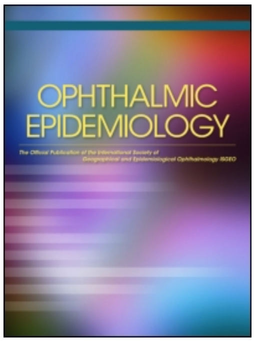

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Association between Age-related Cataract and Mortality in Sweden: A Long-term Population-based Follow-up Study

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ABSTRACT

Purpose: To assess the relationship of age-related cataract with all-cause mortality in a Swedish population.

Methods: Cox regression analyses were performed in a cohort of 746 residents 65–74 years of age, examined in a population survey in the rural district of Tierp, Sweden, 1984–86. To expand the sample size, 1,071 people were recruited by means of glaucoma case records established at the Eye Department in Tierp from 1978 to 2007. In this way, the cohort comprised 1,817 subjects, representing nearly 27,000 person-years at risk. The presence of cataract was determined based on retroillumination with lens opacities evident on slit-lamp examination. Information on deaths was obtained from the local population register.

Results: By the conclusion of the study in April 2020, 1,633 deaths had been reported. Of these cases, 694 were affected by lens opacities or had history of cataract surgery at baseline. In multivariate analysis, including cataract, age, sex, smoking habits, cancer, diabetes, hypertension and ischemic heart disease, no association was found between cataract and mortality (hazard ratio 0.99; 95% confidence interval 0.90–1.10). Adjustment for participation in the population survey had no effect on the estimate.

Conclusion: In this long-term follow-up study of subjects 65–74-years-old in Sweden, cataract was not associated with all-cause mortality.

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Cataract; epidemiology; mortality; risk factor; survival analysis

Introduction

Cataract has been suggested to be a biological marker for accelerating ageing and frailty.[1] To address this issue, numerous researchers have explored a possible association between lens opacities and survival in the past decades. In fact, studies have demonstrated a reduced life span in people with cataract and those who have undergone cataract surgery.[2–4]

Recently, a three-fold increase in 10-year mortality was found in the Liwan Eye Study.[5] Moreover, studies have reported increased mortality in subjects with nuclear but not with cortical opacities.[6–10]

Why cataract should be associated with decreased survival is unclear. However, visual impairment has been found to increase mortality risk.[11] Of note, in the studies referred to previously, comparison of cause-specific deaths revealed increased mortality from cancer for individuals with a component of nuclear opacity. Nonetheless, this tendency was not observed for persons with cortical opacities.

Survival studies on cataract have been inconsistent. In follow-up of the Rotterdam Study[12] and the Beijing Eye Study,[13] cataract was unrelated to mortality. Also, in the Framingham Eye Study, lens changes and survival were associated only among persons with diabetes.[14] Furthermore, in an investigation of American women, cataract surgery was related to lower mortality risk.[15] Clearly, additional studies of cataract and survival are essential for better understanding of this common disease and its related health problems.

The purpose of the present research was to explore the relationship of age-related cataract with all-cause mortality in a Swedish cohort, embracing a substantial number of exposed individuals. The investigation took the form of a long-term follow-up study on people in two rural districts.

Methods

The tierp glaucoma survey

In 1984–1986, a population survey was conducted in the rural district of Tierp, south-central Sweden. Its target population comprised 2,429 residents, aged 65–74-years -old. A representative sample of about one-third of the

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target population was randomly selected. Of the eligible number of 838 residents, 760 (91%) underwent a detailed eye examination, as described elsewhere.[16] The study was primarily designed to address the distribution and determinants of open-angle glaucoma. However, a vast amount of information was collected, including data on cataract.

Briefly, an interview was first held, covering medical and family history. Information was also obtained from medical records. After perimetry, the pupils were dilated to a diameter of at least 3 mm and slit-lamp biomicroscopy undertaken. The presence of cataract was ascertained based on retroillumination using indirect ophthalmoscopy with lens opacities evident on slit-lamp examination. A grading of the amount of opacities in six stages was also performed. Individuals with definite lens opacities of any kind in either eye or those who had undergone cataract surgery in one or both eyes were classified as having cataract. The first stage of lens opacities, described as "early senile changes" in the Framingham Eye Study,[17] was not accepted as definite cataract in the present study.

The cohort

A total of 78 people did not participate in the population survey. Of these, one joined the cohort after being examined in 1993. Six subjects, not examined in Tierp, were defined as ineligible for the study. Thus, this part of the cohort comprised 755 subjects. To expand the sample size, 1,153 subjects were recruited by means of glaucoma case records established at the Eye Department in Tierp from 1978 to 2007. Those enrolled were in the age range 65–74 years, residents of the rural districts of Tierp or Älvkarleby, Uppsala County. These participants had a diagnosis of ocular hypertension, glaucoma, suspicious optic discs or a positive family history. In addition, more than 200 subjects had participated as controls in a case–control study on risk factors for open-angle glaucoma (unpublished data). Apart from visual field testing, they underwent an eye examination comparable to that of the population survey.

Of the total number of 1,908 individuals, 65 were diagnosed with either angle-closure glaucoma or secondary glaucoma. They were excluded from the study, as were 12 subjects with incomplete data (Figure 1). Fourteen people did not want to take part in the study.

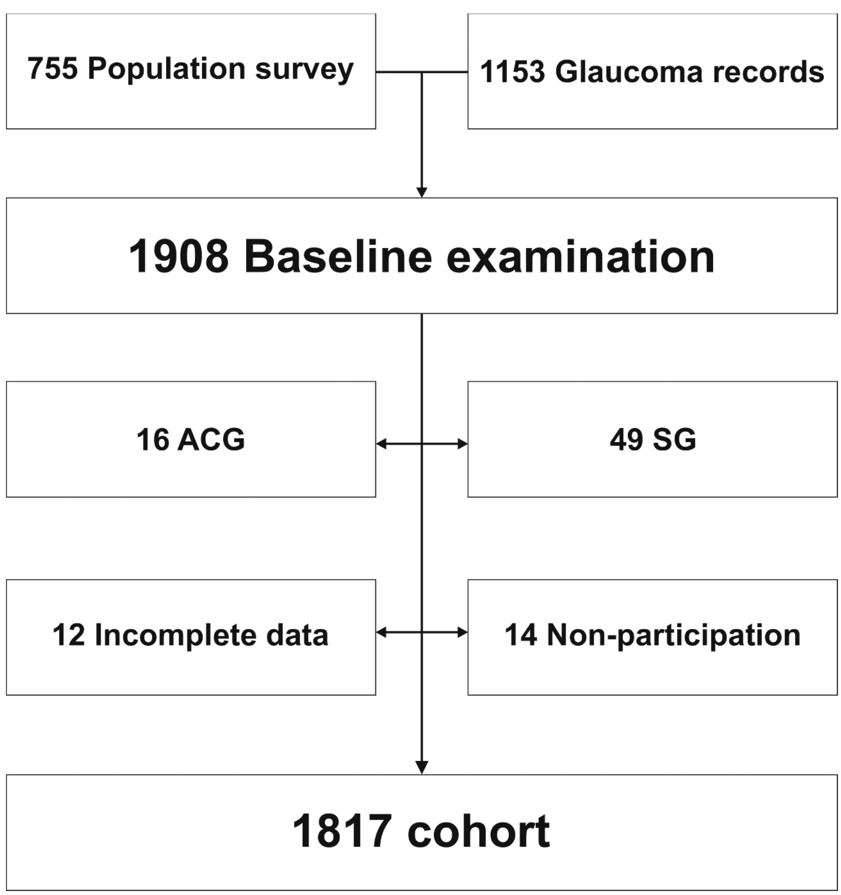

Figure 1. Flowchart showing how the study cohort of 1,817 individuals was derived. ACG, angle-closure glaucoma. SG, secondary glaucoma.

The remaining 1,817 constituted the study cohort, whose characteristics are presented in Table 1–2. The Regional Ethical Review Board of Uppsala University approved the study. The tenets of the Declaration of Helsinki were observed.

Collection of data

Anamnestic information on medical history and smoking habits was collected from study protocols or medical records, as was the presence of cataract. Follow-up started at baseline and ended on 15 April 2020. Date of death was obtained from the local population register (Masterbef) held by Uppsala County Council.

Statistical methods

Age and sex-standardised mortality ratios (SMRs) were computed. Follow-up time was calculated from baseline to date of death ($n = 1{,}633$) or end of the study ($n = 184$), whichever occurred first. Following standardised analyses, Cox proportional hazards models were developed to assess the effect of more than one predictor on the risk of death. Only variables with a substantial number of exposed cases were used in the multivariate analyses. The proportionality assumption was tested by using time-dependant variables. The effect of the covariates on survival was independent on time, apart from sex. For that reason, the Cox models were stratified by sex.

Table 1. Characteristics of the cohort, by age and sex.

	No. of people (*n* = 1,817)		Person–years (*n* = 26,956)	
Age group	Female (%)	Male (%)	Female (%)	Male (%)
65–69 years	560 (54)	408 (52)	10,043 (60)	6,156 (59)
70–74 years	468 (46)	381 (48)	6,558 (40)	4,199 (41)
65–74 years	1,028 (100)	789 (100)	16,601 (100)	10,355 (100)

Mean follow-up time: 14.8 years (standard deviation: 7.4)

Results

The median follow-up time for survivors was 19.5 years (range 12.6–34.4 years). By the conclusion of the study, 1,633 deaths had been reported. Of these cases, 694 were affected by lens opacities or had a history of cataract surgery at baseline. The SMR for exposed versus unexposed subjects was 1.02 (95% confidence interval [CI] 0.92–1.12), indicating no association between cataract and mortality. Thirty-one people had a history of cataract surgery, 27 of whom were dead, equal to a SMR of 1.13 (95% CI 0.77–1.66). Table 2 provides SMRs for potential risk factors and mortality by presence of cataract. Notable differences between those with or without cataract were observed only for variables with a limited number of deaths. The rest of the estimates were substantially identical for the two groups, signifying that cataract was unrelated to mortality.

Cox proportional hazards models included cataract, age, sex, smoking habits, cancer, diabetes mellitus, systemic hypertension and ischaemic heart disease. Adjusting for age and sex, cataract including cataract surgery was not associated with mortality (hazard ratio [HR] 1.02; 95% CI 0.92–1.13). The result remained largely unchanged in multivariate analysis (HR 0.99; 95% CI 0.90–1.10). The HR was slightly lower in the

Table 2. Associations of potential risk factors and all-cause mortality by presence of cataract including cataract surgery in a cohort of 1,817 individuals, adjusted for age and sex.

		Cataract (*n* = 777)		No cataract (*n* = 1,040)	
Baseline characteristics		No. of Deaths	SMR (95% CI)	No. of Deaths	SMR (95% CI)
Age ≥ 70 years[a]	No	281	1.00	547	1.00
	Yes	413	1.38 (1.19–1.61)	392	1.51 (1.32-1.72)
Male sex[b]	No	424	1.00	480	1.00
	Yes	270	1.29 (1.10–1.50)	459	1.29 (1.14–1.47)
Current smoking	No	582	1.00	784	1.00
	Yes	112	1.28 (1.04–1.57)	155	1.32 (1.10–1.58)
Visual impairment	No	629	1.00	924	1.00
	Yes	65	1.37 (1.06–1.77)	15	1.48 (0.89–2.47)
Cancer, all diagnoses	No	615	1.00	823	1.00
	Yes	79	1.13 (0.90–1.43)	116	1.29 (1.06–1.57)
Diabetes mellitus	No	583	1.00	791	1.00
	Yes	111	1.56 (1.27-1.91)	148	1.44 (1.21–1.72)
Hypertension, treatment	No	405	1.00	599	1.00
	Yes	289	1.20 (1.03-1.40)	340	1.21 (1.05–1.38)
Ischaemic heart disease	No	553	1.00	770	1.00
	Yes	141	1.32 (1.10-1.59)	169	1.34 (1.13–1.58)
Diseases of arteries	No	656	1.00	898	1.00
	Yes	38	1.78 (1.28–2.47)	41	1.38 (1.01–1.88)
Obstructive lung disease	No	639	1.00	866	1.00
	Yes	55	1.17 (0.88–1.54)	73	1.37 (1.08–1.74)

CI, confidence interval; SMR, standardised mortality ratio; visual impairment, visual acuity <0.5, better seeing eye.
[a]Adjusted for sex; [b] adjusted for age

Table 3. Association of cataract including cataract surgery with all-cause mortality in a cohort of 1,817 individuals, stratified by sex.

		Hazard ratio (95% confidence interval)	
Status	No	Age-adjusted	Model 1
Population survey			
Censured	1	1.00	1.00
Dead	745	0.94(0.80–1.11)	0.96(0.82–1.13)
Rest of the cohort			
Censured	183	1.00	1.00
Dead	888	1.12(0.97–1.29)	1.07(0.93–1.23)
Total			
Censured	184	1.00	1.00
Dead	1,633	1.02(0.92–1.13)	0.99(0.90–1.10)

Model 1, adjusted for age (continuous variable), current smoking, cancer (all diagnoses), diabetes, hypertension (treated), and ischemic heart disease.

population sample compared with the rest of the cohort (Table 3). In the whole cohort, adjustment for participation in the population survey did not change the risk (HR 1.02; 95% CI 0.92–1.14). Adjustment for birth year had no effect on the estimate (data not shown). There was no indication of interaction between cataract and diabetes or any of the other covariates.

Discussion

To our knowledge, this long-term follow-up study on a defined Swedish population is the first investigation exploring a possible relationship of age-related cataract with survival in the Nordic countries. Lens opacities including a history of cataract surgery were found to be unrelated to mortality. Applying a confidence level of 95% and a power of 80%, the study had the capacity to detect a 15% increased risk. With a hazard ratio of 0.99 and good statistical power, an association between lens opacities and mortality seems to be unlikely in the cohort under study.

Contrary to the present study, a meta-analysis of ten population-based studies on cataract and mortality recently showed a 34% increased risk of mortality.[18] There are several explanations for the discrepancy between our study and other studies. It could not be ruled out that environmental or ethnic factors explain at least part of the lower risk found in Tierp compared with studies in developing countries.[4] However, follow-up of the Beaver Dam Eye Study, conducted on a North American white population, also reported increased mortality in subjects with lens opacities.[2] Furthermore, the study in Tierp involved people aged 65–74-years-old, while the other studies covered a broader age span. Nonetheless, there are no reports of age differences in mortality risk associated with cataract. Compared with most of the studies referred to in this report, the study in Tierp was a small study. Hence, it limits the ability to explore the effect of rare exposures, regardless of the consequence it might have had on the result.

With respect to the method used to identify lens opacities, misclassification of exposure is a possible explanation for the result in Tierp. Particularly, nuclear opacities may have been undiagnosed. In the meta-analysis by Song et al., nuclear cataract was found to have the strongest association with mortality among the three cataract subtypes.[18] In the present study, information on exposure was collected at baseline before registration of deaths. For this reason, the misclassification was nondifferential, thereby "diluting" the effect towards the no-effect value.[19] On the other hand, if cataract had no effect on mortality, nondifferential misclassification of exposure would not bias the result. We believe that misclassification was small or moderate in the Tierp study. Therefore, it is unlikely that misclassification of exposure explains all the lack of relationship with mortality. Misclassification of disease is another type of information bias; however, with respect to the complete and safe reporting of deaths in Sweden, this type of misclassification can be ruled out.

Our study has several strengths, including its community-based design, long-term follow-up and sizeable cohort, nearly half of which was randomly selected, with a substantial number of events. Nevertheless, the study is limited in several respects. Firstly, baseline examination dates extended over nearly 30 years, which might give rise to bias. However, adjustment for birth year in the regression models did not change the estimate. Secondly, as mentioned above, cataract was diagnosed with a rather simple method, likely to underestimate the frequency of lens opacities. Unfortunately, standardised grading systems, like the Lens Opacities Classification System III,[20] were not available at the time of the population survey. Finally, information on cataract subtype was missing for a substantial part of the cohort. There are evidence that cortical and nuclear lens opacities do not share the same modifiable risk factors.[21,22] It is uncertain what effect this might have on the result.

In conclusion, in this long-term follow-up study of subjects 65–74-years-old in Sweden, cataract was not associated with all-cause mortality.

Disclosure of interest

None of the authors have any proprietary interests or conflicts of interest related to this submission.

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