

Cortical, but Not Posterior Subcapsular, Cataract Shows Significant Familial Aggregation in an Older Population after Adjustment for Possible Shared Environmental Factors

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Purpose: To quantify the risk for age-related cortical cataract and posterior subcapsular cataract (PSC) associated with having an affected sibling after adjusting for known environmental and personal risk factors.

Design: Sibling cohort study.

Participants: Participants in the ongoing Salisbury Eye Evaluation (SEE) study ($n = 321$; mean age, 78.1 ± 4.2 years) and their locally resident siblings ($n = 453$; mean age, 72.6 ± 7.4 years) were recruited at the time of Rounds 3 and 4 of the SEE study.

Intervention/Testing Methods: Retroillumination photographs of the lens were graded for the presence of cortical cataract and PSC with the Wilmer grading system. The residual correlation between siblings' cataract grades was estimated after adjustment for a number of factors (age; gender; race; lifetime exposure to ultraviolet-B light; cigarette, alcohol, estrogen, and steroid use; serum antioxidants; history of diabetes; blood pressure; and body mass index) suspected to be associated with the presence of cataract.

Results: The average sibship size was 2.7 per family. Multivariate analysis revealed the magnitude of heritability (h^2) for cortical cataract to be 24% (95% CI, 6%–42%), whereas that for PSC was not statistically significant (h^2 4%; 95% CI, 0%–11%) after adjustment for the covariates. The model revealed that increasing age, female gender, a history of diabetes, and black race increased the odds of cortical cataract, whereas higher levels of provitamin A were protective. A history of diabetes and steroid use increased the odds for PSC.

Conclusions: This study is consistent with a significant genetic effect for age-related cortical cataract but not PSC. *Ophthalmology* 2005;112:73–77 © 2005 by the American Academy of Ophthalmology.

Posterior subcapsular cataract (PSC) has been identified as the most significant risk factor for incident cataract surgery¹ and the most common form of cataract in clinical surgical series.² Cortical cataract is the most common form of lens opacity in population studies of black persons,^{3,4} a group for whom cataract represents a particularly significant visual burden.^{5,6} Despite their importance, comparatively little information has been available regarding the possible role of genetics in these 2 forms of lens opacity. Among genetic

studies of age-related cataract, only the Framingham Offspring Study⁷ has reported on the aggregation of PSC in families (siblings of affected persons had nearly triple the odds of having PSC themselves). Population studies have similarly reported significant familial aggregation of cortical cataract,⁸ and twin studies indicate that the heritability (h^2) of cortical lens opacity may be on the order of 50%.⁹

We report herein on the h^2 and familial aggregation of cortical cataract and PSC in an older population of white and black persons on Maryland's Eastern Shore, derived in part from participants in the Salisbury Eye Evaluation (SEE) project. Familial aggregation of environmentally influenced conditions such as cataract can be due either to shared genes or shared environment, and thus, our models have all been adjusted for various personal and environmental cataract risk factors, including use of tobacco, alcohol, and medications including estrogens and steroids; lifetime exposure to ultraviolet-B light; serum antioxidant levels; and the presence of medical conditions such as diabetes. Finally, to avoid loss of power and possible introduction of bias because of bilateral pseudophakia (prevalent in this

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older population), we describe a method of assigning lens status with regard to cataract subtype on the basis of previous study records and clinical records from the operating ophthalmologist.

Materials and Methods

The study methods have been described in detail elsewhere^{10,11} and are reviewed here in outline form.

After giving informed consent, all participants in Rounds 3 and 4 of the SEE study and their local (<100 miles from Baltimore or Salisbury) siblings underwent questionnaires detailing their use of tobacco, alcohol, and prescription medications, including steroids and exogenous estrogens; lifetime ultraviolet-B exposure (methods detailed elsewhere¹²; and medical and ophthalmologic history, including the presence of diabetes. In addition, height was measured in stocking feet by use of a height board, and weight was obtained in kilograms on a digital scale. Seated blood pressure was measured (average of 2 readings) in the right arm with a mercury sphygmomanometer. Three 7-ml ethylene diamine tetraacetic acid tubes of blood were drawn by sterile venipuncture, 2 for later DNA analysis, and 1 that was centrifuged within 8 hours for 20 minutes at 2200 RPM, with plasma being drawn off, labeled, and frozen at -20° C. Plasma samples were shipped in batches of 100 on dry ice to the laboratory for measurement of tocopherols and retinol levels.

α -Carotene, β -carotene, β -cryptoxanthin, lycopene, lutein, zeaxanthin, retinol, and α -tocopherol were measured in 100 μ l of plasma by high-performance liquid chromatography with a modified method from the Nutrition Laboratory, Inorganic Toxicology and Nutrition Branch, Division of Laboratory Sciences, National Center of Environmental Health, Centers for Disease Control and Prevention.¹³ The internal standards used were tocol (Hoffmann-La Roche, Nutley, NJ) at 300 and 325 nm and all-*trans*-ethyl- β -apo-8'-carotenoate (purified sample courtesy of Dr. Fred Khachik, United States Drug Administration) at 450 nm. Quality control was assessed by repeated analysis of pooled human plasma controls run at the beginning and end of each analysis. Standard curves were run periodically with standard reference material 986C (National Institute of Standards and Technology, Gaithersburg, MD). The mobile phase consisted of 1 pump in acetonitrile with 0.1% triethylamine and a second pump in ethanol with 0.1% triethylene. A gradient method was applied by varying the solvent concentrations from 85% acetonitrile/triethylamine to 50% acetonitrile/triethylamine and again to 85% acetonitrile/triethylamine.

After an examination of the anterior segment by an optometrist, digital retroillumination photographs were made of both eyes while the pupil was dilated (Marcher CASE-R Digital Retroillumination Camera, Marcher Enterprises, Ltd., Hereford, UK). The protocol for capturing retroillumination images has been described elsewhere.¹⁴ For each lens, both an anterior and a posterior retroillumination image were made. These digital files were stored on a local hard drive, copied at the end of the day onto compact disc, and then transferred by both compact disc and file transfer protocol (ftp) to the Wilmer Eye Institute for grading by use of the Wilmer Cataract Grading System.¹⁵ Under the Wilmer System, cortical cataract is graded in units of 1/16 according to the proportion of the retroillumination image of the lens affected by opacity. Posterior subcapsular cataract is graded as present, absent, or questionable. All images were graded by 2 of 5 experienced observers standardized against one another. Posterior subcapsular cataract grades that differed from one another, or cortical grades differing by more than 2/16, were adjudicated by a senior grader (NGC, SKW). All grading was performed under subdued lighting

on 1 of 2 cathode ray tube computer screens that had initially been standardized against one another (Do It Interactive, Inc., Baltimore, MD).

For subjects in whom review of the retroillumination images revealed evidence of bilateral pseudophakia, the presence or absence of both cortical cataract and PSC was determined where possible for each eye on the basis of photographs from previous rounds of SEE (SEE participants only) and/or clinical records obtained from the operating ophthalmologist (for both SEE participants and their siblings). A subject was defined as affected by PSC or cortical cataract if either lens was described in clinical records as having a grade of 2+ or greater, as "dense" or equivalent terminology, or if a photograph from a previous round of SEE had been graded as $\geq 4/16$ (cortical cataract) or "present" (PSC). Cortical cataract and PSC were graded and analyzed independently from nuclear cataract, which was present in many of these subjects, and which is treated in a separate manuscript.¹⁰ For eyes of subjects with bilateral pseudophakia in which no cataract status could be established on the basis of previous study photographs or clinic records, the eye was omitted from analysis. Subjects who were bilaterally pseudophakic and for whom cataract status could be established in neither eye were omitted from analysis.

Senior graders (SKW, NGC) reviewed bilateral photographs for 20 subjects in whom both digital and film images were captured before beginning the study. Interobserver and intraobserver agreement in comparing digital and film images of the same eye was similar to that observed in previous testing with film images alone.

This protocol was approved in its entirety by the Institutional Review Board for the Johns Hopkins University School of Medicine.

Statistical Methods

Cortical cataract was treated in both quantitative (Wilmer grade 0/16) and binary fashion (with an individual defined as "affected" if the photo grade was $\geq 4/16$ or the assigned status on the basis of clinician records was "present" in either eye). Eyes having undergone surgery in which clinician records indicated that cortical cataract was present were assigned a grade of 4/16 in quantitative analyses. Posterior subcapsular cataract was treated only in binary fashion, with grades of "absent" and "questionable" being collapsed into a single category for comparison with "present." The degree of family association for cortical cataract and PSC were assessed by the odds ratio (OR) comparing the odds of being affected by cataract for those with an affected sibling with those without an affected sibling, after adjustment for covariates. In the quantitative analysis of cortical cataract, familial association was measured by the (h^2), which is twice the residual correlation between siblings after adjustment for the various cataract risk factors. Let y_{ij} denote the maximal cortical cataract grade for sibling j in family i , let $z_{ij} = 1$ if $y_{ij} \geq 4$ and $= 0$ otherwise, and let x_{ij} denote a vector of covariates (including an intercept). In the analysis of the quantitative measure, we assumed a linear model, $E(y_{ij} \cdot x_{ij}) = \beta' \cdot x_{ij}$, with constant residual correlation between siblings $\text{corr}(y_{ij}, y_{ik} \cdot x_{ij}, x_{ik}) = \rho$. Note that the h^2 is twice the residual sibling correlation: $h^2 = 2\rho$. The parameters β and ρ were estimated by generalized estimating equations,^{15,16} with the package GEEPACK version 0.2-4 with the R statistical system version 1.7.1 (R Foundation for Statistical Computing, Vienna, Austria).¹⁷

In the analysis of the binary measures, we followed the approach of Liang and Beaty¹⁸ and assumed a logistic model, $\text{logit}\{\text{Pr}(z_{ij} = 1 \cdot x_{ij})\} = \theta' \cdot x_{ij}$, with constant log OR $\ln \text{OR}\{z_{ij}, z_{ik} \cdot x_{ij}, x_{ik}\} = \gamma$. The parameters θ and γ were again estimated by generalized estimating equations, as described by Liang et al.¹⁹

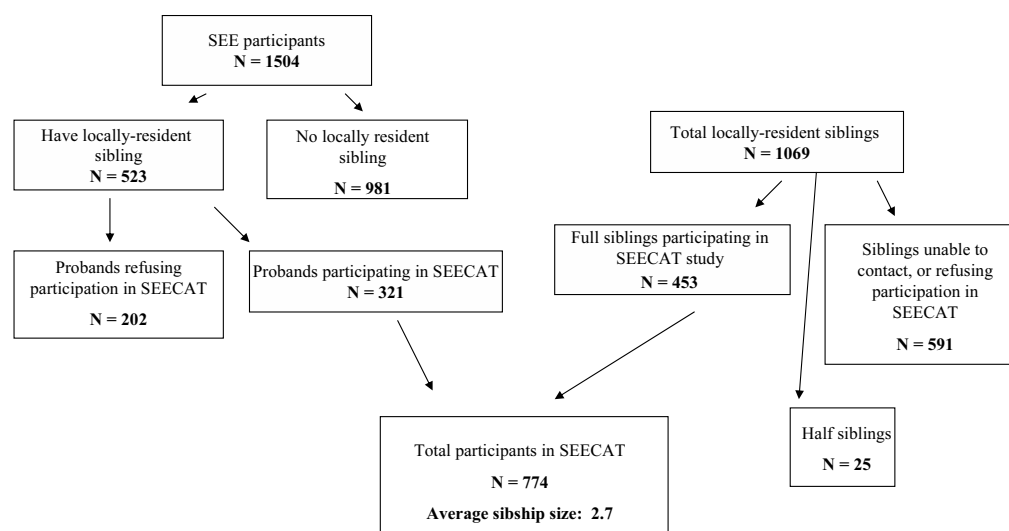


Figure 1. Participants in the Salisbury Eye Evaluation (SEE) Study of Cataract Genetics (SEECAT).

Calculations were performed in R version 1.7.1, using the package GEESIBSOR, available from the authors.

With both analyses, standard errors were obtained by means of the robust sandwich estimator.¹⁴ Covariates were chosen by stepwise selection; a covariate was retained in the model if the corresponding P value was <0.1 . Only full biologic siblings were used in all analyses. Analyses for PSC and cortical cataract were repeated with and without the inclusion of subjects with grades estimated from old photographs and clinical records.

Results

A total of 321 probands and their 453 siblings (total $n = 774$) participated in the study, forming sibships of 1 to 8 individuals, with an average size of 2.7 (Fig 1). Probands were significantly older than their siblings. Nearly 30% of subjects were black.

Significant differences in body mass index (siblings heavier), bilateral pseudophakia, hypertension, and diabetes (all more common among probands) became nonsignificant after adjustment for age (Table 1). Cataract grades could be assigned for 62% of bilaterally pseudophakic probands and 66% of siblings, respectively (Table 1).

In the multivariate model, odds of cortical cataract were significantly increased with increasing age ($P < 0.0001$), female gender ($P = 0.009$), history of diabetes ($P = 0.01$), and black race ($P < 0.0001$). Higher levels of provitamin A were protective ($P = 0.01$) (Table 2). History of diabetes ($P = 0.003$) and topical or oral steroid use ($P = 0.036$) increased the odds of PSC (Table 2). Having a sibling affected by cataract failed significantly to increase the odds of cortical cataract or PSC opacity in the multivariate model (where cataract was modeled as a binary variable, present or absent).

The adjusted h^2 of cortical cataract in this population was 24%

Table 1. Characteristics of Participants in the Salisbury Eye Evaluation Study (Probands) and Their Siblings, with Regard to Demographics, Cataract Risk Factors, Nuclear Cataract Status, and Pseudophakia

Characteristics	Probands	Siblings	Unadjusted Difference	Age-Adjusted Difference
Age (yrs) (mean \pm SD)	78.1 \pm 4.2	72.6 \pm 7.4	<0.001	—
Gender (% female)	190/321 (59.2%)	266/453 (58.7%)	NS	NS
Race (% black)	89/319 (27.9%)	122/451 (27.1%)	NS	NS
Body mass index (mean \pm SD)	28.4 \pm 5.5	29.4 \pm 6.1	0.01	NS
Smoking status (never/former/current)	45%/43%/12%	43%/46%/11%	NS	NS
Alcohol status (never/former/current)	30%/48%/22%	29%/46%/25%	NS	NS
Systolic or diastolic hypertension (%)	211/318 (66%)	249/453 (55%)	0.002	NS
Diabetes (%)	80/319 (25%)	87/453 (19%)	0.052	NS
Current or recent steroid use (%)	26/289 (9%)	47/451 (10%)	NS	NS
Bilateral pseudophakia (%)	82/321 (25.5%)	76/453 (16.8%)	0.004	NS
Able to assign cataract grade (% among pseudophakes)	51/82 (62.2%)	50/76 (65.8%)	NS	NS
Cortical cataract in either eye* (%)	45/282 (16%)	54/420 (13%)	NS	NS
Posterior subcapsular cataract in either eye [†] (%)	42/279 (15%)	64/419 (15%)	NS	NS

NS = not significant; SD = standard deviation.

*Includes persons with cortical cataract grade ≥ 4 of 16 on SEE Round 3 photographs and also persons determined to be “affected” by cortical cataract on the basis of clinical records and/or old photographs.

[†]Includes persons with posterior subcapsular cataract (PSC) grade “present” on SEE Round 3 photographs and also persons determined to be “affected” by PSC on the basis of clinical records and/or old photographs.

Table 2. Effect of Several Independent Variables on Cortical and Posterior Subcapsular Cataract (PSC) in a Multivariate Logistic Regression Model

Independent Variable	Beta Estimate	Standard Error	P Value
Cortical cataract			
Age (per 10 yrs)	0.595	0.101	<0.0001
Female gender	0.378	0.142	0.009
History of diabetes	0.552	0.214	0.010
White race	-0.977	0.231	<0.0001
Provitamin A	-0.211	0.082	0.010
Residual between-sibling correlation	0.079	0.045	NS
PSC			
Age (per 10 yrs)	0.351	0.195	0.071
History of diabetes	0.840	0.280	0.003
Steroid use	0.912	0.435	0.036
Residual between-sibling correlation	-0.002	-0.143	NS

NS = not significant.

(95% confidence interval [CI], 6%–42%), suggesting that roughly one quarter of the variance in cortical cataract grade can be explained by genetic causes. Heritability of PSC was not statistically significant (h^2 , 4%; 95% CI, 0%–11%). In this analysis, cortical cataract was modeled as a quantitative trait (Wilmer cataract grade 0–16), whereas PSC was treated as binary (present or absent). Results of both h^2 and OR calculations did not differ significantly for either cortical cataract or PSC when subjects with estimated cataract grades on the basis of old photographs or clinical charts were excluded from the analysis.

Discussion

Our results suggest that there is a significant genetic role in cortical cataract, but not PSC. This finding may have implications for efforts to devise prevention strategies for cortical cataract, the most common form of lens opacity among black populations, suggesting that genetic studies may be productive. Our binary analysis of cortical cataract (sibling recurrence OR) failed to detect significant familial aggregation, whereas the quantitative analysis (h^2) did suggest a genetic effect. This may reflect the fact that the binary analysis sacrificed power by collapsing the 16-step Wilmer Cataract Grading System for cortical cataract into “present” or “absent.”

Very little context exists within which to interpret our negative results for a genetic role in PSC. Neither Beaver Dam^{8,20} nor Hammond's Twin Studies^{9,21} have reported specifically on the h^2 of PSC. Only the Framingham Offspring Study⁷ has reported a familial aggregation of PSC. The absence of other positive reports could either be due to a true lack of a genetic contribution in the etiology of PSC or simply the fact that PSC is the least prevalent form of cataract in most studies,²² resulting in lower power to detect such a contribution. It should be noted that in this study, the prevalence of PSC was in the range of 15%. Thus, it is unlikely that the low prevalence of PSC alone would explain the failure to detect a significant genetic contribution in this study. The higher prevalence of PSC reported in this

study is due in part to our having determined grades for a high proportion of patients with bilateral pseudophakia, either on the basis of previous photographs from the SEE study or clinical records before surgery.

The observed h^2 of 24% (95% CI, 3%–35%) for cortical cataract in this report is considerably smaller than the figures of 53% to 58% reported by Heiba et al⁸ and Hammond et al.⁹ This might reflect the fact that this study includes a somewhat older population; our subjects had a mean age in the late 70s as opposed to 62 years of age in Hammond's study,⁹ for example. It is plausible that the role of environmental effects such as ultraviolet light might be increased and genetic effects correspondingly reduced in older subjects with 15 years or more of additional exposure. It is unknown what effect the fact that nearly one quarter of our population was black may have had on our results; previous reports on cataract h^2 have dealt largely with white populations, and the number of blacks in our study was too small to permit subgroup analysis. Heritability of PSC and cortical cataract among white persons in our study was not substantially different from the figures for the entire population.

The risk factors showing significant association with PSC and/or cortical cataract in our multivariate model, older age, female gender, black race (for cortical cataract), diabetes, and steroid use, have all been previously reported. The apparent protective effect of provitamin A against cortical cataract is also consistent with mixed reports of protection provided by dietary antioxidants against lens opacity.²³ We failed to find an association between lifetime ultraviolet B light exposure and cortical cataract or PSC opacity, despite the fact that such an association has been well documented in many populations.²¹ It is possible that this may be due, in part, to the relatively modest power to detect such an association in this comparatively small sample. In this model, the binary affection status of the sibling was not significantly predictive of either cortical cataract or PSC opacity. It would seem that, at least for cortical cataract, the additional phenotypic information provided by the cataract grade was critical in revealing significant h^2 of the trait.

Our conclusions with regard to the h^2 of cortical cataract and PSC must be understood in view of the limitations of this study. Possible disadvantages of the older population examined here have been reviewed previously. Some advantages exist as well: the possibility of misclassification as “unaffected” of younger individuals who have not yet manifested the cataract phenotype is reduced. The power of this relatively small sample may also be improved by the increasing prevalence of cataract among older persons, although this increased prevalence and power may be attenuated, to some extent, by elevated mortality among persons with lens opacity.

The use of old photographs and clinical grades by the operating ophthalmologist to estimate grades for bilaterally pseudophakic individuals is also a source of potential inaccuracy. This is the case particularly for subjects in whom only the clinical grade, which did not rely on any formal grading system, could be used. For those persons with old SEE study photographs, available for 60% of subjects with bilateral pseudophakia, the age and environmental/personal

risk data used in all models was that from the time of the previous photograph, thus reducing the impact of the substitution. The alternative would have been a loss of power and even the possible introduction of bias, because the most affected 15% to 25% of the population was systematically censored.

The proportion of eligible probands and siblings for whom blood samples and photographs could be obtained was modest and was less than 50% among siblings. Thus, the possibility of bias is introduced, whereby, for example, subjects who had, or whose siblings had, cataract might be more likely to take part in the study. However, for such participation bias to lead to biased h^2 estimates, we must presuppose that sibling pairs who were concordant in their cataract status (whether affected or unaffected) were more likely to take part than those who were discordant. Although our study design does not allow for a direct answer to this question, such behavior does not seem intuitively likely to have occurred. As has been reported elsewhere,²⁴ probands who participated in the study did not differ significantly from nonparticipants taking part in SEE, with respect to age, gender, or race.

Available evidence from this and other studies suggests that the major forms of age-related cataract are likely to be under some degree of genetic control. The precise mechanism of this control remains, however, to be explained. Although mutations in certain proteins have been reported to be associated with age-related cataract, particularly in Japanese populations,^{25,26} these reports have not generally been confirmed in studies elsewhere.^{27,28} The next challenge for the field will be to identify the specific genetic loci, and ultimately the proteins, involved in determining which individuals will be affected by cataract and at what age.

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