Mortality and cataract: findings from a population-based longitudinal study

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The study was carried out in a rural population in central India. A random sample of 11 village communities provided 1020 persons aged 40–64 years, who were examined in 1982 and again reassessed in 1986. Statistical analysis, based on the Mantel-Haenszel method for stratified data, showed increased mortality in persons who had central lens opacities, compared with those who had trivial or no central lens opacities. The significant age-adjusted death ratio was just over 2 (2.2), as were the age/sex-adjusted and age/vision-adjusted estimates, which indicate doubling of mortality in the cataract cohort. Multiple regression analysis using the Cox proportional-hazards model gave very similar results. Statistical tests for homogeneity of death ratios across the various age/sex/vision strata were carried out, and the observed association between cataract and mortality was found to be consistent, both in males and in females, in the youngest and oldest age groups, and among those with adequate vision of 6/18 or better as well as among persons with serious visual impairment. There were no known diabetics in the study sample, which came from what could reasonably be regarded as a non-diabetic population.

No association between mortality and presence of lens changes was found among the non-diabetic population of Framingham, USA in the only published population-based study of survival in persons with and without lens changes (*1*). The study found increased mortality in persons with cataract, but only among diabetics. Other investigations, with some conflicting results, have focused on survival after cataract surgery (*2–6*). We report here a longitudinal study of a random sample of a rural population in central India and present epidemiological data on age- and sex-specific mortality ratios in relation to cataract. The concurrent influence of poor vision on mortality and the implications of the observed relationship between cataract and survival are briefly discussed.

Methods

A collaborative longitudinal study was started in 1982 in the Raipur District in central India. The baseline data were collected from a random sample of 11 village communities which included 1020 persons aged 40 to 64 years. These constituted the cohorts that were followed up and reassessed in 1986. Examinations and interviews were carried out by an ophthalmologist and an ophthalmic epidemiologist with the help of three specially trained ophthalmic assistants, using standardized and tested methods. An additional independent ophthalmologist was employed as consultant to evaluate the field work during the study.

Baseline assessment

Visual acuity was measured with a standard Snellen's E chart at 6 metres in shaded daylight, without and with the person's spectacles if any. Each person was then assigned to one of three levels of visual impairment according to the visual acuity in the best eye, using the WHO Categories of Visual Impairment (*7*). Level 1 (adequate vision) signified visual acuity of 6/18 or better, level 2 (low vision) indicated best visual acuity of 6/24 to 3/60, and level 3 (blind) comprised persons whose best vision was poorer than 3/60.

Cataracts were graded by assessment of the red reflex on retro-illumination according to a simple method that has been shown to have excellent inter-observer agreement (*8*). Grades 0 and 1, respectively, indicated clear red reflex with no opacities, or few small dot opacities appearing as tiny dark spots which collectively occupy no more than 1 mm^2 of the red reflex.

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These were considered as "normal" non-cataract eyes for the purpose of the study. Grade 2 (2a and 2b) indicated partial obscuration of the red reflex by lens opacities. Grade 3 signified total obscuration of the red reflex by the cataract and grade 4 was used for surgical aphakia.

The study sample was thus grouped into two main cohorts which could be followed up and their mortality ratios compared after appropriate adjustments for differences in age, sex, and levels of visual impairment. Cohort A comprised persons with both eyes classified as "normal". Cohort B comprised persons with at least one eye having cataract grade 2 or worse.

Final assessment

Four years later, in 1986, the study samples were located and again examined and interviewed by the same standardized methods. The families of those who were absent at the time of the re-examination were carefully questioned to ascertain the reason for absence. The survival times for those who had died before the final examination were estimated by ascertaining the time of death through detailed interviews of the families concerned. Any obvious cause of death, such as accidents and suicide, were also ascertained. Particular care was taken to ensure that all absent persons were correctly classified as either dead or alive. The latter were considered as alive at the time of the final family interview; it is possible, but highly unlikely, that an absent person had died but the news had not yet reached the family when interviewed.

Data analysis

The data were entered into a specially designed relational database using a microcomputer and were subsequently analysed at the International Centre for Eye Health (ICEH) in London. The interview procedure enabled computation of fairly exact follow-up times (in months) for each person in the original sample. These were used to arrive at "time-to-death" or "time-to-census" intervals for each individual, as required by the following statistical methods of analysis.

Classical methods of stratified analysis based on the Mantel-Haenszel (M-H) procedures were used to compare the cohorts in respect of death ratios, utilizing person–time denominators. The data were stratified by three main possible confounders—age, sex, and visual acuity and their combinations—and the procedures were used to estimate the relative risks of death, adjusted for possible confounding effects of the three stratification variables. Both M-H and maximum-likelihood estimates of the age-adjusted relative risk were computed and the confidence limits for the latter are reported. Statistical significance tests of homogeneity of the relative risks across the strata were carried out to identify any "effect modification" by age, sex or vision.

To complement this analysis, the Cox proportional hazards regression model was used to compare the survival of the "normal" and cataract cohorts while simultaneously accounting for the possible confounding effects of other factors (variables). The variables used in the model were the same as those used in the classical analysis. Appropriate model extension and fitting procedures (step-up) were also used to look for "effect modification" whereby the possible association between cataract and mortality might be *dependent* upon age or sex or level of visual impairment, so that the association may be absent or even reversed in some of the age/sex/vision strata. Such a phenomenon might show up as a higher-order interaction term (e.g., cataract–sex) which significantly improves the fit of the model when it is added to the model in the appropriate sequence of model-building steps.

Survival curves based on Kaplan-Meier cumulative probabilities of survival were also constructed to provide a graphic comparison of the mortality experience of the cohorts. A typical example for one of the age strata is reported.

Results

There were 1024 persons in the study sample at the start of the follow-up. Four were excluded because the lens could not be assessed mainly because of corneal opacities, leaving 1020 in the study. There were no known diabetics in the sample.

The age and sex distribution for the two main cohorts are shown in Table 1. As expected, persons in the cataract cohort were considerably older. The characteristics of the study sample, in respect of level of visual impairment and lens opacity, at the beginning of the follow-up are shown in Tables 2 and 3.

At the final follow-up examination, 77 persons (7.55%) were ascertained to have died during the follow-up period, leaving 943 survivors. About 19% (197) of the sample were absent at the time of the final assessment but all of these were ascertained to be alive and were not lost to the study. New employment away from the village was a common reason for being absent. During the period of the study there were no major outbreaks of disease or natural disasters in the study area. Mortality in the study sample was similar to that in the rural population of the study area (Raipur District): data from the rural areas

Table 1: **Age and sex distribution of the cataract (grade 2–4) cohort and of the "normal" cohort (cataract grade 0–1)**

	Age groups (years):					
	40–44	45–49	50–54	55–59	60–64	Total
Cataract:						
Males	7	14	30	32	51	134
	(5)[a]	(10)	(22)	(24)	(38)	
Females	8	24	56	38	62	188
	(4)	(13)	(30)	(20)	(33)	
Males+ females	15	38	86	70	113	322
	(5)	(12)	(27)	(22)	(35)	
"Normal":						
Males	112	120	68	35	26	361
	(31)	(33)	(19)	(10)	(7)	
Females	101	88	94	29	25	337
	(30)	(26)	(28)	(9)	(7)	
Males+ females	213	208	162	64	51	698
	(31)	(30)	(23)	(9)	(7)	
Total	228	246	248	134	164	1020
	(22)	(24)	(24)	(13)	(16)	

[a] Figures in parentheses are percentages, by rows (horizontally).

Table 2: **Definition and distribution of visual impairment levels in the study sample (n = 1020), at the start of the follow-up study**

Best vision	Visual impairment level	WHO category	No. of persons
6/18 or better	1 (adequate vision)	0	764 (74.9) [a]
6/24 to 3/60	2 (low vision)	1 and 2	211 (20.7)
Poorer than 3/60	3 (blind)	3, 4 and 5	45 (4.4)

[a] Figures in parentheses are percentages.

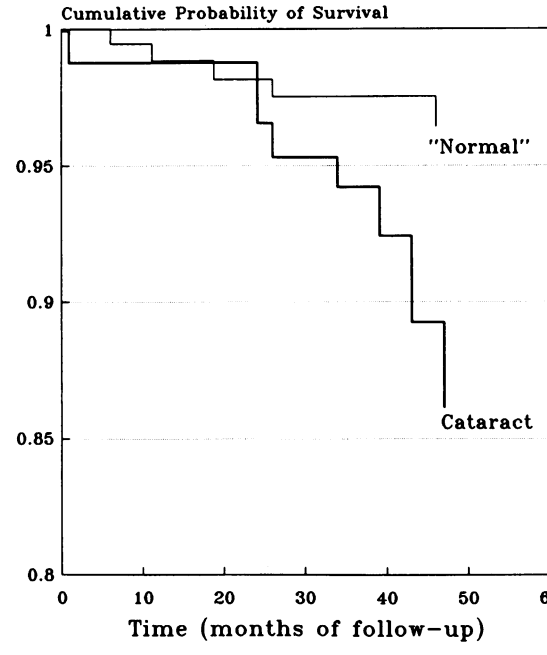
Table 3: **Distribution of cataract, by grade, in the study sample**

	Cataract grade in the worst eye:					
	0	1	2	3	4	Total
No. of persons	486	212	228	55	39	1020
	(47.6)[a]	(20.8)	(22.4)	(5.4)	(3.8)	

[a] Figures in parentheses are percentages.

of Raipur District were available for 1989 and showed that 0.9% of the general population aged 35–64 years died, while the annual age-standardized death ratio in the normal study cohort was 1.2% (1982–86 period). These are approximate estimates as the available general mortality data were grouped by 10-year age classes.

Fig. 1: **Age-specific survival curves based on Kaplan-Meier estimates, comparing the survival of a "normal" cohort (cataract grade 0–1) with that of a cataract cohort (cataract grade 2–4).** This typical example is for persons who were aged 50–54 years at the beginning of the study.



Crude and age-specific death ratios for the cataract and "normal" cohorts are compared in Table 4, which also shows the results of the stratified analysis. The age-adjusted relative risk of death was 2.2 (with approximate 95% confidence limits of 1.3 – 3.8), indicating doubling of mortality in persons with grade 2–4 cataract. As expected, age was a confounder since the crude death rate was about 4 times higher in the cataract cohort. Similar results were obtained when the data were stratified by age and sex simultaneously, and by age and vision. The age/sex adjusted death ratio was 2.3 (95% confidence limits 1.3 – 3.9), and the age/vision adjusted death ratio was 2.2 (95% confidence limits, 1.2 – 4). Statistical tests for homogeneity of death ratios across all the strata yielded high P-values of 0.8, 0.5 and 0.8, respectively, for the stratified analyses outlined above, suggesting a consistently higher risk of death in persons with cataract among all the population subgroups.

Analysis by the Cox proportional-hazards model produced a very similar estimate of the death ratio.

Table 4: **Numbers of deaths among persons with cataract (grade 2–4) and "normals" (cataract grade 0–1), stratified by age.** Results of age-adjusted analysis indicate doubling of the mortality rate in the cataract cohort compared with the "normal" cohort, and homogeneity of relative risks across all age strata

Age group	Number	Person-year follow-up	Died	Death rate[a]	Relative risk of death
40–44 years:					
Cataract	15	54.25	1	1.84	2.74
Normal	213	744.49	5	0.67	
45–49 years:					
Cataract	38	128.00	1	0.78	0.82
Normal	208	732.66	7	0.96	
50–54 years:					
Cataract	86	291.24	8	2.75	3.17
Normal	162	576.83	5	0.87	
55–59 years:					
Cataract	70	239.33	12	5.01	2.18
Normal	64	217.41	5	2.30	
60–64 years:					
Cataract	113	362.91	27	7.44	2.23
Normal	51	179.75	6	3.34	
All ages:					
Cataract	332	1075.73	49	4.56	3.99
Normal	698	2451.14	28	1.14	
Total	1020	3526.87	77		

Overall relative risk (adjusted for age):
Mantel-Haenszel estimate = 2.24
Maximum likelihood estimate = 2.22 (95% confidence limits, 1.32 and 3.75).

Tests for homogeneity of relative risks across all age strata:
Chi square = 1.55; d.f. = 4; *P*-value = 0.82.

[a] Death rates are per 100 persons per year.

For the lens opacity term, the hazard ratio was 2.33 (95% confidence limits, 1.3 – 4.2). This indicates that the mortality ratio in the cataract cohort was on average about double that in the "normal" cohort within the study sample, after the possible confounding effects of age, sex and visual impairment had been taken into account. This may be the best estimate of the relative risk of death in the much larger population from which the sample came. The confidence limits suggest the range which might contain the actual relative risk of death in the population at large.

Fig. 1 is a typical example comparing the survival curves of the two cohorts, in the 50–54-year age stratum.

Discussion

The observed association between cataract and mortality was studied in a population sample which had very few (if any) diabetics. Available data from routine urine or blood tests in the eye hospital and eye camps in the rural area of the study suggest a very low prevalence of diabetes among the cataract patients aged 40 and older. At the start of the study (1982), it was not practicable to take blood or urine specimens systematically during the cross-sectional survey of the village communities. A screening investigation of random (non-fasting) blood sugar and urine sugar is currently in progress in the rural area of the study population. Of the 280 persons with cataract screened so far, only 4 (1.4%) had blood sugar levels of 11 mmol/l or higher. We believe that there were too few (if any) diabetics in the study sample to account for all of the reported excess mortality in persons with cataract.

We assume, with hardly any doubts, that the study sample was free from diabetics and that the reported higher mortality in persons with cataract occurred among the non-diabetic population. The Framingham study found no such association in non-diabetics. A reasonable explanation may be that in our study population in central India, at least one major determinant of cataract (apart from age) is also

a risk factor for death, whereas in the non-diabetic population of Framingham, this may not be so. Evidence against or in favour of this explanation may come from larger studies which allow analysis of cause-specific mortality in relation to cataract and to its severity and morphology. However, we already have strong evidence that severe repeated episodes of dehydrational crises constitute a major risk factor for cataract in central India (*9, 10*). Such episodes could damage the lens proteins through the process of cyanate-induced carbamylation (*11, 12*) and are also potentially damaging to other vital proteins. This longitudinal study in central India has been expanded and extended for a further period to enable more precise estimates and more detailed comparisons.

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Résumé

Mortalité et cataracte: résultat d'une étude longitudinale dans la population

Une étude épidémiologique collective des rapports entre la mortalité et la cataracte, entreprise en 1982 sur un échantillon aléatoire (n = 1020, âge: 40–64 ans) d'une population rurale du centre de l'Inde, a été réévaluée en 1986 et a fait apparaître une surmortalité chez les personnes présentant une opacité du cristallin. Les éventuels facteurs confondants résultant des différences entre les cohortes de sujets atteints de cataracte et de sujets "normaux", en ce qui concerne l'âge, le sexe et le degré de handicap visuel, ont été pris en compte grâce à des techniques d'analyse par régression multiple et stratification. Le modèle d'analyse des risques proportionnels par régression multiple de Cox et la méthode de stratification par âge de Mantel-Haenszel ont donné des taux de mortalité relative de 2,3 et 2,2 respectivement, ce qui indique une mortalité deux fois plus forte chez les personnes atteintes de cataracte. L'association entre la cataracte et la mortalité était la même chez les hommes et chez les femmes, pour les différents groupes d'âge, et parmi ceux dont la vision était égale ou supérieure à 6/18 et ceux qui souffraient d'un grave déficit visuel.

Les cohortes étudiées ne comportaient pas de diabétiques connus. Les données recueillies au début de l'étude, en 1982, à l'occasion d'analyses systématiques d'urine et de sang dans les "camps ophtalmologiques" de la région donnent à penser que la prévalence du diabète chez les personnes atteintes de cataracte à cette époque était très faible. Une campagne de surveillance de la glycémie (pas nécessairement à jeun) est actuellement en cours dans la population à l'étude. Jusqu'à présent, sur 280 personnes atteintes de cataracte, 4 seulement (1,4%) ont présenté une glycémie supérieure ou égale à 11 mmol/l. A supposer qu'il y ait eu des diabétiques dans l'échantillon de population étudié, ils nous paraissent trop peu nombreux pour expliquer à eux seuls la surmortalité observée chez les personnes atteintes de cataracte.

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