#25

SUNLIGHT EXPOSURE AS RISK FACTOR FOR INTRAOCULAR MALIGNANT MELANOMA

MARGARET A. TUCKER, M.D., JERRY A. SHIELDS, M.D., PATRICIA HARTGE, SC.D., JAMES AUGSBURGER, M.D., ROBERT N. HOOVER, M.D., SC.D., AND JOSEPH F. FRAUMENI, JR., M.D.

Abstract In a case–control study, we compared 444 patients with intraocular malignant melanoma with matched controls to evaluate the role of exposure to ultraviolet radiation and other risk factors in the pathogenesis of this tumor. Persons born in the southern United States had a relative risk of 2.7 (95 per cent confidence interval, 1.3 to 5.9) as compared with those born in the North. Subjects with brown eyes were protected as compared with those with blue eyes (relative risk, 0.6; 95 per cent confidence interval, 0.4 to 0.8), but complexion and hair color were not important risk factors. Patients with intraocular malignant melanoma were also more likely to have spent time outdoors in their gardens, to have sunbathed, and to have used sunlamps. Rarely wearing hats, visors, or sunglasses while in the sun was a risk factor for the disease (relative risk, 1.9; 95 per cent confidence interval, 1.6 to 2.2). These data suggest that sunlight exposure is an important risk factor for intraocular melanoma. (N Engl J Med 1985; 313: 789-92.)

INTRAOCULAR malignant melanoma is the most common primary intraocular malignant tumor in adults in the United States and Europe.[1] It seems possible that it is caused by some of the same factors that cause cutaneous malignant melanoma, since the common cell of origin is the melanocyte, and dark-skinned populations are at much lower risk for both tumors.[2] The principal identified environmental risk factor for cutaneous melanoma is ultraviolet (sun) exposure — a finding consistent with the latitudinal gradient in incidence rates observed in the United States, Australia, and other areas.[3] Despite several attempts to evaluate the role of sun exposure in intraocular malignant melanoma through descriptive studies, no support for a causative role of such exposure has been found. No differences in incidence at various latitudes have been found in the United States[4] or Finland[5] or in a comparison of multiple countries.[6] To explore several etiologic hypotheses, including the influence of sunlight, we conducted a case–control study of patients with intraocular malignant melanoma.

METHODS

The cases were 509 consecutive patients with melanoma of the uveal tract (iris, ciliary body, and choroid) evaluated in the ocular oncology service at Wills Eye Hospital from January 1974 through June 1979. All the cases were examined and evaluated by one of us (J.S.). The diagnosis of uveal-tract melanoma either was confirmed histopathologically in 298 cases treated by surgery or was based on highly reliable ancillary studies[7] in the other 211 cases whose disease was managed by radiotherapy or other conservative means.[8] Ten of the cases were disqualified because they did not fulfill the diagnostic criteria.

The controls were patients with detached retinas not due to tumors, who were seen at Wills Eye Hospital during the same period. One control — matched according to age, sex, race, and date of diagnosis — was selected for each case. Patients with detached retinas were chosen as controls because they are etiologically a heterogeneous group, without selection for particular exposures. In addition, they probably reflected the population from which the cases were drawn, with similar patterns of referral that would have led them to be seen at the Wills Eye Hospital. They do not, however, reflect the source population with respect to the known risk factors for detached retina: trauma, hypermyopia, cataracts, diabetes, and hypertension. Of these, only cataracts are related to sun exposure.[9] Thus, the estimates presented here are adjusted for a history of cataracts. Fifteen per cent of the cases and 50 per cent of the controls had such a history, as compared with 19 per cent in a sample population having similar characteristics.[10] The diagnosis of detached retina was confirmed by review of the medical record. For a separate analysis of corrective-lens use, a second group of controls was identified and interviewed. These were patients referred to the oncology service for various ocular tumors and pseudotumors other than uveal melanomas. These were not matched to the cases, but the age, race, and sex distribution of this cohort was similar to that of the cases.

Details of the ophthalmologic examination and medical history were abstracted from the medical records of all cases and controls. All the subjects were then contacted to ascertain their willingness to participate in a telephone interview. A total of 444 (89 per cent) of the cases and 424 (85 per cent) of the controls agreed to undergo a 45-minute telephone interview that sought detailed information about medical history, family history, employment, and exposure to various environmental agents, including sunlight. If the subject was deceased, the next of kin, if willing, was interviewed. Next-of-kin interviews were conducted in 17 per cent of the cases and 14 per cent of the controls. For each group, approximately half the next-of-kin interviews (8 and 6 per cent, respectively) were with spouses; most of the rest were with first-degree relatives (7 and 7 per cent, respectively). Informed consent was obtained, and full confidentiality maintained at all times. The subjects who declined the interview did not differ appreciably in age, sex, race, or location of residence from those who participated in the study.

The measure of association used for evaluating the effects of a host or environmental factor is the estimated relative risk — the ratio of disease incidence in the exposed to the incidence in the unexposed. The effects of potentially confounding variables, including the matching variables, were evaluated by stratified contingency-table analysis. We derived maximal-likelihood estimates of rate ratios and 95 per cent confidence intervals, using Gart's method.[11] For multiple levels of exposures, the P value of a linear trend was measured by the Mantel extension of the Mantel–Haenszel procedure.[12] Multivariate analyses, conducted according to a disease-probability logistic model, were also used to control simultaneously for numerous potential confounding variables.[13]

RESULTS

We restricted the analysis to the 497 white cases and 501 white controls in the series because so few nonwhite patients were given a diagnosis of intraocular malignant melanoma. Blue-eyed subjects had the highest risk of the disease, and they were followed closely by those with green, gray, or hazel eyes.

From the Environmental Epidemiology Branch, Division of Cancer Etiology, National Cancer Institute, National Institutes of Health, Bethesda, Md.; and the Ocular Oncology Service, Wills Eye Hospital, Jefferson Medical College, Thomas Jefferson University, Philadelphia. Address reprint requests to Dr. Tucker at the Environmental Epidemiology Branch, National Cancer Institute, Landow Bldg., Rm. 3C29, Bethesda, MD 20205.

Supported in part by the Ocular Oncology Fund, the Oncology Research Fund, and the Black Patch Invitational, Philadelphia.

Table 1. Estimated Relative Risk of Intraocular Malignant Melanoma, According to Birthplace and Number of Years of Residence in the Southern United States.*

Years Lived in South	Birthplace		Total Group
	North	South	
	relative risk (no. of cases)†		
<10	1.0‡ (367)	3.2 (23)	1.0‡ (390)
10–30	1.3 (12)	2.3 (14)	1.1 (26)
>30	1.3 (4)	3.2 (14)	1.1 (18)
Total group	1.0‡ (383)	2.7 (51) (95 per cent confidence interval, 1.3 to 5.9)	

*In all tables, totals for separate categories may not equal group totals because information was missing for a certain category. The southern United States is defined as south of approximately the 40° N latitude.

†All estimates adjusted for a history of cataracts.

‡Referent category.

Brown-eyed subjects had a significantly lower risk (relative risk, 0.6; 95 per cent confidence interval, 0.4 to 0.8) than blue-eyed subjects. Unadjusted analysis showed that the cases were more likely to have fair skin and blond or brown hair and to be of Eastern European origin. When the analysis was adjusted for eye color, however, these differences disappeared. Conversely, adjusting for these variables did not change the risks for eye color.

To address the question of a latitude gradient in intraocular malignant melanoma as a surrogate measure of exposure to ultraviolet radiation, we classified study subjects according to place of birth, the number of years they had lived in the southern United States, and the number of years they had spent in the tropics and subtropics (Table 1). Being born in the southern United States was associated with an approximately threefold increased risk of intraocular malignant melanoma (relative risk, 2.7; 95 per cent confidence interval, 1.3 to 5.9) after adjustment for the number of years spent in the south and for cataracts. With adjustment for all the other sun-related variables found to be important in the analysis (eyeshade wearing, freckles, and sunbathing) the risk was 3.2 (95 per cent confidence interval, 1.8 to 5.7). After adjustment for having been born in the South, there was no relation between the number of years spent in the South and the risk of intraocular malignant melanoma. More cases than controls, however, had lived in the tropics and subtropics for at least five years (relative risk, 4.1; 95 per cent confidence interval, 0.4 to 100).

To evaluate the possibility that referral bias accounted for the excess risks of being born in the South or living in the subtropics or tropics, we focused on subjects living in the standard metropolitan statistical areas of Philadelphia and Wilmington, Delaware, at the time of diagnosis. The relative risk associated with being born in the southern United States was almost identical: 2.8 (95 per cent confidence interval, 1.03 to 7.7). The number of subjects who had lived for many years in the tropics was too small to allow for detailed analysis, but the trends and risks were similar.

Freckles were used as an indirect measure of both sun exposure and sensitivity. Subjects were asked whether they had fewer than 25, 25 to 100, or more than 100 freckles. As compared with those who had fewer than 25 freckles, study subjects with more freckles had a slightly increased risk of intraocular malignant melanoma (relative risk, 1.4; 95 per cent confidence interval, 1.04 to 2.0))(Table 2). There was no difference in relative risk between those with 25 to 100 and those with over 100 freckles. Among the study subjects with cataracts, the relative risk associated with having more than 25 freckles was 2.5 (95 per cent confidence interval, 1.3 to 4.9), whereas it was 1.2 among those without cataracts. The P value of the difference in relative-risk estimates between subjects with cataracts and those without was 0.05. Cases with iris melanoma were more likely to have freckles (relative risk, 2.2; 95 per cent confidence interval, 1.01 to 4.7) than those with melanoma at sites other than the iris (relative risk, 1.4; 95 per cent confidence interval, 0.97 to 1.9). Cases were more likely to report sunlamp use (relative risk, 1.4; 95 per cent confidence interval, 0.9 to 2.2). There was some evidence of a trend in relative risk according to frequency of sunlamp use, rising to twofold among frequent users (P = 0.10). There was no appreciable confounding of this relation by psoriasis, a risk factor for intraocular malignant melanoma in this study. Among study subjects with cataracts, the relative risk associated with using a sun-

Table 2. Estimated Relative Risk of Intraocular Malignant Melanoma, According to Indexes of Exposure to Ultraviolet Radiation.

	Cases	Controls	Relative Risk*	95% Confidence Interval
	no. of patients			
Freckles				
<25	279	301	1.0	
≥25	157	117	1.4	1.04–2.0
Sunlamp use				
Never	372	373	1.0	
Rarely	49	33	1.3	0.8–2.3
Occasionally	13	11	1.3	0.5–3.6
Frequently	5	2	2.1	0.3–17.9
Sunbathing				
Never	87	104	1.0	
Rarely	113	103	1.4	0.9–2.2
Occasionally	125	107	1.4	0.9–2.1
Frequently	117	105	1.5	0.9–2.3
Eye protection in sun				
Almost always	147	187	1.0	
Occasionally	137	114	1.5	1.02–2.2
Rarely	73	53	1.9	1.2–3.2
Never	83	66	1.4	0.9–2.3

*Estimates are adjusted for age, eye color, and a history of cataracts.

Table 3. Estimated Relative Risk of Intraocular Malignant Melanoma, According to Use of Corrective Lenses.

	Corrective-Lens Use		
	Never	Sometimes	Most of Time
Cases	78	134	230
Controls I*	59	91	271
Estimated relative risk†	1.0	1.1	0.6
95% Confidence interval		0.7–1.7	0.4–0.9
Controls II‡	47	63	148
Estimated relative risk†	1.0	1.0	0.8
95% Confidence interval		0.6–1.7	0.5–1.2

*Indicates control group used for other analyses.

†Estimates are adjusted for age, sex, and eye color.

‡Indicates another group of patients evaluated by one of us (J.S.).

lamp was 2.3 (95 per cent confidence interval, 0.9 to 5.9), whereas among those without cataracts the relative risk was 1.2 (95 per cent confidence interval, 0.7 to 2.0).

To evaluate the relative risks associated with recreational exposure to the sun, we asked study subjects about leisure activities. Cases were more likely than controls to report some sunbathing, but the frequency of sunbathing among sunbathers did not appear to be related to the risk (Table 2). When outdoors, the cases used some form of eye protection (sunglasses, hats, or visors) less frequently than controls (relative risk, 1.6 for those who never, rarely, or occasionally used such protection as compared with those who always used it; 95 per cent confidence interval, 1.2 to 2.2), but again there was no consistent evidence of increased risks with decreased frequency of eye protection. These estimates were not changed by controlling for corrective-lens use, visual acuity, eye color, age, sex, or residence in the southern United States. The eye-shade effect was similar among northerners and southerners. Since the lens filters most of the ultraviolet light,[9] we examined the iris melanomas separately. The relative risks of iris melanoma for those occasionally, rarely, and never using eye protection were 3.2 (95 per cent confidence interval, 1.1 to 9.0), 3.9 (95 per cent confidence interval, 1.2 to 13.0), and 4.9 (95 per cent confidence interval, 1.4 to 13.7), respectively.

To evaluate whether wearing glasses is related to the risk of intraocular malignant melanoma, we examined patterns of corrective-lens use (Table 3). More patients with detached retinas wore glasses most of the time than did patients with melanoma (64 as compared with 52 per cent). Since this difference partly reflected the poorer visual acuity of the patients with detached retinas, the cases were compared with a second group of patients who had visual acuity similar to that of the patients with melanoma. When this control group was used, there was an estimated 20 per cent reduction in risk associated with wearing glasses most of the time (relative risk, 0.8; 95 per cent confidence interval, 0.5 to 1.2).

Cases spent about the same amount of leisure time outdoors as controls overall, but there were differences in the types of sun exposure (Table 4). Gardening as a hobby was associated with an increased risk of intraocular malignant melanoma (relative risk, 1.6; 95 per cent confidence interval, 1.01 to 2.4). This effect was independent of exposure to pesticides, herbicides, or fertilizers. Cases and controls were equally likely to have spent time fishing, hunting, or camping, and controls were more likely to report other outside hobbies. Cases were more likely than controls to have spent more time in the sun during vacations than during normal everyday living (Table 4). Adjusting the effects for vacation length or sunbathing did not change these risks. The risks associated with vacation time were independent of the effect of sunbathing. The occupational histories of cases and controls were very similar; however, those who had ever worked as welders were at higher risk for intraocular malignant melanoma (relative risk, 10.9; 95 per cent confidence interval, 2.1 to 56.5). Four cases and no controls cited welding as their longest-held occupation.

We fitted logistic-regression models, including all the important sun-exposure variables, age, sex, eye color, cataracts, and the site of the melanoma. The resulting estimates were not appreciably different from those presented above and in the tables. We also assessed the constancy of the relative risks for sun-exposure variables among subgroups of the total study population, using the logistic-regression model. There were no important differences between men and women. Sun-related relative risks were slightly higher among subjects younger than 45 at diagnosis than among older subjects. Relative risks were higher for freckles and use of sunlamps among subjects with cataracts than among others, but relative risks for other sun-related variables were lower or the same. Among the cases with melanoma of the iris, the relative risks for the sun-related variables were similar to those for the cases with melanoma at other ocular sites, except as previously noted in the text. There was no difference in the relative risks between the

Table 4. Estimated Relative Risk of Intraocular Malignant Melanoma, According to Sun Exposure during Leisure Time.

	Cases	Controls	Relative Risk*	95% Confidence Interval
Outdoor leisure time				
None, very little	99	89	1.0	
Some	160	163	0.9	0.6–1.4
Great deal	182	164	1.1	0.7–1.6
Gardening				
No	363	364	1.0	
Yes	79	56	1.6	1.01–2.4
Increased sun exposure during vacations				
Never	97	115	1.0	
Rarely	98	93	1.1	0.7–1.8
Sometimes	75	69	1.3	0.8–2.2
Frequently	155	125	1.5†	0.97–2.3

*Estimates are adjusted for age, eye color, and a history of cataracts.

†P value of test for trend = 0.01.

cases with and without pathological confirmation of intraocular melanoma.

Discussion

Several lines of evidence from this study suggest that exposure to sunlight and ultraviolet radiation increases the risk of intraocular malignant melanoma — a finding similar to the associations previously described for cutaneous melanoma.[3] More cases than controls were born in the South. In addition, the cases were more likely to be blue-eyed, to sunbathe, and to increase their sun exposure during vacations, but less likely to shade their eyes during sun exposure. A higher percentage of cases worked in their gardens.

Certain findings of this study suggest that intermittent, intense sun exposure in particular may be an important risk factor for intraocular malignant melanoma, on the basis of the increased risk associated with sunbathing, gardening, and increased sun exposure during vacations, and of the protective effects of eyeshades. This type of sunlight exposure has also been implicated in the genesis of cutaneous melanoma.[14] Although the use of sunglasses and visors appeared to lower the risk of intraocular malignant melanoma, further evaluation of the role of protection of the eyes from the sun is needed. Our study suggested that corrective lenses may also exert a weak protective effect, but the comparison of such factors is hard to interpret, since the control groups in this study were patients from an eye hospital. To clarify this issue, future case–control studies should perhaps use different controls.

Why has an association between intraocular malignant melanoma and ultraviolet radiation not previously been established? Several surveys of the disease have attempted to look at latitude as an index of sunlight exposure and have failed to find a consistent gradient[5,6,15] (and Young JL: unpublished data). In some instances, the latitude differences have been small, and in others, particularly those in the United States, the geographical patterns of the disease from population-based tumor registries could have been confounded by ethnic variations. In the United States[15] (and Young JL: unpublished data) the northern registries cover populations with a high proportion of Scandinavians and Germans,[16] who tend to have blue eyes, whereas some of the southern registries have a high proportion of Hispanics, who are more likely to have brown eyes and should thus be at lower risk for intraocular malignant melanoma. Since the magnitude of the risks associated with eye color and sunlight exposure are similar (about twofold), and since the latitudinal gradients of the two risk factors run in opposite directions, the net effect may be to create the appearance that there is no latitudinal pattern.

Furthermore, since intraocular malignant melanoma is a disease of older persons, a patient's residence at the time of diagnosis may not reflect the actual lifetime exposure to sunlight. Indeed, our data indicate that the important time of exposure may be early in life, as in the effect proposed for cutaneous melanoma.[14] The apparent increased risk associated with living in the South for over 30 years disappears when adjustment is made for place of birth. Our findings are consistent with the observation that most ultraviolet light is screened from the posterior eye by the lens after childhood,[17] so that early-life exposures to sunlight may be especially important in the development of intraocular malignant melanoma. The increased risk of iris melanoma with less eye protection also suggests that the lens is important in screening ultraviolet light.

Although the constellation of findings suggests that exposure to ultraviolet radiation is an important risk factor for the disease, our case–control study was an exploratory one in which multiple comparisons were made, so that some results may be explained by chance alone. Further studies of the disease employing other control groups should clarify the characteristics of exposure to ultraviolet radiation that increase the risk, and the factors that are protective. In this way, it may be possible to take steps to lower the incidence of intraocular malignant melanoma, which is now a serious cause of morbidity and vision loss.

We are indebted to Dr. Mark H. Greene for support and critical review of the manuscript; to the physicians of the Retina Service of Wills Eye Hospital for allowing us to interview their patients; to Lee Ann Taylor for analytic support; and to Veronica McEneaney and Millie Jacobus for their assistance.

References

1. Shields JA. The diagnosis and management of intraocular tumors. St. Louis: CV Mosby, 1983:65-82.
2. Cutler SJ, Young JL Jr, eds. Third National Cancer Survey: incidence data. Bethesda, Md.: National Cancer Institute, 1975. (National Cancer Institute monograph 41).
3. Lee JAH. Melanoma and exposure to sunlight. Epidemiol Rev 1982; 4:110-36
4. Scotto J, Fraumeni JF Jr, Lee JAH. Melanomas of the eye and other noncutaneous sites: epidemiologic aspects. JNCI 1976; 56:489-91.
5. Raivio J. Uveal melanoma in Finland: an epidemiological, clinical, histological and prognostic study. Acta Ophthalmol [Suppl] (Kbn) 1963; 133:1-64.
6. Hakulinen T, Temppo L, Saxén E. Cancer of the eye: a review of trends and differentials. World Health Stat Q 1978; 31:143-58.
7. Shields JA. The diagnosis and management of intraocular tumors. St. Louis: CV Mosby, 1983:194-209.
8. *Idem.* The diagnosis and management of intraocular tumors. St. Louis: CV Mosby, 1983:210-54.
9. Zigman S. The role of sunlight in human cataract formation. Surv Ophthalmol 1983; 27:317-25.
10. Hiller R, Sperduto RD, Ederer F. Epidemiologic association with cataract in the 1971-1972 National Health and Nutrition Examination Survey. Am J Epidemiol 1983; 118:239-49.
11. Gart JJ. Point and interval estimation of the common odds ratio in the combination of 2 × 2 tables with fixed marginals. Biometrika 1970; 57:471-5.
12. Mantel N. Chi-square tests with one degree of freedom, extensions of the Mantel–Haenszel procedure. J Am Stat Assoc 1963; 58:690-700.
13. Breslow NE, Day NE. Statistical methods in cancer research. I. The analysis of case-control studies. Lyon, France: International Agency for Research on Cancer, 1980.
14. Holman DCJ, Armstrong BK, Heenan PJ. A theory of the etiology and pathogenesis of human cutaneous malignant melanoma. JNCI 1983; 71:651-6.
15. Young JL, Percy CL, Asire AJ, eds. Surveillance, epidemiology, and end results: incidence and mortality data, 1973-1977. Bethesda, Md.: National Cancer Institute, 1981. (National Cancer Institute monograph 57).
16. Morin MM, Pickle LW, Mason TJ. Geographic patterns of ethnic groups in the United States. Am J Public Health 1984; 74:133-9.
17. Zigman S. Effects of near ultraviolet radiation on the lens and retina. Doc Ophthalmol 1983; 55:375-81.