

Radiation Dose and Cataract Surgery Incidence in Atomic Bomb Survivors, 1986–2005¹

Kazuo Neriishi, MD
Eiji Nakashima, PhD
Masazumi Akahoshi, MD, PhD
Ayumi Hida, MD
Eric J. Grant, PhD
Naomi Masunari, PhD
Sachiyo Funamoto, BS
Atsushi Minamoto, MD
Saeko Fujiwara, MD, PhD
Roy E. Shore, PhD, DrPH

Purpose:

To examine the incidence of clinically important cataracts in relation to lens radiation doses between 0 and approximately 3 Gy to address risks at relatively low brief doses.

Materials and Methods:

Informed consent was obtained, and human subjects procedures were approved by the ethical committee at the Radiation Effects Research Foundation. Cataract surgery incidence was documented for 6066 atomic bomb survivors during 1986–2005. Sixteen risk factors for cataract, such as smoking, hypertension, and corticosteroid use, were not confounders of the radiation effect on the basis of Cox regression analysis. Radiation dose-response analyses were performed for cataract surgery incidence by using Poisson regression analysis, adjusting for demographic variables and diabetes mellitus, and results were expressed as the excess relative risk (ERR) and the excess absolute risk (EAR) (ie, measures of how much radiation multiplies [ERR] or adds to [EAR] the risk in the unexposed group).

Results:

Of 6066 atomic bomb survivors, 1028 underwent a first cataract surgery during 1986–2005. The estimated threshold dose was 0.50 Gy (95% confidence interval [CI]: 0.10 Gy, 0.95 Gy) for the ERR model and 0.45 Gy (95% CI: 0.10 Gy, 1.05 Gy) for the EAR model. A linear-quadratic test for upward curvature did not show a significant quadratic effect for either the ERR or EAR model. The linear ERR model for a 70-year-old individual, exposed at age 20 years, showed a 0.32 (95% CI: 0.17, 0.52) excess risk at 1 Gy. The ERR was highest for those who were young at exposure.

Conclusion:

These data indicate a radiation effect for vision-impairing cataracts at doses less than 1 Gy. The evidence suggests that dose standards for protection of the eye from brief radiation exposures should be 0.5 Gy or less.

© RSNA, 2012

Supplemental material: <http://radiology.rsna.org/lookup/suppl/doi:10.1148/radiol.12111947/-/DC1>

¹From the Departments of Clinical Studies (K.N., S. Fujiwara), Statistics (E.N., S. Funamoto), Epidemiology (E.J.G.), and Research (R.E.S.), Radiation Effects Research Foundation, 5-2 Hijiyama Park, Minami-ku, Hiroshima 732-0815, Japan; Department of Clinical Studies, Radiation Effects Research Foundation, Nagasaki, Japan (M.A., A.H.); Minamoto Eye Clinic, Hiroshima, Japan (A.M.); and Faculty of Pharmacy, Iwaki Meisei University, Fukushima, Japan (N.M.). Received September 20, 2011; revision requested December 2; final revision received March 2, 2012; accepted March 27; final version accepted April 23. Supported by RERF research protocol 2-75. Address correspondence to K.N. (e-mail: neriishi@rerf.or.jp).

Since the 1950s, the prevailing view has been that only relatively high doses of at least several grays induce vision-impairing cataracts (1). For instance, for many years the International Commission on Radiological Protection judged that a brief exposure of at least 5 Gy was required to cause vision-impairing cataracts (2,3). Those recommendations were recently revised (4), but there remains an ongoing need for additional, informative data on brief radiation exposures of less than 1 Gy and the risk of vision-impairing cataracts.

On the basis of relatively few data, radiation protection groups have long recommended a dose-effect threshold level for vision-impairing cataracts of several grays for brief radiation exposures. The three main objectives of the current study were (a) to quantify the degree of cataract surgery risk from radiation, adjusting for other cataract risk variables that may have been confounders; (b) to determine whether the dose-response association is approximately linear or has upward curvature; and (c) to estimate the dose-effect threshold level. The current study examines the incidence of clinically important cataracts in relation to lens doses between 0 and approximately 3 Gy to address risks at relatively low brief radiation doses.

Materials and Methods

Materials

This study was approved by the Human Investigation Committee (institutional

Advances in Knowledge

- The study results provide evidence that the risk for clinically important cataracts is seen at dose levels less than 1 Gy.
- No significant dose-response non-linearity was seen in the incidence of cataract surgery after brief radiation exposures among atomic bomb survivors.
- The best estimate of a threshold dose for clinically important cataracts is approximately 0.5 Gy, with a 95% confidence interval of 0.1 to 1 Gy.

review board) of the Radiation Effects Research Foundation, or RERF, and informed consents were obtained. Since 1958, the Adult Health Study (AHS) has conducted biennial clinical health examinations (S. Fujiwara, 33 years; and M.A., 24 years) of individuals exposed to the atomic bomb (A-bomb) (5). Beginning in 1986, cataract surgery, as confirmed by using ophthalmoscopic examination (A.M., 25 years), was systematically recorded in the medical charts. For the current study, chart reviews of all study subjects were conducted by experienced physicians (K.N., 32 years; A.M., 25 years; A.H., 13 years) to assure accurate coding of cataracts. Incident cases of surgically removed cataracts (ie, their first cataract surgery) among AHS subjects were identified during 1986 through 2005. A total of 6066 subjects with estimated doses who visited Radiation Effects Research Foundation clinics at least twice during this period were considered eligible for the incidence analysis if they had no indication of cataract surgery at their first visit after 1985.

For dose-response analyses, we used the eye radiation dose in gray equivalents, which is the sum of the gamma dose plus 10 times the neutron dose based on the current Dosimetry System 2002 (6) and adjusted for dose measurement error (7).

Sixteen lens opacity risk factors were identified from the literature (8–11) for which questionnaire or observational information was available, including the following: education; marital status; history of smoking; body mass index; systolic and diastolic blood pressure; platelet count; lactic acid dehydrogenase level; uric acid level; γ -glutamyltransferase level; history of diabetes mellitus, hypercholesterolemia, hypertension, angina pectoris, or myocardial infarction; and corticosteroid medication use. The information on nearly all candidate risk factors was collected during the 1986–1989 baseline period from the AHS health examination database or mail surveys (E.J.G., 10 years; N.M., 10 years; S. Funamoto, 21 years). Information on diabetes was

collected at each health examination during the 20-year period. A number of measures had no missing data, while some had small amounts (< 10%) for which missing data were coded as normal. The correlations between radiation dose and whether information was missing were between -0.1 and zero for the various risk variables, indicating little effect of the missing data on the radiation dose response (8).

Between January 1986 and December 2005, 8055 individuals visited the AHS clinics more than once, so that new incident cases could be identified (at the initial visit during that period, prevalent cases were identified, while at subsequent visits, new, incident cases of cataract surgery were identified), but some were inappropriate for inclusion: 1861 individuals who were prenatally exposed or whose radiation doses were unknown, 122 individuals who underwent cataract surgery before January 1986, and six individuals in whom the date of surgery was unknown. Therefore, 6066 eligible individuals (without a prior cataract surgery) were considered at risk beginning at their first AHS clinic attendance date after January 1, 1986, until cataract surgery was performed, the last date of attendance at

Published online before print

10.1148/radiol.12111947 Content code: OT

Radiology 2012; 265:167–174

Abbreviations:

AHS = Adult Health Study
 CI = confidence interval
 EAR = excess absolute risk
 ERR = excess relative risk
 HR = hazard ratio
 TSE = time since exposure

Author contributions:

Guarantors of integrity of entire study, K.N., S. Funamoto, S. Fujiwara; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, E.N., R.E.S.; clinical studies, K.N., M.A., A.H., N.M., A.M.; experimental studies, E.J.G.; statistical analysis, E.N., R.E.S.; and manuscript editing, E.N., E.J.G., N.M., S. Funamoto, S. Fujiwara, R.E.S.

Potential conflicts of interest are listed at the end of this article.

the AHS clinic, or December 31, 2005, whichever occurred first.

Statistical Methods

The first phase of the analysis (E.N., 31 years; R.E.S., 43 years) consisted of an examination of the 16 identified cataract risk factors to determine which were potential confounder variables by using Cox regression (12). In this analysis, the continuous covariables, platelet count, lactic acid dehydrogenase level, uric acid level, and γ -glutamyltransferase level, were categorized as quartiles, while systolic and diastolic blood pressure and cholesterol level were dichotomized. The basic variables for the risk factor analyses included the demographic variables of city, sex, age at exposure (<10, 10, 20, \geq 30 years) and attained age, plus eye radiation dose (<0.005, 0.005, 0.4, 1.0, 2.0, \geq 3.0 Gy). Information on diabetes mellitus at study onset was used for the risk factor analyses. These were analyzed both as single variables and in a multivariate model adjusted simultaneously for all the other risk factors (Appendix E1 [online]).

In the radiation risk phase, excess incidence was modeled as both excess relative risk (ERR) at 1 Gy and excess absolute risk (EAR) expressed per 10000 persons per year at 1 Gy by using the Amfit program in the Epicure statistical package (13) to perform Poisson regression of grouped data. Poisson regression allows the risk to be partitioned into background risk, dose effects, and dose-effect modifiers. For the analysis, the person-year data were simultaneously stratified according to the following: city (Hiroshima or Nagasaki), sex, diabetes mellitus (yes or no), age at exposure (0 to <5, 5 to <10, 10 to <15, ..., 35 to <40, \geq 40 years), attained age (<60, 60 to <65, 65 to <70, ..., 85 to <90, \geq 90 years), calendar time (1986–1995 or 1996–2005) and eye radiation dose (0 to <0.005, 0.005 to <0.03, 0.03 to <0.1, 0.1 to <0.2, 0.2 to <0.4, 0.4 to <0.6, 0.6 to <0.8, 0.8 to <1.0, 1.0 to <2.0, 2.0 to <3.0, \geq 3.0 Gy). Diabetes mellitus status was coded as positive for a diabetes diagnosis prior to lens surgery or at any time

during an individual's follow-up if there was no surgery. Both ERR and EAR models were fitted, including city, sex, diabetes mellitus, age at exposure, and either attained age or time since exposure (TSE) to model background risk and as potential radiation dose-effect modifiers. Because TSE is a more natural way of describing radiation risk than is attained age, unless the attained-age model fit the data appreciably better than the TSE model, the TSE model was chosen. In both the ERR and EAR models, the eye dose term was modeled both as linear and linear-quadratic to better assess low-dose risk levels. Further details of the models are given in Appendix E1 (online).

For model selection, a 5% significance criterion was used for inclusion of the optional variables (city, sex, diabetes mellitus, age at exposure, and attained age or TSE) in the model. Possible two-way interactions were considered for the background models, and interactions of single factors with dose were considered for effect-modification terms. The Akaike Information Criterion (14) was used to compare the goodness of fit of nonnested models. Both the two-sided significance tests and 95% confidence interval (CI) were based on likelihood ratio tests applied to the profile likelihood (15).

The magnitude of the dose-response threshold level was estimated on the basis of the optimal model from the radiation-risk analysis. Details of the methods are given in Appendix E1 (online).

Results

There were 1028 persons with initial cataract surgery between 1986 and 2005 among the 6066 study subjects who contributed 84209 person-years. Table 1 shows the numbers of cataract surgery cases and person-years according to eye radiation dose, sex, city, and age at exposure. The cumulative incidence of cataract surgery was similar in the two cities, but the crude cumulative incidence of cataract was higher in female individuals (18.5%, 745 of 4035) than in male individuals (13.9%, 283

of 2031). The mean age at exposure was 20.4 years (range, 0–54 years). For both sexes, the mean age at cataract extraction was 74.4 years, and the range was 49–95 years. For male individuals, the mean age was 73.8 years, and the age range was 51–95 years, and for female individuals, the mean age was 74.7 years, and the age range was 48–94 years. The mean lens dose across all study subjects was 0.50 Gy (range, 0.0–5.14 Gy).

Risk Factor Analysis for Potential Confounding Variables

Table 2 shows the distribution of cataract risk factors and the Cox HRs for dose, the basic demographic adjustment variables, and the most relevant covariates. The first column of HRs presents the single risk factor analysis results (ie, adjusting for the basic demographic variables only), and the second column of HRs shows the HRs while simultaneously adjusting for all 16 potential risk factors by using multivariate analysis. Significant risk variables in the multivariate analysis were diabetes mellitus, angina pectoris, no college education, and a high body mass index. Adjustment for all the covariates simultaneously had almost no effect on the radiation risk, indicating they were not material confounders. Specifically, the dose response for Cox regression analyses, including dose as a continuous variable and only the basic demographic variables (HR, 1.28; 95% CI: 1.19, 1.37), was nearly the same as when all 16 potential confounders also were included (HR, 1.26; 95% CI: 1.17, 1.35), indicating the absence of confounding effects. Nevertheless, because diabetes mellitus was a strong risk factor for cataract, we included it in further Poisson regression analyses.

Radiation Risk Analysis

For the Poisson regression, the best sets of background rates (which included some interactions among city, sex, and age) and effect-modification terms were found. For the ERR models, the TSE model (deviance of 1835.5, 14 parameters, Akaike Information Criterion of 1863.5) fit the data slightly better than

Table 1

Person-Years, Crude Incidence Rates per 10 000 Person-Years, and Age at Exposure according to Parameters

Parameter	Total	Crude Incidence Rate	Age 0 to <10 y	Age 10 to <20 y	Age 20 to <30 y	Age ≥30 y
Sex						
Male	28 097 (283)	101	6916 (22)	14 785 (139)	3441 (64)	2956 (58)
F	56 112 (745)	133	9351 (44)	22 619 (273)	16 017 (286)	8125 (142)
City						
Hiroshima	53 724 (646)	120	9710 (43)	22 215 (239)	13 625 (220)	8174 (144)
Nagasaki	30 485 (382)	125	6556 (23)	15 188 (173)	5833 (130)	2907 (56)
Dose (Gy)						
0 to <0.005	35 821 (386)	108	6757 (23)	16 436 (147)	8028 (146)	4600 (70)
0.005 to <0.4	19 101 (234)	123	3230 (14)	7666 (79)	4896 (87)	3308 (54)
0.4 to <1.0	14 345 (182)	127	2536 (6)	6534 (78)	3536 (61)	1739 (37)
1.0 to <2.0	10 328 (148)	143	2347 (13)	4636 (70)	2148 (35)	1197 (30)
2.0 to <3.0	2764 (43)	156	845 (7)	1260 (17)	511 (12)	148 (7)
≥3.0	1849 (35)	189	552 (3)	870 (21)	337 (9)	89 (2)
Overall	84 209 (1028)	122	16 266 (66)	37 404 (412)	19 458 (350)	11 081 (200)

Note.—Data are person-years, except where otherwise indicated. Numbers in parentheses are numbers of cataract surgery cases. Ages are ages at exposure.

the attained-age model (deviance of 1840.2, 13 parameters, Akaike Information Criterion of 1866.2), so the TSE model was used. However, for the EAR models, the attained-age model provided a better fit (Akaike Information Criterion of 1866.6 was smaller by 4.9) than the TSE model, so it was used. In the following, risk estimates are presented for an attained age of 70 years after exposure at age 20 years, unless otherwise noted.

ERR models.—With the best background model, the simplest TSE ERR model with no dose-effect modifiers yielded a linear dose-response ERR estimate of 0.32 (95% CI: 0.20, 0.47) at 1 Gy. When a quadratic dose-squared term was added to the model, its effect was positive, suggesting slight upward curvature, but the improvement in fit was not significant ($P = .34$), so it was not pursued further. Evaluation of potential effect modifiers showed that city ($P = .05$), sex ($P = .03$), age at exposure ($P = .006$), and TSE ($P < .001$), but not diabetes mellitus, modified the radiation effect, with Nagasaki, male sex, younger age at exposure, and shorter TSE having greater radiation ERRs.

With the effect modifiers of city, sex, age at exposure, and TSE, the

Table 2

Cox Regression HR and 95% CI for Demographic Factors, Radiation Dose and Cataract Surgery Risk Factors

Covariate	CataractCases/Total Subjects	Analysis with Basic Covariates*		Analysis with Adjustment†	
		HR	95% CI	HR	95% CI
City					
Hiroshima	646/3985	1	...	1	...
Nagasaki	382/2081	1.15	1.01, 1.31	1.19	1.03, 1.36
Sex					
M	283/2031	1	...	1	...
F	745/4035	1.07	0.93, 1.23	1.16	0.96, 1.41
Age at exposure (y)					
0 to <10	66/967	1 [‡]	...	1 [‡]	...
10 to <20	412/2376	2.96	2.30, 3.87	2.68	2.08, 3.52
20 to <30	350/1459	5.59	4.31, 7.36	4.99	3.81, 6.63
≥30	200/1264	8.42	6.37, 11.3	7.64	5.67, 10.4
Dosimetry system 2002 eye dose (Gy)					
0 to <0.005	386/2530	1 [‡]	...	1 [‡]	...
0.005 to <0.4	234/1402	1.10	0.93, 1.30	1.10	0.93, 1.30
0.4 to <1.0	182/1027	1.17	0.98, 1.39	1.15	0.96, 1.37
1.0 to <2.0	148/750	1.40	1.16, 1.69	1.37	1.13, 1.65
2.0 to <3.0	43/212	1.91	1.37, 2.60	1.92	1.38, 2.60
≥3.0	35/145	2.30	1.60, 3.20	2.19	1.52, 3.06
Education					
Junior high [§]	434/2646	1	...	1	...
High school	529/2854	1.08	0.95, 1.23	1.08	0.94, 1.23
College	65/566	0.77	0.58, 0.99	0.76	0.57, 0.98

Table 2 (continues)

Table 2 (continued)

Cox Regression HR and 95% CI for Demographic Factors, Radiation Dose and Cataract Surgery Risk Factors

Covariate	CataractCases/Total Subjects	Analysis with Basic Covariates*		Analysis with Adjustment†	
		HR	95% CI	HR	95% CI
Smoking					
Never [§]	686/3774	1	...	1	...
Ex-smoker	173/956	1.23	1.01, 1.49	1.20	0.98, 1.45
Current	169/1336	0.87	0.71, 1.06	0.87	0.71, 1.07
Body mass index (kg/m²)					
<20 [§]	244/1624	1	...	1 [‡]	...
20 to <25	554/3190	0.98	0.85, 1.15	0.92	0.79, 1.08
25 to <30	210/1123	1.01	0.84, 1.22	0.89	0.73, 1.09
≥30	20/129	0.80	0.49, 1.24	0.63	0.38, 0.99
Diabetes mellitus					
No	891/5478	1	...	1	...
Yes	137/588	1.81	1.51, 2.17	1.85	1.53, 2.22
Hypercholesterolemia					
No [§]	949/5713	1	...	1	...
Yes	79/353	1.11	0.87, 1.38	1.07	0.84, 1.34
Hypertension					
No	572/3484	1	...	1	...
Yes	456/2582	1.10	0.97, 1.25	1.05	0.90, 1.23
Angina pectoris					
No	960/5762	1	...	1	...
Yes	68/304	1.29	1.00, 1.64	1.31	1.01, 1.66
Myocardial infarction					
No	1020/6002	1	...	1	...
Yes	8/64	1.04	0.47, 1.95	0.87	0.40, 1.64
Oral or injected corticosteroid use					
No [§]	1003/5944	1	...	1	...
Yes	25/122	1.08	0.70, 1.57	1.12	0.73, 1.63

Note.—Hypercholesterolemia was determined as a value of 220 mg/dL (5.7 mmol/L) or less. HR = hazard ratio.

* Analyses of the named variable with adjustment for the basic variables of city, sex, age at exposure, and radiation dose.

† Analyses included adjustment for the basic variables plus all 16 risk-factor variables (additional risk factors).

‡ *P* for trend was less than .05.

§ Included unknown or missing data (for <10% of the total subjects).

ERR estimate was calculated as follows: $0.77 \cdot d \cdot \exp(-0.88 \cdot c - 0.89 \cdot s - 0.66 \cdot e - 1.59 \cdot \text{TSE})$, where *d* is eye radiation dose, *c* is city, *s* is sex, and *e* is (years of age at exposure - 20)/10, and TSE is (years since exposure - 50)/10. With use of this model, the sex-averaged ERR for Hiroshima for a 70-year-old individual exposed at age 20 years (ie, 50 years after exposure) was 0.32 (95% CI: 0.17, 0.52; *P* < .001) (Fig 1). The estimated number of excess cases caused by radiation

was 109. Averaged across city, the estimated ERR was 0.49 for male individuals and 0.20 for female individuals. When averaged across city and sex, the estimated ERR was greater at younger ages at exposure; estimates for 50 years after exposure were 0.61, 0.32, and 0.15 for exposure at ages 10, 20, and 30 years, respectively. The negative coefficient shown for the TSE modifier in the above equation indicates that the ERR diminished at longer times since radiation exposure.

EAR models.—With the best background model, the simplest EAR model with no dose-effect modifiers yielded a linear dose-response EAR estimate of 19.0 (95% CI: 11.7, 27.2) excess cases per 10000 person-years at 1 Gy. When a quadratic term was added to the model, the effect was positive but the improvement in the fit was not significant (*P* = .14). Evaluation of potential effect modifiers showed that city (*P* = .1), sex (*P* = .31), age at exposure (*P* = .31), and diabetes mellitus (*P* = .44) effects were not significant. Only a positive log attained age effect (*P* < .01) modified the radiation effect.

The final EAR model was as follows: $33.2 \cdot d \cdot \exp(3.76 \cdot \log \text{ age})$, where log age is log attained age. The EAR was 33.2 (95% CI: 22.1, 45.2; *P* < .001) excess cases per 10000 person-years at 1 Gy, modeled at age 70 years after exposure at age 20 years (Fig 2). On the basis of this model, the estimated number of excess cases caused by radiation was 117. The estimated EAR (averaged across city, sex, and age at exposure) increased with attained age: The EAR was 19 (95% CI: 12, 26) at age 60 years, 33 (95% CI: 22, 45) at age 70 years, and 55 (95% CI: 31, 83) at age 80 years, but it was not significantly affected by age at exposure (*P* = .31).

Threshold Level Search

With the best models shown above, we searched for a threshold dose effect by using a profile likelihood search. The threshold-dose point estimates were similar for the two models: 0.50 Gy (95% CI: 0.10 Gy, 0.95 Gy) for the ERR model and 0.45 Gy (95% CI: 0.10 Gy, 1.05 Gy) for the EAR model.

Discussion

This study provides quantitative evidence for risk of vision-impairing cataracts at lens doses less than 1 Gy. The dose response was nearly linear, implying there may be risk at fairly low doses. The best estimate was a 0.32 ERR at 1 Gy for a 70-year-old individual who received radiation exposure at age 20 years. The risk was highest for those who were young at exposure,

Figure 1

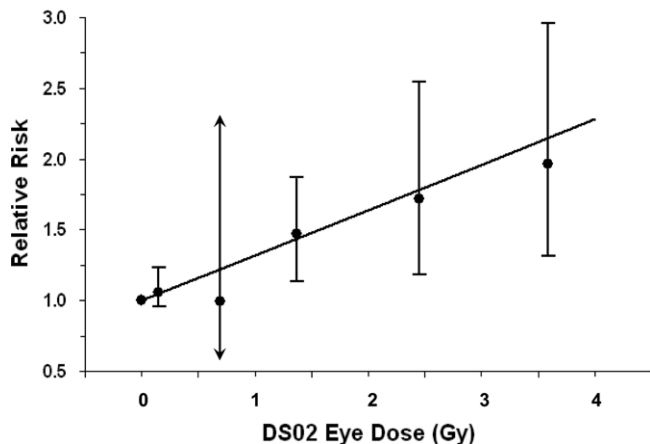


Figure 1: Radiation dose response for the relative risk of cataract surgery for 20 years of age at exposure and attained age of 70 years and averaged across sex and city. The ERR per gray was 0.32 (95% CI: 0.17, 0.52) ($P < .001$). DS02 = Dosimetry System 2002.

Figure 2

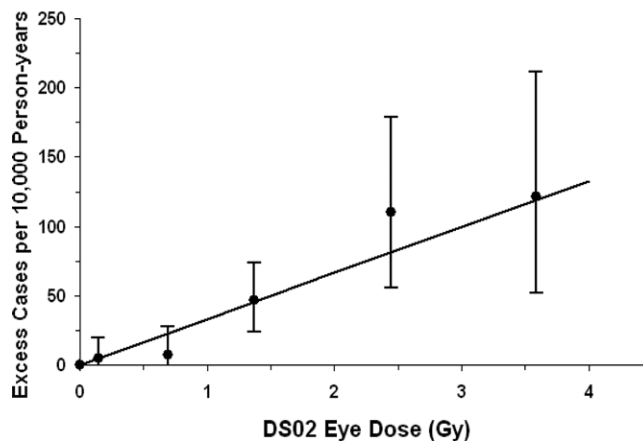


Figure 2: Dose response for the EAR per 10000 persons per year modeled for 20 years of age at exposure and attained age of 70 years and averaged across sex and city. The number of excess cases per 10000 persons per year per gray was 33.2 (95% CI: 22.1, 45.2) ($P < .001$). DS02 = Dosimetry System 2002.

suggesting that children are especially sensitive to cataract induction by means of radiation. A formal dose–threshold level analysis provided a best estimate of a threshold level at about one-half of a gray but indicated that the threshold level may be as low as 0.1 Gy and is unlikely to exceed 1.0 Gy. As such, these data strengthen the foundation for the more current International Committee on Radiological Protection guidelines in which the threshold level for absorbed dose to the lens has been appreciably reduced to 0.5 Gy (4).

A substantial number of screening studies (16–26), including several of medical radiation personnel (23–26), have reported that doses of low–linear energy transfer radiation less than 1 Gy are associated with posterior subcapsular and cortical opacities, but they were primarily low-grade opacities that have little effect on visual acuity. Further details are given in two reviews (27,28). Researchers in two previous studies (29,30) have reported on clinically important cataracts, but one was based on alpha irradiation with uncertain dosimetry, and the other did not show a significant association but, because of the very low dose distribution, had limited statistical power (8).

We previously reported (31) on the prevalence of cataract surgery in a subset of the present study population, but that study was much smaller and prevalence data have a greater potential for bias than incidence data (eg, data reported by Gordis [32]). Thus, the present study provides more convincing evidence than that in previous studies of lens irradiation and vision-impairing cataracts caused by radiation in the 0–1-Gy dose range (81.8% [4959 of 6066] received doses less than 1 Gy), given that it reflects cataract-surgery incidence during a 20-year period in a large cohort of whom more than 1000 individuals underwent cataract surgery. Past estimates of threshold doses have been based on prevalence analyses in A-bomb survivors (22,31,33) and Chernobyl cleanup workers (18); all except one (33) suggested a low-dose threshold level.

This study had a number of strengths. It characterized the radiation risk for cataract surgery incidence in a well-defined cohort with a wide range of reasonably accurate dose estimates and a high participation rate for up to 60 years after the bombings. Those who performed the medical examinations for confirmation of cataract were blinded to the radiation dose so as not to bias the assessment. Furthermore,

bias from differential care seeking is unlikely because there were no economic incentives for some subgroups to get more health care than others, as health care is free for all study subjects. Comparisons of the risk factor findings with findings in other studies did not suggest sample bias, as the relative risks for various cataract risk factors, such as age, diabetes mellitus, hypertension, and others, were well within the range of findings reported by researchers in other studies (9,10,34,35).

The study also had certain limitations. We did not account for possible temporal changes in smoking habits, alcohol consumption, or obesity (body mass index) during the study period. Information on individual sunlight exposure was not available, although it is known that the cohort contained few individuals who had marked occupational sunlight exposure, and there is no apparent reason why sunlight exposure should be correlated with radiation dose. We adjusted for city, because background cataract rates suggested intercity differences in ultraviolet exposure levels (36). There may have been losses to follow-up or survival biases in the cohort before 1986 (which was 41 years after the bombings). However, losses to follow-up (participant attrition)

have been independent of radiation dose in the AHS, and the modest dose-related differences in survival as a result of the radiation-cancer association are unlikely to be related also to cataract outcomes. Cataract surgery is an imperfect surrogate for a vision-impairing cataract because surgery may depend on health status, age, visual acuity in the other eye, and other factors that limit the sensitivity in ascertaining vision-limiting cataracts (37), but there is no reason to think that the sensitivity varied by radiation dose. Because the study was based on a brief, single radiation exposure, the generalization of the risk estimates to groups exposed to protracted or highly fractionated radiation is uncertain.

In conclusion, the incidence of cataract surgery was found to be 0.32 (95% CI: 0.17, 0.52) higher at 1 Gy, an excess of 33 cases per 10000 persons per year per gray. A linear model provided an adequate fit to the dose response. The near-linear dose response suggests radiation risk for clinically important cataracts at relatively low doses, and the data are compatible with a dose-response threshold level between about 0.1 and 1 Gy but not with threshold values above 1 Gy. This factor provides further evidence that past radiation protection standards for the eye in which a dose threshold level of several grays was assumed may have been insufficiently protective. Finding a near-linear dose response and an estimated-dose threshold level of approximately 0.5 Gy for clinically important cataracts among A-bomb survivors significantly strengthens the scientific foundation for the more current International Commission on Radiological Protection statement (4) that considers the threshold dose for the lens of the eye to be 0.5 Gy rather than a much higher value.

Acknowledgments: RERF is a private, nonprofit foundation funded by the Japanese Ministry of Health, Labour and Welfare and the U.S. Department of Energy, the latter partly through the National Academy of Sciences. The funding agencies played no role in the conduct or conclusions of the study.

Disclosures of Potential Conflicts of Interest: K.N. No potential conflicts of interest to disclose. E.N. No potential conflicts of interest to

disclose. M.A. No potential conflicts of interest to disclose. A.H. No potential conflicts of interest to disclose. E.J.G. No potential conflicts of interest to disclose. N.M. No potential conflicts of interest to disclose. S. Funamoto No potential conflicts of interest to disclose. A.M. No potential conflicts of interest to disclose. S. Fujiwara No potential conflicts of interest to disclose. R.E.S. No potential conflicts of interest to disclose.

References

- Merriam GR Jr, Focht EF. A clinical study of radiation cataracts and the relationship to dose. *Am J Roentgenol Radium Ther Nucl Med* 1957;77(5):759-785.
- International Commission on Radiological Protection. Radiopathology of skin and eye and radiation risk. In: Avoidance of radiation injuries from medical interventional procedures. ICRP publication 85. *Ann ICRP* 2000;30(2):25-31.
- International Commission on Radiological Protection. The 2007 recommendations of the International Commission on Radiological Protection. ICRP publication 103. *Ann ICRP* 2007;37(2-4):1-332.
- International Commission on Radiological Protection. ICRP statement on tissue reactions. Approved by the Commission on April 21, 2011. ICRP report no. ref 4825-3093-1464. Ottawa, Canada: International Commission on Radiological Protection, 2011.
- Beebe GW, Ishida M, Jablon S. Studies of the mortality of A-bomb survivors. I. Plan of study and mortality in the medical subsample (selection 1), 1950-1958. *Radiat Res* 1962;16:253-280.
- Young RW, Kerr GD, eds. Reassessment of the atomic bomb radiation dosimetry for Hiroshima and Nagasaki, Dosimetry System 2002 (DS02). Hiroshima, Japan: Radiation Effects Research Foundation, 2005.
- Pierce DA, Stram DO, Vaeth M. Allowing for random errors in radiation dose estimates for the atomic bomb survivor data. *Radiat Res* 1990;123(3):275-284.
- Chodick G, Bekiroglu N, Hauptmann M, et al. Risk of cataract after exposure to low doses of ionizing radiation: a 20-year prospective cohort study among US radiologic technologists. *Am J Epidemiol* 2008;168(6):620-631.
- Hennis A, Wu SY, Nemesure B, Leske MC; Barbados Eye Studies Group. Risk factors for incident cortical and posterior subcapsular lens opacities in the Barbados Eye Studies. *Arch Ophthalmol* 2004;122(4):525-530.
- Risk factors for age-related cortical, nuclear, and posterior subcapsular cataracts. The Italian-American Cataract Study Group. *Am J Epidemiol* 1991;133(6):541-553.
- Younan C, Mitchell P, Cumming R, Rochtchina E, Panchapakesan J, Tumuluri K. Cardiovascular disease, vascular risk factors and the incidence of cataract and cataract surgery: the Blue Mountains Eye Study. *Ophthalmic Epidemiol* 2003;10(4):227-240.
- Cox DR. Regression models and life tables. *J R Stat Soc Series B Stat Methodol* 1972;34(2):187-220.
- Preston DL, Lubin JH, Pierce DA, McConey ME. *Epicure users guide*. Seattle, Wash: HiroSoft International Corporation, 1993.
- Akaike H. A new look at statistical model identification. *IEEE Trans Automat Contr* 1974;19(6):716-723.
- Cox DR, Hinkley DV. *Theoretical statistics*. New York, NY: Chapman & Hall, 1974.
- Day R, Gorin MB, Eller AW. Prevalence of lens changes in Ukrainian children residing around Chernobyl. *Health Phys* 1995;68(5):632-642.
- Hall P, Granath F, Lundell M, Olsson K, Holm LE. Lenticular opacities in individuals exposed to ionizing radiation in infancy. *Radiat Res* 1999;152(2):190-195.
- Worgul BV, Kundiyeve YI, Sergiyenko NM, et al. Cataracts among Chernobyl clean-up workers: implications regarding permissible eye exposures. *Radiat Res* 2007;167(2):233-243.
- Chylack LT Jr, Peterson LE, Feiveson AH, et al. NASA study of cataract in astronauts (NASCA): report 1—cross-sectional study of the relationship of exposure to space radiation and risk of lens opacity. *Radiat Res* 2009;172(1):10-20.
- Hsieh WA, Lin IF, Chang WP, Chen WL, Hsu YH, Chen MS. Lens opacities in young individuals long after exposure to protracted low-dose-rate gamma radiation in 60Co-contaminated buildings in Taiwan. *Radiat Res* 2010;173(2):197-204.
- Minamoto A, Taniguchi H, Yoshitani N, et al. Cataract in atomic bomb survivors. *Int J Radiat Biol* 2004;80(5):339-345.
- Nakashima E, Neriishi K, Minamoto A. A reanalysis of atomic-bomb cataract data, 2000-2002: a threshold analysis. *Health Phys* 2006;90(2):154-160.
- Kleiman NJ, Cabrera M, Duran G, Ramirez R, Duran A, Vano E. Occupational risk of radiation cataract in interventional cardiology [abstract]. *Invest Ophthalmol Vis Sci* 2009;49(suppl):511.
- Vano E, Kleiman NJ, Duran A, Rehani MM, Echeverri D, Cabrera M. Radiation cataract

- risk in interventional cardiology personnel. *Radiat Res* 2010;174(4):490–495.
25. Ciraj-Bjelac O, Rehani MM, Sim KH, Liew HB, Vano E, Kleiman NJ. Risk for radiation-induced cataract for staff in interventional cardiology: is there reason for concern? *Catheter Cardiovasc Interv* 2010;76(6):826–834.
26. Mrena S, Kivelä T, Kurttio P, Auvinen A. Lens opacities among physicians occupationally exposed to ionizing radiation: a pilot study in Finland. *Scand J Work Environ Health* 2011;37(3):237–243.
27. Ainsbury EA, Bouffler SD, Dörr W, et al. Radiation cataractogenesis: a review of recent studies. *Radiat Res* 2009;172(1):1–9.
28. Shore RE, Neriishi K, Nakashima E. Epidemiological studies of cataract risk at low to moderate radiation doses: (not) seeing is believing. *Radiat Res* 2010;174(6):889–894.
29. Chmelevsky D, Mays CW, Spiess H, Stefani FH, Kellerer AM. An epidemiological assessment of lens opacifications that impaired vision in patients injected with radium-224. *Radiat Res* 1988;115(2):238–257.
30. Taylor DM, Thorne MC. The potential for irradiation of the lens and cataract induction by incorporated alpha-emitting radionuclides. *Health Phys* 1988;54(2):171–179.
31. Neriishi K, Nakashima E, Minamoto A, et al. Postoperative cataract cases among atomic bomb survivors: radiation dose response and threshold. *Radiat Res* 2007;168(4):404–408.
32. Gordis L. *Epidemiology*. Philadelphia, Pa: Saunders, 1996.
33. Otake M, Schull WJ. Radiation-related posterior lenticular opacities in Hiroshima and Nagasaki atomic bomb survivors based on the DS86 dosimetry system. *Radiat Res* 1990;121(1):3–13.
34. Foster PJ, Wong TY, Machin D, Johnson GJ, Seah SKL. Risk factors for nuclear, cortical and posterior subcapsular cataracts in the Chinese population of Singapore: the Tanjong Pagar Survey. *Br J Ophthalmol* 2003;87(9):1112–1120.
35. Hodge WG, Whitcher JP, Satariano W. Risk factors for age-related cataracts. *Epidemiol Rev* 1995;17(2):336–346.
36. Minamoto A, Neriishi K, Nakashima E. UV radiation may explain intercity difference for cataract in A-bomb survivors. *J Photochem Photobiol B* 2011;103(2):105–110.
37. Nakashima E, Fujii Y, Neriishi K, Minamoto A. Assessment of misclassification in a binary response: recovering information on clinically significant cataract prevalence from cataract surgery data in atomic-bomb survivors. *J Jpn Stat Soc* 2011;41(1):1–15.