Mixed Lens Opacities and Subsequent Mortality

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Background: Previous studies have found an association between cataract or lens opacity and increased risk of mortality. Further work on determining explanatory factors for this association is needed.

Objectives: To determine, in a population-based cohort of older persons, the 2-year risk of death associated with different types of lens opacities; whether an association of mortality and lens opacity is explained by confounding risk factors such as smoking, diabetes, age, race, and sex, which are known to be related to opacity and mortality; whether lens opacity is a marker for health status; and whether there are differences in cause-specific mortality for persons with and without lens opacity.

Main Outcome Measure: Two-year mortality rate.

Methods: The Salisbury Eye Evaluation Project consists of a random sample of 2520 residents of Salisbury, Md, aged 65 to 84 years. At baseline, lens photographs were taken to document nuclear, cortical, posterior subcapsular cataract, and mixed opacities. Data on education, smoking, alcohol use, hypertension, diabetes and other comorbid conditions, handgrip strength, and body mass index were also collected. Two-year follow-up was conducted for mortality and cause of death.

Results: Nuclear opacity, particularly severe nuclear opacity, and mixed opacities with nuclear were significant predictors of mortality independent of body mass index, comorbid conditions, smoking, age, race, and sex (mixed nuclear: odds ratio, 2.23; 95% confidence interval, 1.26-3.95).

Conclusion: Lens opacity status is an independent predictor of 2-year mortality, an association that could not be explained by potential confounders.

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The Salisbury Eye Evaluation (SEE) Project is a population-based, longitudinal study of the impact of visual impairment and age-related eye diseases on functional status in older, community-dwelling adults. To achieve the aims of this project, a random sample of residents of Salisbury, Md, aged 65 to 84 years was recruited for a home interview and an examination at the SEE clinic. The sample was selected from the Health Care Financing Administration Medicare database. The sample included 100% of the African American population and 56% and 62% of the white population aged 65 to 74 years and 75 to 84 years, respectively. The older age group was oversampled in anticipation of a higher refusal rate among older persons. We included all African Americans aged 65 to 74 years to have sufficient numbers for race-specific analyses. Eligibility criteria excluded residents who were institutionalized or completely homebound and those who scored less than 18 on the Mini-Mental State Examination.

Written informed consent was obtained at the home interview in accordance with the tenets of the Declaration of Helsinki. Details about the population and recruitment are described elsewhere. In summary, of the original sample, 73% participated in the home interview only and 65% participated in the interview and the clinical examination. Permission was also sought to administer a 12-item screening questionnaire to refusers and participants to investigate the comparability between the 2 groups. Of 1301 people who refused to participate in the clinic examination or the home questionnaire, 65% agreed to answer the questions on the screening questionnaire. There were no differences in age, race, or sex between refusers who did and did not answer the screening questionnaire. There was no difference in participation rates by race; participation rates declined with age from 68% in 65- to 69-year-olds to 55% in 80- to 84-year-olds. Those who reported needing help with everyday tasks were more likely to refuse.

There was no difference in the sex- and age-adjusted proportion rating their vision as 6 or better on a scale of 1 to 10, with 10 being excellent. Eighty-three percent of participants rated their vision as 6 or better compared with 84% of refusers. These data provide some assurances that the sample of 2520 participants was not biased on self-reported vision status.

LENS OPACITY ASSESSMENT

At the examination center, each participant’s eyes were dilated and lens photographs were taken using standardized protocols previously described. Photographs were graded for the type and severity of opacity using the Wilmer grading scheme. Nuclear opacification was graded against 4 standard photographs of increasing opacification. An integer grade was assigned between 1 and 4, with decimalized interpolation between the standards. Cortical opacification was graded by estimating the amount of pupillary area obscured, in 1/16th sectors, with grades from 0/16 to 1/16/16 areas affected. Posterior subcapsular opacities were graded as present or absent.

All grading was done for each eye independently by 2 trained graders masked to the grade given by the other and the grade of the fellow eye. Differences greater than 0.3 for nuclear, 1/16 for cortical, and present or absent in posterior subcapsular cataract were openly adjudicated with a third grader (S.K.W.). Interobserver variation was monitored during the study by the periodic circulation of 33 photographs, and agreement was high.

Nuclear opacity was defined as present at baseline if at least 1 eye had a grade of 2.0 or higher. Severe nuclear opacity was defined as present if at least 1 eye had a grade of 3.0 or higher. Cortical opacity was defined as present if at least 1 eye had a grade of greater than 3/16. Photographs were not taken or not gradable in either eye of 165 persons (7%). Bilateral cataract surgery had been performed in 245 participants, which precluded lens photographs at baseline.

The second set of models was designed to investigate the hypothesis that lens opacity status is a marker for general health status. To measure health status, several variables were investigated, including grip strength, BMI, cognitive score, level of depression, and number of comorbid conditions. Of these variables, only grip strength, BMI, and number of comorbid conditions were significantly related to mortality after adjustment for age, race, and sex (data not shown). Moreover, only BMI and number of comorbid conditions independently contributed to risk of death; handgrip strength was not significantly related to mortality once BMI was entered into the model.

Nuclear opacity, severe nuclear opacity, and mixed opacities remained significant predictors of mortality, independent of BMI, but the risk with mixed and nuclear opacities was slightly diminished in the presence of comorbid conditions. The opacity status groups have significant overlap. Of severe nuclear opacities, 32% are mixed. Of mixed opacities, 61% have some nuclear combined with other opacity types. Thus, the association of mortality with
ASSESSMENT OF CONFOUNDERS OF CATARACT AND MORTALITY

Data on age, race, sex, educational level, smoking, and alcohol use were available from the interviewer-administered home questionnaire. Data on diabetes were based on self-report and validated by use of insulin or oral hypoglycemic agents or by hospital or physician records. For those who did not report diabetes, we included participants with a hemoglobin A1c value greater than 7% as having diabetes.\(^18\)

ASSESSMENT OF HEALTH STATUS

Participants were weighed, without shoes, and their height was measured by trained observers, as described previously.\(^19\) These data were used to calculate body mass index (BMI) as weight in kilograms divided by the square of height in meters. Low BMI, independent of diseases, was one index of frailty.

Grip strength was assessed on the dominant hand with a dynamometer following a standard protocol. Two tests were taken, with a 30-second rest between trials, and the results (in kilograms) were averaged. Values on the test ranged from 3.5 to 60.0 kg. Low values for age and sex were also considered a measure of frailty.

The General Health Questionnaire was administered in the clinic, and the subscale on depressive symptoms was used as a measure of depression.\(^20,21\) Cognitive status was assessed at the home visit using the Mini-Mental State Examination. To be eligible for the study, persons had to score above 17; thus, possible scores for this study range from 18 to 30.

Hypertension was based on self-report plus evidence of a thiazidehypertensive medication. In addition, blood pressure was measured in a sitting position, 3 times, according to a standard protocol.\(^22\) Persons who did not report hypertension but had an average diastolic blood pressure of 90 mm Hg or greater or systolic blood pressure of 160 mm Hg or greater were classified as possibly having hypertension for our study. Other conditions were based on self-report, such as opacity could be driven by an association with nuclear opacity, or by mixed opacity (regardless of the mix), or by both. To examine this question, opacity groups were restructured as nuclear alone, mixed opacity with nuclear, and mixed opacity without nuclear. After adjustment for age, race, sex, diabetes, smoking, BMI, and number of comorbid conditions (excluding diabetes), only persons with mixed opacities that included nuclear had significantly higher odds of 2-year mortality (Table 5). This marker was independent of confounding variables and independent of our markers of frailty and diabetes.

Causes of death were broadly grouped into cardiovascular, cancer, and miscellaneous for cause-specific analyses. Most deaths were from cardiovascular disease (41%), with cancer causing 33% of deaths. In models predicting cause-specific mortality, mixed nuclear opacities were significantly associated with cancer deaths (Table 6). Cardiovascular deaths and other causes were also associated with mixed nuclear opacities with similar odds ratios but were not statistically significant.

DEATH AND CAUSES OF DEATH

All 2520 participants enrolled at baseline were followed up for 2 years with monthly telephone calls. When mortality was reported, death was confirmed and the cause of death was abstracted from hospital records; if the death occurred out of state or outside the hospital, the National Death Index provided a copy of the death certificate, from which the cause was abstracted. Cause of death could not be determined for 5 participants.

STATISTICAL ANALYSES

The major outcome variable was death within 2 years of the baseline visit. Age-, sex-, and race-adjusted logistic models were created, with opacity status or bilateral cataract surgery at baseline as an independent variable. Because age is closely, and nonlinearly related to mortality, models were fit with age as a squared and cubic term. Results were unchanged. The additional confounding variables of smoking and diabetes were then added to the model, and statistical significance determined with \(P = .05\). Cataract surgery during follow-up was not modeled as a predictor, only baseline status.

The next step was to construct a second model predicting mortality with health status indicators. To avoid collinearity of this model, single variables were entered into the mortality model with age, race, and sex. If a health status indicator by itself was not related to mortality, it was not considered further. If there was evidence of a relationship between the health status indicators and death, opacity status was subsequently entered. The diminution of the odds ratio for opacity, as observed in the model without health status indicators, was taken as evidence that the opacity was a marker for the health status indicator.

Results of this study confirm a link between lens opacities and subsequent risk of mortality. Other population-based studies\(^4,6-8\) have associated nuclear opacity with an increased death rate. However, mixed opacities were not specifically addressed in these studies, and it is likely that a substantial proportion of nuclear, particularly severe nuclear, opacity was mixed with other types. Other researchers adjusted for diabetes as we did, but we also adjusted for other confounding factors simultaneously, and the risk remained.

We expected that lens opacity might be a marker for frailty or health status or systemic diseases. However, after adjustment for comorbid conditions, BMI, and handgrip strength, the association of mixed opacity and subsequent 2-year mortality remained. Conversely, if lens opacity was a better marker of frailty or health status, we would have expected some diminution in the odds ratio with the other markers in the models, but little was observed. Thus, mixed lens opacity remains an independent marker for mortality in our data. Klein et al\(^7\) showed

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an association with increasing severe nuclear opacity and decreased survival. The odds ratio remained of the same magnitude but became nonsignificant once adjusted for a variety of other systemic factors. Factors that dropped the level of significance were not further described but included some that we did not evaluate, such as proteinuria, pulse, and active lifestyle. No evaluation of the association of mixed opacities with mortality was carried out in that study.

Cataract surgery before baseline was not associated with subsequent 2-year mortality in our study, although other studies have reported an association with cataract surgery. In another population-based study, cataract surgery was not significantly associated with decreased survival. In most of the surgery studies, a cohort of incident cases was defined at the time of cataract surgery and followed up prospectively for mortality. In our population-based study and that of Klein et al, we
follow-up. Of the original 2520 persons enrolled in the study, 94% of those still alive 2 years later participated in the second round of data collection. The other 6% were known to be alive and had refused to participate or had moved out of state. Bias in the determination of lens opacity status is also unlikely because gradings were done in a masked fashion before data on mortality were gathered. Age-, race-, and sex-adjusted mortality among those with few or no lens photographic data was no different from that among those with photographs.

It is tempting to speculate that cellular or subcellular processes occurring in the lens might be a window into the processes leading to accelerated mortality. Certainly, mixed opacity status is as good a marker as other predictors of mortality in our study. Further research to elucidate this association is warranted.

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