The Differential Effect of Ultraviolet Light Exposure on Cataract Rate across Regions of the Lens

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PURPOSE. In studies of cortical cataract, a severity score representing the area covered by cataract is often used as the primary outcome. However, additional disease information may exist in the spatial distribution of opacities. Further, it has been hypothesized that the lower nasal region of the lens is the most susceptible to damage by environmental ultraviolet light exposure.

METHODS. In a sample of 107 lens images from the Salisbury Eye Evaluation Study, a digital cortical cataract grading algorithm was used to capture the location of opacities in binary images. These images were used to estimate the severity of cataract in 16 regions around the lens. The effect of individual cumulative lifetime ocular exposure to ultraviolet B light on cortical cataract risk for each lens region was examined, as estimated by using an empiric model and baseline occupation and leisure activities data, in a linear mixed-effects model.

RESULTS. The lower nasal regions had the highest cortical cataract severity in both the right and left eyes. In the combined data, region 9 (the lower nasal corner of the lens) was estimated to have the highest severity. In an assessment of the high- and low-exposure ultraviolet light groups (dichotomized at the median exposure level), higher exposure had the most effect in the lower regions of the lens.

CONCLUSIONS. These results indicate that there are regional lens differences in the association between cataract and exposure to ultraviolet light but that ultraviolet light may not entirely explain the variations in cortical cataract severity across the lens. (*Invest Ophthalmol Vis Sci.* 2010;51:3919–3923) DOI: 10.1167/iovs.09-4557

Cortical cataract outcomes are evaluated by using retroillumination images that capture the patterns of opacity on the lens cortical surface. These images are commonly used in cataract research and clinical practice to characterize the severity in terms of the area of involvement. Cataracts that cover more lens area are considered more severe and correlate with increased visual impairment. However, additional etiologic information may be contained in the spatial distribution of opacities across the cortical surface of the lens.

Several studies have been conducted to examine the location of cortical opacities by using standard cortical grading or

classification methodology^{1–7} in which trained lens image reviewers assign a percentage involvement to a specified number of regions (typically four to eight sections) in the lens image. Percentages are averaged over the study sample to get an approximate spatial distribution by quadrant. The reviewers uniformly found a concentration of cortical cataract in the lower nasal quadrant of the lens. This pattern was more predominant in older individuals, suggesting more accumulated exposure over time to a factor that primarily affected the lower nasal quadrant of the cortical surface. Several investigators have hypothesized that ultraviolet light (UVB) may in part or wholly explain the distinct pattern.^{1,7–10} The bony configuration of the orbit and the most probable gaze position during peak sunlight hours suggest that the lower nasal lens region receives the greatest dose of UVB.^{7,11} Optical and computational modeling studies, as well as in vitro experiments, have provided additional evidence and a theoretical basis for a regional effect of UVB.^{9,10,12} Although other mechanisms have been postulated,³ UVB is an established risk factor for cortical cataract, lending credence to the theory that differential exposure by region could account for spatial variation in cataract severity. However, to our knowledge, this hypothesis has not been tested with individual UVB exposure data.

Using a novel methodology, we examined the severity of cortical cataract opacity as a function of location on the cortical surface of the lens in a sample of participants with measurable cataract from the Salisbury Eye Evaluation (SEE) Study. Digital images of the lens provided estimates of the severity of cortical opacities within 16 regions of the lens, yielding an estimate of the spatial distribution of cataract on a finer scale than has been achieved with standard lens image-grading methods. The modifying effect of lens region on the association between UVB exposure and cortical cataract severity was assessed with linear mixed-effects models.

METHODS

Subjects

The SEE study sampled individuals aged 65 to 84 years who were living in Salisbury, Maryland.¹³ Participants were recruited from 1993 to 1995 and were followed up for 8 years and evaluated at various time points for the presence of ophthalmic disease. The study was approved by the Institutional Review Board of the Johns Hopkins School of Medicine and was conducted in accordance with the Declaration of Helsinki. At baseline, UVB cumulative lifetime ocular exposure was estimated by using an empiric model of ambient exposure levels based on measurements from a UVB pyranometer located on Maryland's Eastern Shore.^{14–17} The model corrected for geographic location, cloud cover, and personal habits, such as the use of hats and sunglasses, and time spent outdoors. Personal exposure information was obtained from an occupation and leisure history questionnaire.¹⁸ Ocular exposure ratios were determined on the basis of measurements made in Salisbury residents during the course of their daily activities. The exposure units were in Maryland sun years (MSY) with 1 MSY = 75.9 J/cm². Digital retroillumination images were collected from 601

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FIGURE 1. Binary image of opacities. The computerized grading algorithm produces a binary image of the opacities identified on the lens cortical surface from a digital retroillumination image. The 16 regions used in the analysis are shown in the image and the corresponding anatomic region.

participants at the 8-year follow-up visit, of which approximately 90% were gradable and had some degree of measurable cortical cataract.

Lens Image Data

The gray scale representations of the retroillumination images were used with an 8-bit scale (256 levels) providing the discrimination between degrees of light intensity. To evaluate the spatial distribution of cortical cataract and factors that are associated with location on the lens, we included lens images with an opacity severity score greater than 0. A pupillary diameter of at least 7.0 mm was necessary to capture as much cataract information on the periphery of the lens as possible. Included images were selected independently, based on the inclusion criteria, from the available digital images, (i.e., the selection process was blinded to participant and eye information). Each image was processed with a computer algorithm, described elsewhere,¹⁹ that classified each image pixel (the smallest unit of information in the image) as having opacity or not. Briefly, fuzzy c-means clustering methods were used to discriminate between background and opacity pixels in the retroillumination images after processing to remove lighting artifacts. Thus, a light-intensity threshold for opacity classification was uniquely set for each image on the basis of the sample of observations (pixels) available for analysis. This technique accommodated differences across images in the background lighting intensity and other factors. Computerized assessment of cataract in each image was validated by a trained lens image grader to minimize misclassification of opacity.

For each binary opacity image, the lens was divided into 16 regions, and the number of pixels classified as having opacity was divided by the sum of the total number of pixels within the region, to obtain a region-specific opacity severity score. Thus, each eye in the dataset

contributed 16 measurements of opacity severity (Fig. 1). Since the minimum pupillary diameter of the selected images was 7.0 mm, cataract information was assessed only within 7.0 mm in all images included in the study. Thus, equivalent pixel samples were used for the calculation of opacity severity in each region for each lens in the sample.

Statistics

A linear mixed-effects model was used to evaluate the main effects of UVB, age, sex, race, and lens region on the opacity-severity score. An interaction term for region and UVB was included in the model, to assess differences in the effect of UVB exposure between regions of the lens. Individual exposure to UVB was used as a dichotomous variable with high exposure defined as a value greater than the median 0.037 MSY. Age was dichotomized to less than or equal to 70 years and greater than 70 years, and race was categorized as black or white. The variance of the cataract scores was stabilized by arcsin square-root transformation. The right and left eye data were pooled for the analysis. A hierarchical structure was used to account for the correlation between eyes within an individual and between lens regions within an eye. The covariance structure for the random effects between lens regions was specified to be a function of the distance between region centroids such that $\text{cov}(G) = \sigma^2 \rho^{d_{ij}}$ where G is the random error associated with a single individual's repeated measurements, d_{ij} is the Euclidean distance between the centroids of the i th and j th regions of the lens, and σ^2 and ρ are parameters describing the variance and correlation. The covariance structure between eyes was assumed to have equal variance across subjects.

RESULTS

Of the 107 images that were included in the study, 46 were right eye images and 61 were left eye images. Twenty-two individuals contributed to both left and right eye samples. The UVB exposure ranged from 0.0 to 0.40 MSY. The characteristics of the right eye, left eye and overall samples are shown in Table 1.

Figure 2 shows the two-dimensional distribution of cortical cataract obtained by summing the binary images. These distributional images show the highest severity of cortical cataract was found in the lower nasal area of the lens in both the right and left eyes, indicating a similar pattern of spatial susceptibility to cortical cataract in the two eyes. When the left and right eye data were combined, the average cataract severity in the 16 regions of the lens reflected this pattern, with the highest opacity severity found in the lower nasal region and the lowest severity found in the upper nasal region (Fig. 3). When we compared the cataract severity between the high- and low-UVB exposure groups categorized by using the median UVB exposure in the sample (UVB > 0.037 MSY and UVB ≤ 0.037 MSY, respectively) we saw higher severity with high UVB exposure from the lower nasal through the temporal regions. Looking at just the subsample ($n = 19$ lens) within the high-UVB exposure group with exposures greater than 0.100 MSY, we saw a much higher magnitude of cataract severity in regions 7 through 16 than in the low-UVB exposure group. The difference in the

TABLE 1. Characteristics of the Right Eye, Left Eye, and Overall Sample of Participants

	Right Eye* ($n = 46$)	Left Eye* ($n = 61$)	Overall* ($n = 107$)
Age, y	71.5 (69.3, 74.0)	71.0 (69.0, 75.0)	71.0 (69.0, 74.0)
Cumulative UVB, MSY	0.012 (0.006, 0.023)	0.070 (0.042, 0.114)	0.037 (0.014, 0.082)
White, %	65	74	70
Male, %	50	43	46

Twenty-two individuals contributed to both left and right eye samples.

* Median (interquartile range) unless otherwise indicated.

FIGURE 2. Distribution of cataract. Summing the binary images from the sample of 107 lenses shows the distribution of cataract across the lens in the right (A) and left (B) eyes. Bright areas corresponded to more frequent occurrence of cataract, and darker regions corresponded to less frequent cataract among the participants.

average severity was greatest in regions 10 and 11, which corresponded to the lower quadrant of the lens. This difference was not statistically significant, however, given the small number of lenses in the sample from individuals with UVB exposures above 0.1 MSY.

The results from the mixed model of 1712 measurements (107 images $\times$ 16 regions) of cataract severity from the combined left and right eye data are shown in Tables 2 and 3. Estimates of the effect of region on cataract severity indicated that there were differences across the lens. With region 16 as the comparison, the main-effect estimates for region indicated that regions 5 through 14 had significantly higher severity ($P < 0.05$). The highest average cataract severity was found in region 9 and was estimated to be 11.4 per 100 pixels (95% confidence interval [CI], 7.5–16.1) higher than that in the comparison region 16. When those greater than 70 years old were compared with those less than or equal to 70 years, the average cortical cataract severity across the lens was roughly equivalent (0.01 per 100 pixels). The women and the men were estimated to have equivalent cataract severity across regions in our sample as well. Blacks had a severity that was 0.10 per 100 pixels (95% CI, –0.01 to 0.56) higher than

FIGURE 3. Mean cataract rate. The average cataract severity across the sample of 107 lens images per 100 pixels is shown for the 16 regions of the lens. The overall severity function is shown, as well as the severity stratified by low (UVB $\leq$ 0.037 MSY) and high (UVB $>$ 0.037 MSY) UVB exposure groups, with the median UVB exposure in the sample used for dichotomization. The cataract severity across regions for the subset of 19 lenses with the highest UVB exposure UVB $>$ 0.100 MSY is presented for comparison.

whites, although the estimated effect did not reach statistical significance.

The effect of UVB exposure was evaluated by a main effect and an interaction with region, to assess differences across the lens in the relationship between UVB and cataract severity. Comparing the effect of UVB exposure on the average cataract severity, we estimated that those with high UVB exposure had

TABLE 2. Main-Effect Results from Linear Mixed Model Analysis

Covariate	Estimated Effect (Per 100 Pixels)	95% CI
Intercept	0.46	–0.03 to 2.33
High UVB (region 16)*	1.37	0.16 to 3.77
Region 1	0.00	–0.45 to 0.47
Region 2	0.01	–0.35 to 0.58
Region 3	0.03	–0.27 to 0.70
Region 4	0.15	0.08 to 1.14
Region 5	0.38	0.00 to 1.67
Region 6	4.01	1.78 to 7.08
Region 7	7.51	4.34 to 11.46
Region 8	9.56	5.95 to 13.90
Region 9	11.43	7.48 to 16.08
Region 10	6.57	3.62 to 10.31
Region 11	2.93	1.08 to 5.64
Region 12	1.30	0.21 to 3.27
Region 13	0.57	0.01 to 2.04
Region 14	0.53	0.00 to 1.97
Region 15	0.15	–0.08 to 1.14
Age $>$ 70 years	0.01	–0.26 to 0.09
Female	0.00	–0.18 to 0.14
Black race	0.10	–0.01 to 0.56

Reference is UVB $\leq$ 0.037 MSY, white race, male, age $\leq$ 70 years, and region 16.

* UVB $>$ 0.037 MSY.

TABLE 3. Estimated Modifying Effects of Lens Region on the Main Effect of High UVB Exposure from the Linear Mixed-Model Analysis

Interaction	Estimated Effect (Per 100 Pixels)	95% CI
High UVB×region 1	−0.16	−1.83 to 0.30
High UVB×region 2	−0.28	−2.18 to 0.18
High UVB×region 3	−1.04	−3.86 to 0.00
High UVB×region 4	−1.29	−4.31 to −0.03
High UVB×region 5	−1.38	−4.48 to −0.05
High UVB×region 6	−3.24	−7.45 to −0.73
High UVB×region 7	−1.59	−4.84 to −0.10
High UVB×region 8	−0.68	−3.13 to 0.02
High UVB×region 9	−0.29	−2.22 to 0.82
High UVB×region 10	0.00	−1.00 to 0.82
High UVB×region 11	0.10	−0.42 to 1.59
High UVB×region 12	0.55	−0.05 to 2.85
High UVB×region 13	0.25	−0.20 to 2.11
High UVB×region 14	0.01	−0.70 to 1.15
High UVB×region 15	−0.02	−1.18 to 0.67

High UVB defined as UVB > 0.037 MSY.

1.37 per 100 pixels (95% CI, 0.16–3.77) higher severity than did those with low UVB exposure in region 16, the reference region (shown in Table 2). The changes in the effect of UVB across the regions of the lens as estimated by the interaction terms are shown in Table 3. The estimates indicated that the effect of UVB exposure estimated for region 16 was significantly different from the average UVB effect in regions 3 through 7, which corresponded to that in the upper nasal quadrant of the lens. The estimated interactions decreased the magnitude of the expected effect of high UVB exposure in those regions. Although not presented in the final model, interaction terms between age and region, race and region, and sex and region were evaluated, and none of the terms was significant. However, the direction of the effect estimates indicated that age had a differential effect on the cataract severity by region with positive effect estimates in the lower nasal regions in both eyes and negative estimates in the other regions (comparing to region 16). Similar results were recorded for the interaction with race, whereas sex appeared to have an equivalent effect on all regions.

DISCUSSION

In this study, we used novel methods for assessing the contribution of lens region to cortical cataract severity in a sample of lenses from the SEE study with varying degrees of opacity. Using individual cumulative lifetime UVB exposure data collected 8 years before opacity assessment, we investigated the influence of lens region on the effect of UVB exposure. Results in studies in which the location of cortical cataract in lens images has been examined have consistently shown the lower nasal quadrant of both eyes to be most affected, as judged by the average area involved.^{1–7} The results from this sample of lenses echoed these findings. Among individuals in the SEE study with measurable cortical opacity, the distribution of cortical cataract was biased toward the lower nasal regions of the lens in both eyes, as clearly shown in Figure 2.

UVB, which has been associated with cortical cataract risk in numerous studies in various populations,²⁰ may contribute to the noted spatial pattern of cortical opacities. Age-related cataractous changes originating in the deep equatorial cortex of the lens (perhaps as a result of increasing shear stress on fibers) are most likely exacerbated by UVB exposure through mechanisms such as increased oxidative radical burden and lipid peroxidation.^{21,22} If, as a result of anatomy or gaze posi-

tion, UVB exposure is differential by lens region, any effect of higher UVB exposure on cataract risk would similarly be expected to be differential by region. In our data, crude comparisons of the cataract severity between high- and low-UVB exposure groups across regions of the lens suggested this to be the case (Fig. 3). UVB exposure had a variable effect on cataract severity, with little to no effect in the upper nasal regions of the lens and a maximum effect in the lower regions. The differences in effect were amplified when those in the lower 50% of UVB exposure were compared to the subset of 19 lenses with the highest UVB exposure (UVB > 0.1 MSY). Although the differences in cataract severity in the affected regions were not significant, the apparent dose-response of the regional effect is noteworthy.

The results from the linear mixed-effects analysis indicated, similarly, that in all but regions 3 through 7, high UVB-exposure was associated with increased cataract severity, with cumulative exposure to UVB of greater than 0.037 MSY increasing severity by 1.37 per 100 pixels on average. Further there was a substantial regional association, even with adjustment for UVB exposure, such that, compared with region 16 in the upper temporal quadrant, the risk of cataract severity steadily increased to a peak in region 9 (the lower nasal quadrant). The linear mixed-model results suggest that there is an effect of lens region on cataract severity that is independent of UVB exposure, hinting at the presence of a more inherent susceptibility to cataract in the lower nasal regions. Observations by Coroneo⁹ on the albedo effect and by Kwok and Coroneo¹² on spatial heterogeneity in patterns of lens fiber elongation may provide the mechanism whereby the nasal region of the lens would exhibit higher sensitivity to damage, particularly from UVB. The effect of UVB exposure was to amplify the regional differences and perhaps modestly shift the peak toward the lower regions 10 and 11.

Of additional note were the results from examining eyes grouped according to age, race, and sex. Study results have implicated all three as associated with the risk of cortical cataract.^{3,18,23–25} Studies of cortical cataract location have noted an age trend in the lower nasal quadrant cataract predominance,^{3–5} with similar patterns observed for men and women. The main effect estimate from the mixed models did not indicate a difference between age ≤70 years and >70 years, on average, looking across regions of the lens. The range of ages was small, with 75% of the participants between 69 and 74 years. Results for nonwhite race and women similarly indicated little difference between the black and white or male and female groups. Although these factors appear to increase the risk of occurrence of cortical cataract among individuals who are opacity free, among individuals with measurable opacity, age, race, and sex may not have a strong impact on severity. Further, if cataract severity had been assessed on a regional scale, the size of the effects may have been reduced compared with whole lens severity comparisons, and our sample may have been underpowered for detecting their presence.

There were limitations in the present study that merit discussion. The conservative inclusion criteria resulted in a modest sample size that limited the analysis in terms of the number of risk factors that could be explored and the complexity of their representation in the model. Given that a linear representation of UVB was found to be inappropriate, the dichotomization of UVB exposure in particular may have resulted in a loss of information that would have yielded a more complete picture of the effect of UVB on regional cortical cataract severity. However, the restriction on pupillary diameter served to maximize the available cataract information in each lens image by capturing most of the lens cortical surface. Although the final study sample included only approximately 10% of the available images from SEE, it is unlikely that the restrictions on pupillary

diameter would bias the inferences. In addition, the assessment of UVB exposure was a cumulative lifetime measure at baseline, 8 years before the assessment of the cortical cataract outcome. There is a question as to the period of UVB exposure that is relevant to the increased later risk. UVB radiation may contribute to cataract formation through a number of mechanisms (e.g., producing reactive oxygen species^{26,27} or generating cytotoxic products²⁸) that potentially take years to produce the result of clinically apparent cortical cataract. Given that, we felt it reasonable to assume that cumulative UVB exposure could contribute to cortical cataract severity 8 years later.

In summary, the results from this study sample indicate that the highest rate of cortical cataract is observed in the lower nasal regions of the lens. These results support findings in other studies of cortical cataract location. Of higher import is the indication that there are regional differences across the lens in the effect of UVB exposure. However, the effect of UVB appeared strongest in the lower regions of the lens, and region appeared to have an independent effect on cataract severity, which may reflect a higher susceptibility of the lower nasal regions to cataract.

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