

Patterns of Tumor Initiation in Choroidal Melanoma¹

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ABSTRACT

This study attempts to document the occurrence of tumors with respect to clock hour location and distance from the macula and to evaluate tumor location in relation to retinal topography and light dose distribution on the retinal sphere. Analysis of patterns of tumor initiation may provide new evidence to clarify the controversy regarding the possible light-related etiology of choroidal melanoma. Incident cases of choroidal and ciliary body melanoma in Massachusetts residents diagnosed between 1984 and 1993 were the basis for analysis. Conventional fundus drawings and photos were used to assess the initiation site of each tumor. The initiation site was defined as the intersect between the largest tumor diameter and the largest perpendicular diameter of the tumor. Initiation sites were recorded using spherical coordinates. The retinal sphere was divided into 61 mutually exclusive sectors defined according to clock hour and anteroposterior distance from the macula. Rates of initiation were computed for each sector, overall, and according to gender and other clinical factors. Results were similar in left and right eyes; therefore, these were combined in analysis. Tumor initiation had a predilection for the macula ($P < 0.0001$). Overall, no significant clock hour preference was observed ($P = 0.63$). However, the parafoveal zone showed a strong circular trend ($P < 0.01$), with highest rates occurring in the temporal region, and the lowest rates occurring in the nasal region. Rates of occurrence in six progressively more anterior concentric zones (designated as the foveal, parafoveal, posterior, peripheral, anterior, and ciliary body zones) were 21.4, 14.2, 12.1, 8.9, 4.5, and 4.3 counts per spherical unit per 1000 eyes, respectively. Concentric zone location did not vary by gender ($P = 0.93$) or laterality ($P = 0.78$). However, posterior location was associated with light iris color ($P = 0.01$). Tumor diameters were largest in the peripheral region of the fundus and smallest in the macular and ciliary body zone ($P < 0.001$). Clock hour location was not influenced by gender ($P = 0.74$), laterality ($P = 0.53$), iris color ($P = 0.84$), or tumor diameter ($P = 0.73$). Results suggest that tumor initiation is not uniformly distributed, with rates of occurrence concentrated in the macular area and decreasing monotonically with distance from the macula to the ciliary body. This pattern is consistent with the retinal topography and correlates positively with the dose distribution of solar light on the retinal sphere.

INTRODUCTION

Uveal melanoma is the only life-threatening intraocular tumor; approximately one-fourth of the patients die of melanoma-related metastasis within 5 years of treatment. However, the etiology of these tumors remains poorly understood. Solar radiation has long been suspected as a causal factor (1–6), although this remains controversial (3, 7–10). Early life exposures to sunlight (1), intense sun exposure (4), severe eye burn, history of snow blindness, and light iris color (11) have been found to be possible risk factors in the development of uveal melanoma.

UV or near UV light exposure varies greatly by personal behavior, geographic location, and time, factors that make it difficult to measure

cumulative lifetime exposure. However, the pattern of light exposure on the retina is invariant. Studies have shown that light illuminance (dose distribution) on the retina declines progressively from the macular region to the periphery (12, 13). These patterns can be mapped on the retinal sphere and compared with retinal and choroidal topography (14–18). Therefore, systematic documentation of the occurrence pattern of tumors on the retinal sphere *in vivo* may shed light on the relationship between patterns of tumor initiation, retinal topography, and photochemistry and thus help resolve the controversy on these tumors' light-related etiology.

This study, based on all occurrences of choroidal melanoma in a defined geographic area (Massachusetts) over a 10-year period, attempts to document the occurrence of ocular melanoma with respect to clock hour location and distance in relation to the macula and to examine relationships of tumor initiation sites with the distribution of solar radiation on the retina.

MATERIALS AND METHODS

Incident cases of choroidal melanoma in Massachusetts residents diagnosed between 1984 and 1993 were identified from statewide and hospital tumor registries, from ophthalmologists throughout New England and bordering states, and at referral centers in New York and Philadelphia. All cases were confirmed by their surgeons or referring ophthalmologists. All of the tumors were unifocal, and none of the patients had bilateral involvement. Fundus drawings (19, 20) or photos and surgical reports of localization during treatment were used to assess tumor location. Before grading, photographs were translated into fundus drawings.

We assumed that the growth of the ocular melanoma was isotropic. The center of a tumor (the presumed initiation site) was defined as the geometric center of the tumor, which was approximated as the intersect of the largest anteroposterior tumor diameter and the largest perpendicular diameter for tumors with regular shape [*e.g.*, round, ellipse (96%)] or a centermost point by judgment for tumors with irregular basal shape (4%). Location of the tumor center was recorded in spherical coordinates (θ, Φ), where θ is the azimuth (the angle from a tumor center to the foveal center), and Φ is the zenith (the clock hour angle measured in the equatorial plane). Based on their spherical coordinates, tumors were mapped onto a standardized grid with sectors defining both clock hour location and one of six concentric anteroposterior zones (see Fig. 1). The grid was constructed based on an azimuth equidistant projection of the choroid (19, 20). The choroid was defined as a unit sphere truncated at the limbus, which has an azimuth ranging from 0° (fovea) to 150° (limbus) and a zenith ranging from 0° to 360°. The six zones were defined in spherical angle intervals as follows: (a) foveal zone, 0° to 10°; (b) parafoveal zone, 10° to 40°; (c) posterior zone, 40° to 65°; (d) peripheral zone, 65° to 90°; (e) anterior zone, 90° to 122°; and (f) ciliary body, 122° to 150°. The 12 clock hours were defined at a 30° interval. The centralmost zone (fovea) was considered directionless, and in total, 61 sectors were defined by the 6 zones and 12 clock hour intervals. In this analysis, we define the area of the centralmost (foveal) sector as a spherical unit area, which is equal to 0.8142% of the total area of the ciliary/choroidal sphere. Consequently, each sector in the five zones from parafoveal to ciliary body has a 1.20, 1.88, 2.32, 2.91, and 1.84 unit area, respectively.

Analysis indicated similar initiation patterns in the right and left eye, and data were therefore collapsed, except where noted. Summary statistics of patient age, gender, race, laterality, and tumor dimension were computed to characterize the subjects and tumors. Summary statistics of cases with standard fundus drawing and those without drawings were compared using Wilcoxon's rank-sum test.

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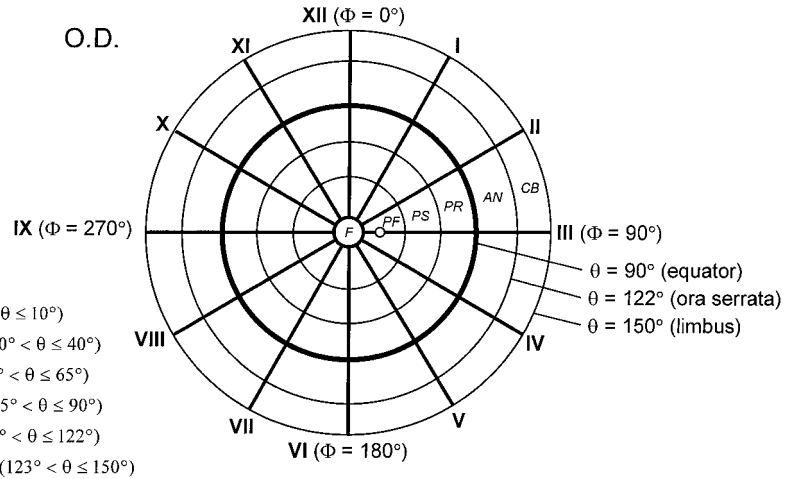


Fig. 1. Classification grid of the choroidal sphere based on equidistant projection.

Rates of occurrences of tumor initiation in each sector were computed and adjusted to sector spherical area and recorded in ca/1000ua.³ Pearson's χ^2 tests were used to examine the association between initiation sites and spherical location. The χ^2 tests were constructed using likelihood according to the fraction of spherical area of each zone (sector or clock-hour section) in relation to the total spherical area of choroidal sphere and under the null assumption that tumors are uniformly distributed on the choroidal sphere.

RESULTS

A total of 448 incident cases of choroidal melanoma were identified, including 302 choroidal, 109 ciliochoroidal, 10 iridociliary, 12 iridociliochoroidal, and 3 ciliary body only tumors. In the 12 remaining tumors, the site of involvement was unknown. A total of 420 (94%) cases had fundus drawings or photographs available for examination. Clinical and demographic data on the total series are presented in Table 1. There was no significant difference in gender ($P = 0.65$) and largest tumor diameter ($P = 0.47$) between the cases with fundus drawing and those without drawings.

As shown in Fig. 2 and Table 2, tumor initiation had a significant predilection for the macula in all quadrants ($P < 0.01$ for all quadrants). In each quadrant, initiation rates decreased with distance from the macula: the mean initiation rate in all quadrants combined was 21.4, 14.2, 12.1, 8.9, 4.5, and 4.3 ca/1000ua for the foveal, parafoveal, posterior, peripheral, anterior, and ciliary zones, respectively. Such a gradient agrees with the decreasing gradient of light illuminance on the retina from the macular region to the periphery. However, the largest gradient was observed in the inferiortemporal and superotemporal quadrants, where the rates were 4.3–4.7 times higher in the parafoveal zone than in the ciliary zone; in the nasal quadrants, the trend was less pronounced but statistically significant.

Overall, no significant clock hour preference was observed ($P = 0.28$). However, a circular trend in rates was observed in the parafoveal zone ($P < 0.01$), with the highest rates occurring in the temporal parafoveal region (range, 17.9–23.8 ca/1000ua), which is the region subject to the highest sunlight exposure in the eye, and the lowest rates occurring in the nasal parafoveal region (range, 2.0–6.0 ca/1000ua), which encompasses the optic disc. Overall, rates were nonsignificantly higher in the inferior hemisphere than in the superior hemisphere ($P = 0.20$). Otherwise, rates of initiation were not significantly different between quadrants and hemispheres ($P > 0.50$; Table 2).

Patients with lighter iris color were more likely to have a tumor in the most posterior zones compared with those with a darker iris ($P = 0.01$). The mean of the largest tumor diameter was greatest in the peripheral region (15.1 mm; SD = 3.54 mm), and smallest in the fovea and parafoveal regions (10.7 mm; SD = 4.02 mm). In contrast, concentric zone location was unrelated to gender ($P = 0.93$) or laterality ($P = 0.78$). Clock hour location was not associated with gender ($P = 0.74$), laterality ($P = 0.53$), iris color ($P = 0.84$), or tumor diameter ($P = 0.73$).

DISCUSSION

Results suggest that tumor initiation is not uniformly distributed, with rates of occurrence concentrated in the macular area and decreasing progressively with increasing distance from the macula to the ciliary body. This pattern is consistent with the dose distribution of light on the retinal sphere (10) and the eccentricity of topography of RPE (14–16, 21), choroidal melanin (22), and light-induced oxidation (23). The findings support the hypothesis that solar exposure plays a role in the induction of uveal melanoma.

Various studies have demonstrated the inherent susceptibility of ocular tissue to visible and UV light-induced damage. Solar light may act as both initiator and promoter in the course of carcinogenesis (24–26). Radiation energy of visible or UV light not only elevates photochemical reactions (27) and the formation of free radicals in the retina (28–30) but also induces alternation of immunological function

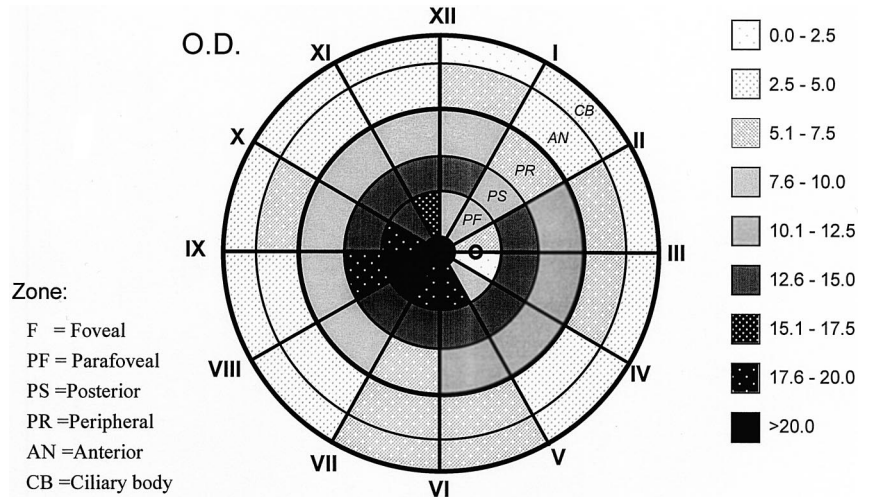
Table 1 Characteristics of study subjects

Factor	Level	No. of tumors	Percentage (%)
Gender	Male	223	49.8
	Female	225	50.2
Race	Caucasian	436	99.1 ^a
	Non-Caucasian	3	0.9 ^a
	Unknown	10	
Age at diagnosis (yrs)	≤55	142	31.7
	56–65	113	25.2
	66–75	122	27.2
	>75	71	15.9
Eye color	Blue	153	45.7 ^a
	Green/Gray	87	26.0 ^a
	Brown	95	28.4 ^a
	Unknown	113	
Laterality ^b	OD	211	47.1 ^a
	OS	234	52.2 ^a
	Unknown	3	

³ The abbreviations used are: ca/1000ua, counts per unit area per 1000 eyes; RPE, retinal pigment epithelium.

^a Percentage among knowns.
^b OD, right eye; OS, left eye.

Fig. 2. Distribution of tumor initiation sites (ca/1000ua).



(31, 32). Visible blue light was found to be particularly efficient in causing dysfunction of the blood-retinal barrier (33). The elevated photo-oxidation and dysfunction of blood-retinal-barriers may allow photo-toxicants to be released into the blood and choroid (23).

The posterior region of the fundus is subject to much higher light exposure and is less protected by RPE melanin than are the peripheral and anterior regions, which may explain the more frequent tumor onset in this region. Relative illumination (dose distribution) on the retina declines progressively from the macular region to the periphery (10, 12, 13, 34). Conversely, the RPE melanin concentration, which protects the retina from overexposure via its antioxidant capability (31–33), is lowest in the macula-perimacular area and increases with distance from the macula (22, 35). When subjected to intense or prolonged oxidative insult, the melanin may lose its antioxidant efficiency or even become an efficient pro-oxidant (23), which in turn may result in the malfunctioning of the choroiretinal complex (29). The greatest rates of tumor occurrences were observed in the foveal and temporal parafoveal regions, where the retina is subject to the highest light exposure. Thus, our findings indicating a decreasing gradient in tumor initiation away from the macular region adds support to the hypothesis that light is a contributing factor in the genesis of these tumors.

The higher concentration of tumor occurrence toward the macula in light-colored eyes is in line with the findings from studies on iris and retinal pigmentation. Compared with dark-colored eyes, light-colored eyes have a less pigmented iris epithelium. Consequently, in blue eyes, the macular and perimacular region is exposed to more transmitted light (34), and at the same time, the melanin in the overlying RPE is significantly reduced relative to darker eyes (36).

Schwartz *et al.* (10) concluded that there is no association between

UV dose distribution and initiation site based on a spherical model using data from a small clinical cohort ($n = 93$). However, conclusions from this previous study may not be valid because the likelihood function was incorrectly specified in their analysis. Also, unlike the previous analysis, our study was based on a complete, population-based series and thus was free of any possible referral bias. The estimated incidence rate in Massachusetts based on these data (7.5 cases per million persons per year) is in line with previously published estimates in Caucasian populations (3); therefore, we assume that few cases, if any, were missed.

The larger average tumor diameter at diagnosis in the peripheral zone implies later diagnoses of these tumors compared with those in other zones. A likely explanation is that the impact of these tumors on vision is less severe compared with those located in the macular region. For the same reason, it is possible that tumors arising peripherally are underdiagnosed compared with posterior tumors. However, presumably, most such tumors would eventually become symptomatic as the tumor progressed or would be detected during fundus examination for other reasons, and this would not explain the marked patterns observed.

The study had several limitations to consider. Tumor location was based on clinical drawings that recorded the tumor's position and shape in a two-dimensional plane. Spherical distortion in the drawings may have contributed to error in clock hour assignment, particularly in the most anterior tumors. Seven percent of the tumors were assessed based on fundus drawings translated from fundus photographs. This might have introduced some error in the analysis. Finally, some of the fundus drawings did not include the ciliary body zone ($n = 21$), and in these cases, we assumed that the tumor extended to the limbus. This approach may have misclassified some tumors to a more anterior

Table 2 Tumor initiation rates^a (counts) by zone and quadrants

Foveal zone was considered as directionless, and its initiation rate was 21.43 ca/1000ua.

Concentric zone	Quadrants ^b				Overall rates (counts)	P ^c
	ST	IT	SN	IN		
Parafoveal	16.53 (25)	22.49 (34)	7.94 (12)	9.92 (14)	14.22 (85)	0.006
Posterior	13.48 (32)	12.22 (29)	10.11 (23)	12.64 (32)	12.11 (116)	0.751
Peripheral	8.90 (26)	7.87 (23)	8.56 (25)	10.27 (32)	8.90 (106)	0.801
Anterior	4.64 (17)	4.64 (17)	4.10 (15)	4.10 (15)	4.51 (64)	0.981
Ciliary	3.87 (9)	4.74 (11)	3.01 (7)	5.60 (13)	4.30 (40)	0.572
P ^d	<0.001	<0.001	0.011	0.004	<0.001	

^a Tumor counts, per spherical area, per 1000 eyes.

^b S, superior; I, inferior; T, temporal; N, nasal.

^c χ^2 tests for differences by quadrants.

^d χ^2 tests for differences by zone.

location, and our results, if anything, would underestimate the predilection for these tumors to arise in the posterior fundus.

In summary, these results document the nonuniform distribution of melanomas arising in the uveal tract in a population-based series and add further data supporting a light-related etiology. More research is needed to determine the nature and timing of exposure causing DNA damage in the eye before effective public health measures for prevention can be adopted.

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