Risk Factors for Incident Cortical and Posterior Subcapsular Lens Opacities in the Barbados Eye Studies

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Objective: To evaluate risk factors for the 4-year incidence of cortical and posterior subcapsular (PSC) lens opacities.

Design: Population-based cohort study with 85% participation at 4-year follow-up.

Participants: Three thousand one hundred ninety-three black participants of the Barbados Eye Studies, Barbados, West Indies, of whom 2040 and 2954 were free of cortical and PSC lens opacities, respectively, at baseline.

Methods: The standardized protocol at baseline and follow-up included an interview, anthropometric and blood pressure measurements, and ophthalmic measurements including slitlamp lens grading, fundus photography, and an ophthalmologic examination. Factors associated with incident cortical and PSC opacities (Lens Opacities Classification System II, ≥2) were evaluated by logistic regression.

Main Outcome Measure: Relative risks (RRs) with 95% confidence intervals.

Results: The 4-year incidence of cortical lens opacities was 22.2% (452/2040); the factors increasing risk were older age, female gender (RR=1.3), low socioeconomic status (RR=1.4), and a history of diabetes mellitus (RR=2.4), while aspirin use was associated with a lower RR (RR=0.2; 95% confidence interval, 0.1-0.8), a result based on small numbers. The 4-year incidence of PSC opacities was lower at 3.3% (97/2954), and risk also increased with age and a history of diabetes mellitus (RR=2.9). A dose-response relationship was evident between incident opacities and increased levels of glycated hemoglobin at baseline, with the highest risk of cortical (RR=3.60; 95% confidence interval, 2.23-5.81) and PSC (RR=4.93; 95% confidence interval, 2.69-9.05) opacities at more than an 11.5% glycated hemoglobin level.

Conclusions: Diabetes mellitus and hyperglycemia are major modifiable risk factors for the development of cortical and PSC lens opacities in this African-descent population with a high rate of diabetes mellitus. Prevention and improved control of diabetes mellitus are likely to reduce the burden of cataract. The finding of a reduced incidence of cortical lens opacities in aspirin users merits further investigation, given its potential for cataract prevention.

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A s the leading cause of blindness worldwide, age-related cataract has major public health significance. In recognition of its importance, the World Health Organization designated cataract as the priority condition for a global initiative to eliminate avoidable blindness.1 Many epidemiological studies have attempted to identify potentially modifiable cataract risk factors, with the aim of developing preventive interventions. Current evidence suggests that cataract is multifactorial in origin, with different associations reported for opacities in different regions of the lens.2-18

Populations of African origin are known to have high prevalences of lens opacities; among black populations in the United States and the Caribbean, cortical cataract is particularly more frequent than in white persons.4,10,13,15,17 Possible causes for the high cataract risk in black populations have been examined in cross-sectional studies, but there is still a dearth of longitudinal, population-based data available. We have previously reported factors predictive of incident nuclear cataract in black participants of the Barbados Incidence Study of Eye Diseases18 such as age, female gender, iris color, myopia, leaner body mass, and topical intraocular pressure (IOP)-lowering medications. The current article evaluates associations with incident cortical and posterior subcapsular (PSC) lens opacities in this popula-
Table 1. Baseline Characteristics of Groups With and Without Incident Cortical Lens Opacities

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n = 1588)</td>
</tr>
<tr>
<td>Age, mean (SD)[median], y†</td>
<td>50.9 (8.6) [48.0]</td>
</tr>
<tr>
<td>Female gender</td>
<td>55.0</td>
</tr>
<tr>
<td>BMI, mean (SD)[median]</td>
<td>27.5 (5.3) [26.8]</td>
</tr>
<tr>
<td>Low SES†</td>
<td>27.2</td>
</tr>
<tr>
<td>Blood pressure, mean (SD)</td>
<td></td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>130.2 (21.0) [128.0]</td>
</tr>
<tr>
<td>DBP</td>
<td>80.9 (12.0) [80.0]</td>
</tr>
<tr>
<td>IOP&gt;21 mm Hg‡</td>
<td>10.1</td>
</tr>
<tr>
<td>IOP treatment§</td>
<td>1.1</td>
</tr>
<tr>
<td>Myopia</td>
<td>18.1</td>
</tr>
<tr>
<td>Regular use of supplements</td>
<td>16.8</td>
</tr>
<tr>
<td>Regular use of aspirin therapy†</td>
<td>2.6</td>
</tr>
<tr>
<td>History of DM†</td>
<td>9.9</td>
</tr>
<tr>
<td>GHb level, mean (SD)[median], %†</td>
<td>7.3 (1.8) [6.9]</td>
</tr>
<tr>
<td>Smokers</td>
<td>9.5</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); DBP, diastolic blood pressure; DM, diabetes mellitus; GHb, glycosylated hemoglobin; IOP, intraocular pressure; SBP, systolic blood pressure; SES, socioeconomic status.

†P=.05 in logistic regression models adjusting for age and gender.
‡P=.09 in logistic regression models adjusting for age and gender.
§P=.07 in logistic regression models adjusting for age and gender.

The Barbados Eye Studies, funded by the National Eye Institute, Bethesda, Md, are a series of population-based investigations of the prevalence, incidence, and risk factors for major causes of visual loss in a preponderantly African-origin population. The baseline study, the Barbados Eye Study (BES) (1987-1992) measured prevalence and risk factors for major eye diseases in a random sample of Barbadian-born citizens, aged 40 to 84 years, with 84% participation. Surviving members of the cohort were invited to return for a 4-year (SD=5 months) follow-up visit in the Barbados Incidence Study of Eye Diseases (1992-1997). A total of 3427 persons participated (85% of the eligible population). Study methods have been described in detail elsewhere. In summary, the study protocol at baseline and follow-up comprised an interview, blood pressure and anthropometric measurements, and ophthalmic measurements including best-corrected visual acuity, visual fields, IOP, and color stereo fundus photography. A blood sample was drawn for glycosylated hemoglobin (GHb) measurement.

Lens gradings were based on the Lens Opacities Classification System II and performed with direct reference to photographic standards at the slitlamp, under maximum dilatation with tropicamide. Cortical, PSC, and nuclear lens opacities were defined by a Lens Opacities Classification System II score of 2 or higher. Four-year incidence of cortical or PSC lens opacities was defined as the development of the specific opacity type in at least 1 eye, among persons without that opacity in both eyes at baseline. The incidence for each opacity type, for example, cortical, did not consider if other opacity types, for example, nuclear or PSC coexisted in the same individual. Independent replicate gradings among different graders, evaluated throughout both the BES and Barbados Incidence Study of Eye Diseases data collection periods, demonstrated high intergrader agreement.

As previously reported, potential baseline risk factors investigated included age, gender, socioeconomic status (SES), iris color, skin pigmentation, body mass index and waist-hip ratio, use of nutritional supplements (such as multivitamins or cod liver oil), use of corticosteroids and aspirin therapy prior to evaluation, smoking and alcohol use, sunlight exposure, use of ocular medications, and a family history of cataract. Diabetes mellitus (DM) was defined by self-reported physician-diagnosis and GHb levels were also evaluated (the level of GHb was not measured in the first months of the study; therefore, results were unavailable for 19% of the participants). Hypertension was defined as systolic blood pressure of 140 mm Hg or higher and/or diastolic blood pressure of 90 mm Hg or higher measured by random zero sphygmomanometer at the clinic visit, and/or a history of antihypertensive treatment. Ocular variables included IOP and myopia, defined as a spherical equivalent less than −0.5 diopter. The effects of ocular variables were evaluated in the eye in which lens changes of interest developed. If neither eye or both eyes developed opacities, evaluations were based on the worse eye.

Age- and gender-adjusted univariate logistic regression analyses were used to evaluate possible factors associated with incident cortical and PSC opacities separately. Significant (P<.10) variables from these analyses were then retained for multivariate logistic regression analyses. The final models included age, gender, and the significant variables related to individual risk of incident cortical and posterior subcapsular cataract. Factors with P<.05 were considered as statistically significant. The results are presented as relative risks (RRs) and 95% confidence intervals (CIs), based on the results from logistic regression models.

Table 1 compares the baseline characteristics of persons with and without incident cortical opacities. The incident group was, on average, older (P=.001) with more female participants (P=.02). The group developing new cortical opacities had a higher proportion of persons of lower SES with a positive history of DM and elevated mean GHb levels. In contrast, the group not developing cortical opacities reported more regular aspirin use (2.6% vs 0.7%). After age-gender adjustment, borderline significant differences between the groups were found for an IOP of more than 21 mm Hg and for IOP-lowering treatment. The association was not significant, however, in the model that included other significant variables from Table 1.

Table 2 provides data on factors associated with risk of incident cortical lens opacities, based on logistic regression results. Compared with those aged 40 through

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products was infrequent in this population. Regular use of aspirin products prior to evaluation was associated with an 80% reduction in incident cortical opacities (RR=0.2), although the use of such products was infrequent in this population.

**Table 3** presents the baseline characteristics of the groups with and without incident PSC lens opacities. While the distribution of variables examined varied between the groups, a greater proportion of the group with incident PSC lens opacities reported a positive history of DM, which was consistent with the higher mean GHb level documented in this group.

As indicated in **Table 4**, the risk of new PSC lens opacities also increased with higher age at baseline, with RR increasing from 1.9 at age 50 through 59 years to 12.1 at age 70 years and older. Unlike cortical lens opacities, there was no relationship between incident PSC lens opacities and gender; however, a self-reported history of DM was associated with increased risk of new PSC lens opacities (RR = 2.9).

In addition to a DM history, we also evaluated the relationship between GHb values and the development of lens opacities. **Table 5** demonstrates that higher levels of GHb significantly increased the risks of the 2 lens opacity types: each percentage increase in GHb level at baseline was associated with a 16% and 23% increased risk of incident cortical and PSC lens opacity, respectively. In analyses based on GHb categorized into 4 groups, incidence and risk of both opacity types progressively increased above a GHb level of greater than 8%. Persons with a GHb level higher than 11.5% had a greater than 3-fold risk of developing either lens opacity type, with RR being 3.60 for cortical and 4.93 for PSC lens opacities.

**COMMENT**

This study determined baseline characteristics associated with the risk of developing cortical and PSC lens opacities. As expected, increased age was related to risk of both lens opacity types. Diabetes mellitus also increased the risk of both cortical and PSC lens opacities, as did higher values of GHb at baseline, while female gender, lower SES, and myopia were related to increased risk of cortical lens opacities. Another interesting observation was the very low risk of cortical lens opacities among regular users of aspirin, given the conflicting findings among studies evaluating associations between aspirin and cataract. A discussion of these results follows.

As widely documented, age was the principal risk factor related to the development of cortical and PSC lens opacities in the BES population. It is likely that age is representative of duration of exposure to many factors leading to oxidative damage of the lens, such as UV radiation and low levels of antioxidant nutrients.

Consistent with cross-sectional data, lower SES was related to increased risk of incident cortical lens opacities in this study. The 40% increased risk seen when comparing the low and high SES groups was identical to the measure of effect in cross-sectional comparisons in this study population. While a recent review suggests a possible independent association between a low educational level and cataract, confounding is still likely to account for this association in many populations.
As an example, a longer duration of education was related to a higher frequency of nutritional supplement use (including vitamins) in the BES population at baseline.9

Data from several cross-sectional studies including the BES indicate higher risk of cortical cataract among women.4,6,9,11,13,16,17 Thus at baseline, women in the BES had a 40% increased risk of cortical lens opacities compared with men,8 a measure of effect similar to that observed at 4-year follow-up (Table 3). Evaluation of associations between gender and incident cataract would assist our understanding of whether there are truly gender-related cataractogenic factors such as hormonal influences,37 rather than such observations being due to confounding.

In the BES prevalence phase, hypertension, DM, and central obesity often accompanied cortical lens opacities.8 While hypertension and obesity were not related to incident lens opacities, DM and a high GHb level at baseline increased the risk of cortical lens opacities 2- to 3-fold. Furthermore, each unit increase in GHb level was associated with a 16% increased risk of cortical lens opacity over 4 years. Klein et al7 similarly reported a 12% increased risk of cortical cataract per unit increase in GHb level over a 5-year period in persons with DM evaluated in the Beaver Dam Eye Study (BDES), Beaver Dam, Wis. While the higher risk in the overall black BES population might be partly explained by differences in diagnostic criteria for cortical cataract and laboratory methods for evaluation of GHb levels, the prevalence of self-reported DM in the BES was almost twice that in the BDES (17.5% vs 8.9%).38

The ability to detect risk factors for incident PSC was compromised by the few cases developing during the 4-year period. Gender was unrelated to PSC, but DM was strongly predictive, increasing risk about 3-fold. In particular, high GHb values at baseline (>11.5%) increased risk almost 5-fold (Table 5). The BDES also reported significant associations between DM and increased risk of incident PSC opacities.7

The role of DM and hyperglycemia in cataractogenesis has been clearly established,2,3 the underlying mechanisms being the direct toxic effect of sugar alcohols formed through the aldose reductase pathway on lens fibers.39 However, studies that document opacity type consistently link hyperglycemia to cortical, PSC, or mixed cortical and PSC lens opacities.7 Data available from the BDES7 and this study18 indicate that DM also increases the risk of incident nuclear cataract, consistent with associations with the level of baseline GHb also seen in this study (odds ratio = 1.13, 95% CI, 1.06-1.20). These findings can contribute to clinical and public health strategies for the management of patients with DM.

Regular use of aspirin products at baseline was infrequent in this population (n=44), being reported by 2.6% of the nonincident cases and only by 0.7% of the incident cases of cortical lens opacities. Aspirin use was, however, associated with a substantially lower risk of incident cortical cataract. There are conflicting reports about the association between aspirin use and cataract. While data from several cross-sectional studies have suggested that aspirin or aspirinlike analgesics may protect against cataract,1,2,4,11 others found no association or an increased risk of lens opacities.4,6,16,18,19 Data from prospective observational studies are also inconclusive. Aspirin use was associated with a reduced incidence of nuclear cataract after 5 years in the BDES while nonsteroidal anti-inflammatory medications were not protective as a group and showed a tendency to increased risk of incident cortical lens opacities.14 Associations between aspirin use and a tendency to increased likelihood of cataract extraction have also been reported.30,31 Data from clinical trials did not demonstrate a reduced frequency of cataract extraction in patients with DM who were treated with aspirin.32 Randomized trials conducted among British male physicians33 and the US Physicians’ Health Study,34 failed to demonstrate clear benefit from aspirin use on incident cataract or cataract extraction. Five-year follow-up of the US Physicians’ Health Study trial population suggested a possible reduced risk of cataract extraction in the aspirin intervention group compared with placebo, while subgroup analyses suggested a lower risk of treatment-related incident PSC lens opacity.35 Longer-term follow-up failed to confirm benefit from aspirin, and findings instead suggested an increased risk of cataract in the aspirin-treated group.36 Given the few persons using aspirin in the BES, the association between aspirin use and reduced likelihood of incident cataract must be interpreted with caution. Confounding may also partly explain this association as individuals taking aspirin could have higher SES and might also differ in lifestyle practices.

Table 4. Four-Year Incidence of Posterior Subcapsular Lens Opacities and Relative Risks (RRs)*

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Incidence, %</th>
<th>Multivariate Adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>0.8</td>
<td>1.0</td>
</tr>
<tr>
<td>50-59*</td>
<td>1.7</td>
<td>1.9 (0.8-4.5)</td>
</tr>
<tr>
<td>60-69*</td>
<td>3.8</td>
<td>4.1 (1.8-9.1)</td>
</tr>
<tr>
<td>≥70*</td>
<td>10.3</td>
<td>12.3 (5.7-26.2)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Female</td>
<td>3.3</td>
<td>1.0 (0.6-1.5)</td>
</tr>
<tr>
<td>History of DM*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7.9</td>
<td>2.9 (1.9-4.5)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; DM, diabetes mellitus.

*P<.05 in logistic regression model.
Diabetes mellitus is a well-established risk factor for cataract, most often associated with cortical and PSC cataract. This article provides evidence that DM and hyperglycemia are major risk factors for the development of cortical and PSC lens opacities in an African-descent population with a markedly high rate of DM. This result has particular public health significance, as cortical cataract is the principal opacity type in this population. One inference of the current findings is that improved prevention and treatment of DM might reduce the burden of cataract.

This study also provides evidence of a reduction in incident cortical lens opacities resulting from regular aspirin use, an observation that must be interpreted with caution. The result merits further investigation because of its potential for prevention.

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CONCLUSIONS

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