ORIGINAL CONTRIBUTIONS

Risk of Incident Age-related Eye Diseases in People with an Affected Sibling

The Beaver Dam Eye Study

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The purpose of this investigation was to determine whether age-related cataract and maculopathy in older siblings predicts development of the same in younger siblings. A population-based study of age-related eye diseases was conducted in 1988–1990 in Beaver Dam, Wisconsin, and a follow-up examination was performed 5 years later. Diagnoses of age-related eye diseases were assigned on the basis of gradings of study photographs. There were 1,088 people from 488 sibships with at least two siblings who could contribute information for these analyses. The authors computed odds ratios and 95% confidence intervals for developing the specific lesion and identifying it 5 years later if an older sibling had it at baseline. The odds ratios were 1.65 (95% confidence interval (CI): 0.91, 2.99) for nuclear cataract, 1.62 (95% CI: 0.92, 2.85) for cortical cataract, 1.95 (95% CI: 0.48, 7.95) for posterior subcapsular cataract, 1.82 (95% CI: 0.91, 3.66) for soft drusen, 8.18 (95% CI: 3.34, 20.08) for retinal pigment epithelium depigmentation, 3.59 (95% CI: 1.71, 7.57) for increased retinal pigment, and 10.32 (95% CI: 0.83, 128.58) for exudative age-related maculopathy. These findings suggest that strong family determinants of lesions of age-related maculopathy are likely, less so for age-related cataract, which confer risk of the same lesion in a younger sibling. *Am J Epidemiol* 2001;154:207–11.

age of onset; cataract; family characteristics; follow-up studies; macular degeneration

Cases of age-related cataracts and maculopathy (or macular degeneration) have been found to cluster in families (1–9). While the relative contributions of environmental and genetic factors are unknown and are likely to vary for these diseases, there are data consistent with the likelihood of genetic effects for age-related cataracts and maculopathy. For example, segregation analyses of data from the Beaver Dam Eye Study are consistent with Mendelian inheritance of nuclear (1) and cortical cataracts (2) and of age-related maculopathy (ARM) (7). Data from the Framingham Eye Study and the Framingham Offspring Eye Study suggest the possibility of familial effects on posterior subcapsular cataract (8). Twin studies are particularly persuasive regarding the importance of genetic factors in these diseases. Farber et al. reported increased concordance of macular drusen in monozygotic compared with dizygotic twins (10). Similar results were found by Klein et al. (4). In addition, Klein et al. reported on nine pairs of monozygotic twins who

had more extensive lesions of age-related macular degeneration and described remarkable similarity within the pairs (4). These authors were unable to systematically compare these findings with those for dizygotic twins but reported anecdotally that they found less similarity in the lesions of macular degeneration in the five such pairs they examined.

In a study of White female twins, Hammond et al. used nuclear density as a measure of nuclear sclerosis and found that genetic effects were the most important determinants of nuclear cataract, even more important than age; genetic factors were estimated to account for 48 percent, age for 38 percent, and environmental factors for the remaining 14 percent of this disease (9). Estimates of heritability of cortical cataract from the same twin cohort suggest that genetic factors accounted for 55 percent, age for 30 percent, and environmental exposures for 15 percent of the variance of these lesions (11). The relative rarity of posterior subcapsular cataract may explain the relative dearth of twin data concerning these cataracts. Thus, our expectation, based on these past studies, was that the genetic propensity of these age-related ocular conditions would be manifest in all types of sibling groups, not only twin pairs, and that the experience of older siblings might provide information for predicting such lesions in younger siblings. Therefore, we evaluated the 5-year incidence of age-related cataracts and maculopathy in data from the Beaver Dam Eye Study by using generalized estimating equations to derive the odds of a younger sibling developing such a lesion given that an older sibling had the same lesion 5 years before.

MATERIALS AND METHODS

The Beaver Dam Eye Study is a population-based study of age-related ocular disorders. Details of the methods have been published previously (12). In brief, a private census of the population of Beaver Dam, Wisconsin, was performed from 1987 to 1988 to identify all persons 43–84 years of age living in Beaver Dam in 1987–1988. Of the 5,925 persons eligible, 4,926 (83.1 percent) were examined. The examined group was 99 percent Caucasian. Tenets of the Declaration of Helsinki were followed, institutional human experimentation committee approval was granted, and an informed consent statement was signed by each subject. During 1993–1995, a 5-year follow-up examination of the cohort was conducted by using the standard measurements and questionnaires used during the baseline examination. There were 4,541 persons who survived to 1993; 423 (9.3 percent) refused to participate, 259 (5.7 percent) completed a questionnaire, 191 (4.2 percent) died before the examination, and 4 (0.1 percent) could not be located. Differences between participants and nonparticipants at baseline (12) and follow-up (13) have been published previously. In brief, those who were alive but did not participate in the second visit were significantly older and had poorer visual acuity. Those who had died were significantly older, were more likely to be male, had poorer visual acuity, were more likely to have diabetes, and were more likely to have more severe nuclear sclerosis (14).

Educational achievement, smoking status, and age were asked about during the interview. Diabetes and hypertensive status were based on standardized measures, including historical and laboratory criteria (15).

The lens and the ocular fundus of each subject were photographed according to standard protocols. Photographs of the lenses were taken with two different cameras: a slit-lamp camera and a retro-illumination camera. Grading procedures for the lens photographs were based on detailed, codified decision rules, and scores for nuclear sclerosis were based on comparisons with standard photographs. The scale has five steps of severity based on opacity of the nucleus. Levels 4 and 5 were considered cases of nuclear cataract (15). Scores for cortical and posterior subcapsular cataracts were based on weighted estimates of the degree of opacity of the lens area as defined by a circular grid, divided into eight "pie-wedged" peripheral areas, and a central circular area overlaid on the photograph. Prevalent cases of cortical cataract were those that showed an opacity of 5 percent or more of the lens "surface." Posterior subcapsular opacity was defined as 5 percent or more of a grid segment.

Retinal photographs of three standard photographic fields were taken with a fundus camera. Grading procedures for the fundus photographs were based on detailed, codified protocols. Grading procedures, lesion descriptions, and detailed definitions for the presence and severity of specific lesions—including drusen retinal pigment epithelium (RPE) depigmentation, RPE detachment or serous detachment of the sensory retina, subretinal or sub-RPE hemorrhages, subretinal fibrous scars, and geographic atrophy—have been published elsewhere (15).

To evaluate change in lesions in an eye between visits, it was necessary to have data from corresponding gradable subfields at both visits. For example, the inner superior subfields for the right eye would have to be gradable for a specific lesion at both visits to contribute to the estimates of incidence, progression, regression, and disappearance of that lesion for that eye. Incidence implies the appearance of a lesion at follow-up when it was absent at baseline.

The incidence of early ARM was defined by the presence of either 1) soft, indistinct drusen or 2) any type of drusen associated with RPE depigmentation or increased retinal pigment at follow-up when none of these lesions was present at baseline. The incidence of late ARM was defined by the appearance of either exudative macular degeneration or pure geographic atrophy at follow-up when neither lesion was present at baseline. Age was defined as the age of the person when the baseline examination was conducted.

The Statistical Analysis System was used for analyzing the data, including producing proportions and means (16). Age was treated continuously, by year. All participants in both the baseline and follow-up examinations were paired with their older siblings participating in the baseline examination. An affected older sibling's status at baseline was the independent variable, and the younger sibling's outcome became the dependent variable. It was assumed that each family contributed information independently to the model. However, there were some families with multiple sibling pairs whose information was entered into the model. These pairs could not be assumed to be independent, so generalized estimating equations methodology, as described by Liang and Zeger, was used to adjust for correlations between multiple pairs within a family (17, 18).

During the baseline examination, participants were asked the name and city of residence of all of their siblings. On the basis of these responses, in some instances supplemented by information from obituaries, preliminary family relationships were established. During the follow-up examination, these family relationships were confirmed. As a final confirmation, a follow-up telephone inquiry was made to at least one member of each family for Beaver Dam Eye Study participants who had at least one sibling who was also eligible to participate (all calls were made by the same interviewer). A total of 1,997 people participating in the baseline examination were members of one of 440 family groups. A family group consisted of sibships (sibling groups with the same mother and father), children, parents, and spouse's siblings (if they existed) for all members of a sibship. We estimated that 40 percent of the population was part of a family. These relationships were not confirmed by genetic testing.

Although data were complete for cataract types and lesions of ARM for most subjects, occasionally some data were missing for one or more of the endpoints of interest. To be eligible for these analyses, two or more siblings with baseline data were required, and the youngest of these siblings must have been free of disease at baseline and have made a follow-up visit. Of the 1,997 people evaluated during the baseline examination and part of a family group, 594 had no siblings who participated in the baseline examination, and 315 were not eligible for any of the analyses (they had disease at baseline or were not evaluated at the follow-

up examination). Thus, 1,088 people in one of 287 families remained eligible for at least one of these analyses.

The actual number of people for each analysis was slightly different. For example, only 890 people were included in the nuclear cataract analyses. In families with two or more siblings, 59 people were eliminated because all of their siblings had disease at baseline, and 454 were eliminated because of a lack of follow-up data or because they could not be paired with another sibling. For the RPE depigmentation analyses, 1,024 people were eligible. Eight were excluded because all siblings had the disease at baseline, and 371 were excluded because of a lack of follow-up data or because they could not be paired with another sibling.

We defined a sibship as a group of siblings, all of whom were eligible for these analyses. Each sibship contained two to eight siblings. We found that 48 of the 287 families contained multiple sibships. One of the basic statistical assumptions required for these analyses was that although outcomes for people within a sibship could be correlated, the sibships themselves should be independent. In the 48 families with multiple sibships, this assumption could have been violated. Therefore, to achieve independence between sibships, we randomly excluded related sibships in these families. All sibships in each family were identified. From this list, one sibship was selected at random. Sibships containing any direct relative (cousins, aunts/uncles, children, nieces/nephews) of the selected sibship were excluded. Another sibship was randomly selected from the remaining sibships, and the process continued until no groups remained.

A description of the age, sex, body mass index, education, diabetes status, hypertension status, and smoking status of those included in the full population analyses and those included in any sibling analysis is given in table 1. Those participating in sibling analyses were less likely to be female, had a lower level of education, and were less likely to be current smokers than the full population.

RESULTS

Sibships were categorized by whether a given ocular lesion was present in at least one member of a sibship at the baseline examination. The odds of a younger sibling having the same lesion at the 5-year follow-up examination were calculated by adjusting for age. Age-adjusted odds of all cataract types were greater than 1 (table 2). When all sibships were included, the associations for nuclear and cortical cataracts were of borderline significance. When analyses were restricted to randomly selected independent sibships, the odds ratios changed little.

The odds ratios for lesions of ARM were all greater than 1, in some cases substantially so. When all sibships were considered, the odds of soft drusen and of exudative ARM were of borderline significance, and RPE depigmentation and increased retinal pigment were highly significant. When these analyses were restricted to randomly selected independent sibships, the odds changed little. However, the odds of pigment abnormalities and of exudative ARM were significant. Analyses for geographic atrophy, another severe

TABLE 1. Baseline characteristics of participants in sibling analysis of the risk of incident age-related eye diseases, Beaver Dam Eye Study, Wisconsin, 1988–1990

Characteristic	Full population analysis ($n = 4,926$)	Any sibling analysis ($n = 1,088$)
Age (years) (mean (SD*))	62.0 (11.2)	62.3 (9.7)
Sex (% female)	56.1	51.7
Body mass index (kg/m²) (mean (SD))	28.8 (5.4)	29.4 (5.7)
Education (%)		
High school	43.4	51.7
Some college	14.2	8.4
College or higher level	13.1	4.9
Diabetes (% yes)	9.1	8.9
Hypertension (% yes)	37.1	37.9
Current smoker (% yes)	19.7	17.6

* SD, standard deviation.

form of ARM, were not included because there were too few people with this condition.

In general, environmental exposures were expected to affect family similarity. An important environmental exposure with respect to nuclear cataract and exudative macular degeneration was current smoking. Therefore, we repeated the analyses of all sibships by confining the analyses to nonsmokers (table 3). For RPE depigmentation, exudative ARM, and cortical and posterior subcapsular cataracts, the odds ratios were increased compared with the odds when smoking status was ignored.

DISCUSSION

These data are compatible with a family effect on incident lesions of ARM, such that an older sibling who has a specific age-related ocular lesion is associated with the incidence of the same lesion 5 years later in a younger sibling. These findings are consistent with other reports of the importance of a positive family history of ARM. Of course, we could not determine the relative importance of shared environment and genetic factors as causes of this sibling similarity. However, when the potential effect of smoking was eliminated, the odds ratios for virtually the only environmental factor associated with a form of late-stage ARM, RPE depigmentation and exudative maculopathy, increased. This finding is compatible with the notion that smoking patterns increase the heterogeneity of the expression of a genetic predisposition to these lesions. We were limited in our ability to control for all possible environmental effects on these endpoints because of sample size and because of the statistical models available, but these data are compatible with the hypotheses of important genetic influences on ARM.

The findings with respect to sibling risk for cataracts were not as strong as those for ARM, perhaps because the presence of cataracts may be more influenced by personal and environmental factors than are lesions of ARM. For example, in this

TABLE 2. Odds of incident age-related ocular lesion 5 years later if present in an older sibling at baseline, Beaver Dam Eye Study, Wisconsin, 1988–1990

Outcome	Prevalent in older sibling	All sibships				Randomly selected independent sibships			
		No.	Incident in younger sibling	OR†	95% CI†	No.	Incident in younger sibling	OR	95% CI
Nuclear cataract	No	539	13.4	1		446	11.7	1	
	Yes	109	34.9	1.65*	0.91, 2.99	86	30.2	1.43	0.70, 2.92
Cortical cataract	No	544	9.6	1		441	10	1	
	Yes	100	20	1.62*	0.92, 2.85	82	19.5	1.69	0.88, 3.23
Posterior subscapular cataract	No	627	2.9	1		513	2.5	1	
	Yes	36	5.6	1.95	0.48, 7.95	31	3.2	1.20	0.16, 9.04
Soft drusen	No	653	6.3	1		525	5.5	1	
	Yes	92	13	1.82*	0.91, 3.66	65	12.3	2.07	0.83, 5.15
Retinal pigment epithelium depigmentation	No	729	1.2	1		591	1.2	1	
	Yes	59	11.9	8.18***	3.34, 20.08	51	9.8	7.26***	2.65, 19.90
Increased retinal pigment	No	647	2.8	1		522	2.9	1	
	Yes	90	11.1	3.59***	1.71, 7.57	68	11.8	4.06***	1.78, 9.29
Exudative age-related maculopathy	No	819	0.4	1		659	0.2	1	
	Yes	9	11.1	10.32*	0.83, 128.58	9	11.1	25.79**	1.29, 517.3

* $0.05 < p < 0.10$; ** $0.001 < p \leq 0.05$; *** $p \leq 0.001$.
† OR, odds ratio from generalized estimating equations model adjusted for age of each sibling; CI, confidence interval.

TABLE 3. Odds of incident age-related ocular lesion if an older sibling had the same lesion at baseline, nonsmokers, all sibships, Beaver Dam Eye Study, Wisconsin, 1988–1990

	No.	OR*	95% CI*
Nuclear cataract	439	1.5	0.75, 2.93
Cortical cataract	433	2.0	1.09, 3.68
Posterior subscapular cataract	452	3.3	0.78, 13.83
Soft drusen	515	1.5	0.60, 3.51
Retinal pigment epithelium depigmentation	544	10.7	3.43, 33.52
Increased retinal pigment	511	3.1	1.17, 8.43
Exudative age-related maculopathy	575	14.6	1.19, 179.7

* OR, odds ratio from generalized estimating equations model, adjusted for age of each sibling; CI, confidence interval.

study population, smoking and, to a lesser extent, current alcohol intake are associated with nuclear cataract (19); diabetes (20), sunlight exposure (21), and use of some medications (22) are associated with cortical cataract; and diabetes (20), body mass index (20), and use of some medications (22) are associated with posterior subcapsular cataract. These associations may obscure or overwhelm some family effects. In support of this possibility is the finding that when smokers were eliminated from the analyses (table 3), the odds ratios for cortical and posterior subcapsular cataract increased.

Another consideration is that for sibships to contribute to the current analyses, there had to have been at least one sib-

ling who was free of the specific cataract at baseline, and that sibling had to have returned for evaluation at the 5-year follow-up. In addition, nuclear cataract is an independent risk factor for death in this cohort (23), further limiting our ability to detect important family relationships for this type of cataract. In addition, cataract surgery at baseline or follow-up diminished our ability to find significant family effects. In view of the findings from other studies and the limitations of the approach taken in this exploration, we may have underestimated familial effects. That was not the primary aim of this study, however.

The analytical technique of using randomly selected independent sibships is appealing because one can be more comfortable about accepting conventional *p* values. However, this technique reduces, in some cases substantially, the number of sibships contributing data to the analyses, which, in most instances, is reflected in the size of the confidence interval. While this trade-off may be acceptable, a review of data on all sibships suggests that no great harm is done by including related sibships. Furthermore, since selection of sibships is random, it is possible that large sibships, which for some characteristics may be more informative, may not have been selected; thus, potentially useful information may be lost.

We limited our analyses to sibships, both for simplicity and because we anticipated that this relationship would be most informative about family similarity. However, when Mendelian or other specific genetic models are invoked, inclusion of other kinship relationships may provide valuable additional information.

Our underlying data regarding ocular conditions were based on gradings of retinal and lens photographs. While these photographs provided a documented record of the status of the eye with regard to the lesions of interest, neither

the imaging nor the gradings were without technical and grader variability, which may have limited our estimate of important family effects. The power of these analyses also was limited, and the small sample sizes may be one explanation for lack of statistical significance in some analyses. We look forward to other studies of these age-related ocular conditions using other methods of disease documentation and other mathematical models, which may further our understanding of familial effects on these diseases.

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