasons. First, we can think of no biologically plausible mechanism for the association. Second, although risk estimates were slightly elevated, we observed no statistically significant increased risk for male coffee drinkers. Third, women in the control group had an unusually high proportion (30%) of non-coffee drinkers compared to control women in two other large studies that examined the adverse effects of coffee drinking (31, 32). The proportions of women who did not drink coffee in these two studies (31, 32) were similar to the proportion (15%) of women patients who did not drink coffee in our study. Finally, the proportions of women who drank one to five cups of coffee per day were similar in both the patient and control subjects. Only the proportions for zero and six cups of coffee drunk per day were dissimilar between the two groups.

It is unlikely that our overall study results are explicable by bias. Case-control studies are subject to recall bias, in that the patients may recall events that are related to their disease more clearly than will control subjects. The validity of this study is supported by the negative results relating to numerous eye diseases, with the only statistically significant condition related to the eye (that of severe burns to the eye) also associated with UV exposure and our a priori hypothesis of a uveal melanoma–UV light association. Selection bias of subjects is also a potential concern in case-control studies. To minimize selection bias related to exposures, we used population-based controls and limited the study to those subjects who lived in the 11 western United States. We found cases and control subjects in this study to be nearly identical on numerous personal and demographic variables, such as sex-specific height and weight, income and education, and disease history, which would support an absence of selection bias. Further, clinical measures on cases who did not participate were nearly identical to those of participants.

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REFERENCES


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