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Epidemiological Studies of Cataract Risk at Low to Moderate Radiation Doses: (Not) Seeing is Believing

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The prevailing belief for some decades has been that human radiation-related cataract occurs only after relatively high doses; for instance, the ICRP estimates that brief exposures of at least 0.5–2 Sv are required to cause detectable lens opacities and 5 Sv for vision-impairing cataracts. For protracted exposures, the ICRP estimates the corresponding dose thresholds as 5 Sv and 8 Sv, respectively. However, several studies, especially in the last decade, indicate that radiation-associated opacities occur at much lower doses. Several studies suggest that medical or environmental radiation exposure to the lens confers risk of opacities at doses well under 1 Sv. Among Japanese A-bomb survivors, risks for cataracts necessitating lens surgery were seen at doses under 1 Gy. The confidence interval on the A-bomb dose threshold for cataract surgery prevalence indicated that the data are compatible with a dose threshold ranging from none up to only 0.8 Gy, similar to the dose threshold for minor opacities seen among Chernobyl clean-up workers with primarily protracted exposures. Findings from various studies indicate that radiation risk estimates are probably not due to confounding by other cataract risk factors and that risk is seen after both childhood and adult exposures. The recent data are instigating reassessments of guidelines by various radiation protection bodies regarding permissible levels of radiation to the eye. Among the future epidemiological research directions, the most important research need is for adequate studies of vision-impairing cataract after protracted radiation exposure. © 2010 by Radiation Research Society

INTRODUCTION

The lens of the eye is a unique organ in that it is non-vascular and has no loss of cells over the lifetime, which means there is no mechanism for the removal of damaged cells. Cataractogenic radiation damage occurs at the ''germinative zones'' at the anterior surface where dividing cells form a clear crystalline-protein fiber that migrates toward the posterior pole of the lens, the posterior subcapsular (PSC) region. Radiation damage by both direct and oxidative mechanisms causes DNA breaks, aberrant cell migration and complex biochemical alterations that result in aberrant crystalline protein folding and dysregulation of lens cell morphology (*1–3*). Historically, PSC opacification was thought to be the signature lesion of radiation damage to the lens, although more recent data suggest that radiation-induced opacities can be found in the lens cortex as well.

Cataract was one of the earliest radiation-associated pathologies found after Roentgen discovered X rays; Chalupecky reported an experiment showing radiation-induced cataract only 1 year later, and Treutler reported on a cataract in an X-ray worker within 10 years (*4, 5*). However, cataract was long thought to result from only high doses of radiation to the lens of the eye. This was compatible with the data from early cyclotron workers with cataract after substantial neutron doses (*6, 7*) and with early Japanese A-bomb studies that reported excess cataracts among those who received over 2–3 Gy (*8, 9*). A number of other, more recent high lens-dose studies have continued to report substantial cataract excesses [e.g. refs. (*10, 11*)].

Induction of cataracts in humans has been viewed as a deterministic effect that had a dose threshold and for which the severity increased and the latency decreased as the radiation dose increased above that threshold. This viewpoint was particularly strengthened by a seminal paper by Merriam and Focht in 1957 (*12*) that showed all the aforementioned features in a series of persons who had received medical radiation therapy. They concluded that the latent period between exposure and cataract manifestation was strongly inversely correlated with dose and that there was no cataract induction below 2 Gy. However, inspection of the Merriam and Focht paper shows that the observation periods after irradiation were mostly quite short (average of 8 years) and that they studied only 20 individuals who had estimated lens doses under 2 Gy, a rather limited basis for establishing a prudent protection policy. Another influential paper was based on an early systematic ophthalmological study of A-bomb survivors by Nefzger

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TABLE 1
ICRP Guidelines on Minimal Lens Doses for Cataract Induction (*15, 16*)

End point	Brief exposures (Sv)	Fractionated or protacted exposures (Sv)	Annual dose rate (Sv)
Detectable opacities	0.5–2	5	>0.1
Visual impairment	5	>8	>0.15

et al. (*13*). They described an excess of "axial opacities" in their highest dose group, which they indicated was approximately 2 Gy or greater. A later reanalysis based on the improved DS86 dosimetry system estimated the γ-radiation threshold dose as 1.4 Gy (*14*). Those papers were highly influential as a basis for the recommendations of radiation protection groups such as the ICRP and NCRP (*15–17*).

The current guidelines of the ICRP regarding radiation protection against cataracts are shown in Table 1. For brief exposures, the dose threshold was considered to be 0.5–2 Sv for minor opacities but 5 Sv for cataracts that cause visual impairment. For protracted or fractionated exposures the corresponding dose thresholds were thought to be 5 and 8 Sv, respectively. The guidelines for an annual dose rate were based on an assumption of dose limits when substantial exposures were received over many years.

PRINCIPAL DATA PROMPTING A RE-EVALUATION OF CATARACT RISK GUIDELINES

The present summary will focus primarily on low-LET radiation, although there are a small number of studies of high-LET radiation in the literature (*6, 18, 19*). There is now a body of data suggesting that the guidelines for allowable lens dose might not be sufficiently conservative. Another recent review reaching similar conclusions was published by Ainsbury *et al.* (*3*).

In a 1968 report, a blinded ophthalmological screening study of 234 New York City children given X-ray treatment for scalp ringworm and 232 without X-ray treatment indicated a significant, but imprecise, increased age-adjusted odds ratio (OR) of 5.9 [95% confidence interval (CI): 1.4–24] in minor opacities at an early age after an eye dose of about 0.5 Gy (*20*).

A Swedish cohort of 484 treated with radium plaques in infancy for skin hemangiomas received >0 to 8.4 Gy (mean, 0.4 Gy; 10% received >1 Gy) of γ radiation to the lens. An ophthalmological screening at a mean age of 46 years showed dose-related risks of minor lens opacities for both PSC (OR_{1Gy} = 1.50, CI: 1.1–2.1) and cortical opacities (OR_{1Gy} = 1.35, CI: 1.1–1.7) (*21*).

Persons exposed to γ radiation for up to 15 years from living in radiocontaminated buildings in Taiwan were given ophthalmological examinations (*22*). No radiation effect was observed among the 53 examined at ages 22–65 years. The reported 61 examinees at ages 3–20 years, with an estimated dose range of 1–1200 mGy (mean ~170 mGy), showed a dose–response association (OR_{1Gy} = 1.18, CI: 1.02–1.36) for subclinical lesions described as "focal lens defects." An average 4.7-year update of those originally examined before age 20 showed a further dose-related increase in the size and number of focal lens defects (*23*)

Studies of opacities among NASA astronauts have used a radiation exposure database that includes lens doses from diagnostic X rays, trapped radiation and galactic cosmic rays (GCR). The first report of screenings for opacities indicated that astronauts with relatively higher lens doses (>8 mSv, average 45 mSv) had a higher incidence and earlier appearance of lens opacities than those with lower doses (<8 mSv) (*24*). This was recently updated and extended by Chylack *et al.* (*25*). They compared lens opacity prevalence in 171 astronauts who had flown in space with 53 astronauts who had not flown in space, 95 military aircrew and 99 military non-aircrew. The digitized Nidek EAS 1000 lens images were graded by computer software for nuclear, cortical and PSC lens opacities. Adjustment was made in the analysis for individual sunlight-exposure scores, demographics, medical history items, smoking, gender and age. They reported that cortical opacity frequency was significantly higher in exposed astronauts than in the comparison groups. The number and size of PSC opacities was greater among the astronauts who had flown compared to those who had not. No association was found between space radiation exposure and nuclear opacities. These results suggest increased cortical and PSC cataract risks at relatively low radiation doses, although dose units were not reported (*25*).

An occupational study of 8,600 Chernobyl clean-up workers reported statistically significant dose–response relationships for several opacity end points based on two blinded ophthalmological examinations administered 2 years apart (*26*). A dose reconstruction was performed to estimate both γ-ray and β-particle doses to the eye lens with some account taken of dose uncertainties (*27*). The median dose was 123 mGy, and 95% had estimated doses <500 mGy. Significant dose–response associations were seen for most of the categories (*28*) of non-nuclear type cataracts: Stage 1 PSC cataracts (OR_{1Gy} = 1.42, CI: 1.01, 2.00), Stage 1 posterior cortical cataracts (OR_{1Gy} = 1.51, CI: 1.09, 2.10), and all (Stage 1–5) non-nuclear cataracts (OR_{1Gy} = 1.65, CI: 1.18, 2.30) (*26*). For Stage 2–5 non-nuclear cataracts, the association was only suggestive (OR_{1Gy} = 1.82, CI: 0.82, 3.72). As expected, no association was seen for nuclear cataracts (OR_{1Gy} = 1.07, CI: 0.56, 2.04). An analysis by age at the time of work at Chernobyl showed a higher radiation risk among those who were younger at exposure (Shore, unpublished, 2009). The analyses were able to adjust for a number of other risk factors for cataract (e.g., age,

smoking, diabetes), but the results should be tempered by the fact that there were substantial uncertainties in estimated lens doses for individuals.

Several recent studies of cataract frequency in relation to radiation dose among A-bomb survivors have been conducted in the Adult Health Study (AHS), which provides biennial clinical examinations to a fixed subcohort of survivors. An ophthalmological screening study (*29*) was conducted of 873 AHS participants, including as many as possible of those under age 14 at exposure and those who had participated in an earlier cataract screening study (*30*). Using a standardized opacity scoring system (*31*), the investigators found statistically significant dose–response associations for posterior subcapsular opacities, with an $OR_{1Gy} = 1.41$ (CI: 1.21, 1.64), and for cortical opacities, with an $OR_{1Gy} = 1.29$ (CI: 1.12, 1.49). Since the lenses were photographed, it was possible to conduct blinded rescoring of the lens photographs by a single ophthalmologist for better standardization; this led to risk estimates virtually identical to those indicated by the original scoring (*32*). In addition, they found greater radiation risk for PSC opacities among those exposed at younger ages. A dose-threshold analysis of those data gave a best estimate of 0.6 Gy (CI: <0, 1.2) for cortical opacities and 0.7 Gy (CI: <0, 2.8) for PSC opacities. The investigators did not observe a statistically significant excess ($P > 0.2$) among those who were exposed *in utero*, but the statistical power for that observation was quite limited.

Since a major question regarding radiation cataract induction pertains to the risk and dose threshold for cataracts that cause visual impairment, a second AHS study examined the prevalence of cataract surgeries among 3,761 study subjects 55–57 years after the bombings, in which 479 surgical-cataract cases were documented (*33*). The study subjects were primarily 0–35 years old at exposure. The analysis examined the association with radiation dose, after adjusting for city, gender, age at exposure (and age at risk), and history of diabetes. A linear model provided a good fit to the data, which was not materially improved by adding a quadratic term. The radiation risk estimate for lens removal surgery was an $OR_{1Gy} = 1.39$ (CI: 1.24, 1.55). There was no indication that age at exposure modified the magnitude of the radiation effect. A key finding was that the dose-threshold analysis showed a best dose-threshold estimate of 0.1 Gy (CI: <0, 0.8 Gy), i.e., the data were compatible with no dose threshold or a threshold up to 0.8 Gy but not higher. A subsequent unpublished analysis of the somewhat enlarged data set (645 persons with surgically removed cataracts among 3,994 examined) yielded a risk estimate very similar to the others reported (Fig. 1) and a best dose-threshold estimate of 0 Gy (CI: <0, 0.7) (Neriishi and Nakashima, unpublished, 2008).

Currently, a cataract-surgery incidence study is being conducted for 1986–2005, the interval in which cataract surgery was systematically recorded in the medical records of AHS participants. The value of an incidence study is that it minimizes the potential biases that might have occurred in the prevalence studies described above; it also permits a better assessment of age- and time-related variables. Preliminary analyses, after potentially adjusting for a large variety of cataract risk factors, show a risk estimate and a dose-threshold estimate very similar to the prevalence data.

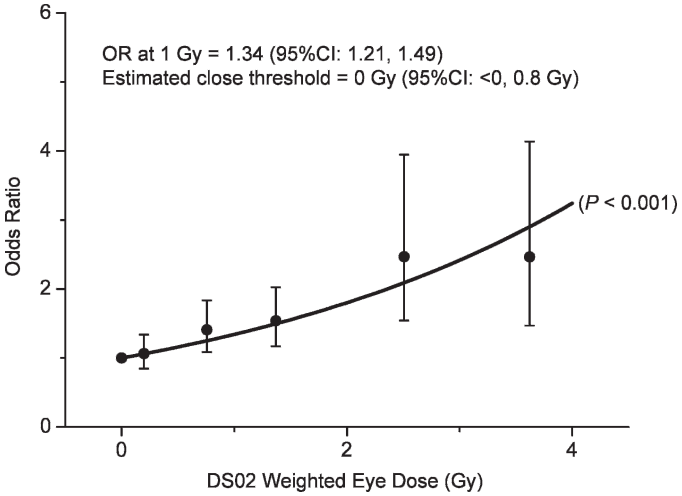

FIG. 1. Prevalence of surgically removed cataracts ($n = 645$ persons) by dose among 3,994 A-bomb survivors in the Adult Health Study, 2000–2002. Adjusted for age, gender, city and history of diabetes.

LOW-DOSE STUDIES

Although the low-dose studies generally had insufficient statistical power to make major contributions to a risk assessment, they may give indications of whether the risk at those doses is generally compatible with the risk estimates derived from higher-dose studies. An ophthalmological screening study of Ukrainian children exposed downwind of the Chernobyl accident, compared with those upwind, showed an excess of posterior subcapsular opacities (OR = 2.8, CI: 1.3, 6.1) in the downwinders with estimated Chernobyl doses of around 30 mGy (*34*). However, because of the voluntary screening-participation process and the fact that the ophthalmologists could not be blinded as to exposure status (which was defined by screening location), potential biases due to self-selection or differential screening sensitivity cannot be ruled out.

A low-dose occupational study of 35,700 U.S. radiologic technologists did not observe a statistically significant dose–response trend for self-reports of either total cataracts ($ERR_{1Gy} = 2.0$, CI: −0.7, 5.7) or surgically removed cataracts ($ERR_{1Gy} = 1.5$, CI: −3.4, 6.4) (*35*). The mean estimated dose was 28 mGy, and the highest dose group was ~60 mGy. However, the excess

risk for total cataracts in the highest dose group was nearly statistically significant (OR = 1.18, CI: 0.99, 1.40). The authors also found that self-reports of the number of diagnostic X rays to the head or neck were associated with the risk of total cataracts but not surgically removed cataracts. Another study, involving an ophthalmological examination of Chinese radiation workers and an unexposed comparison group, suggested a higher risk among the radiation workers (*36*), but insufficient study details are available to fully evaluate the results.

Two studies have retrospectively assessed whether patients with CT scans to the head are at elevated risk for cataracts, but the studies have yielded mixed results. An initial report suggested an association with posterior subcapsular opacities (OR = 1.5, CI: 1.1, 2.0) (*37*), but a second study of approximately the same size did not (OR = 0.9, CI: 0.6, 1.3) (*38*).

STATUS OF RISK ASSESSMENT

A preliminary question to be addressed is whether the existing studies have been able to take into account possible bias or confounding by other risk factors for lens opacities. A number of the main risk factors have been evaluated in various studies, for example, age (all studies), diabetes mellitus (*21, 22, 25, 26, 29, 33–35*), corticosteroid use (*21, 22, 26, 35*), and smoking (*25, 26, 29, 33, 35*). Ultraviolet-radiation exposure was grossly examined by a few studies (*22, 26, 33, 35*), but only the astronaut study had detailed data concerning it (*25*). In general, there is little evidence to suggest that confounding factors have been a serious problem in the studies reported here.

While it clearly would be useful to have more confirming data and studies with fewer limitations, there nevertheless is enough information to make tentative weight-of-evidence judgments regarding several important issues. A first question is whether there is a risk for minor opacities at low to moderate doses to the lens. Several studies with doses primarily below 1 Gy were positive (*20–22*) but did not specifically analyze their data for a dose threshold. Two other studies have directly addressed this question. The Chernobyl clean-up worker study obtained dose-threshold estimates for stage 1 PSC and cortical opacities of about 0.35 Gy, with CI of about 0.2–0.65 (*26*). The A-bomb screening study analyzed a range of opacity severities together, though most were early opacities, and found estimated dose thresholds of 0.6–0.7 Gy for both PSC and cortical opacities, though the wide CI encompassed both no threshold and a rather high threshold (*29*). The similarity in the dose-threshold results between the A-bomb study with a single brief exposure and the Chernobyl clean-up workers with fractionated/protracted exposures is notable. Ainsbury *et al.* (*3*) have also pointed out that protraction of doses does not appear to affect risk significantly. However, more data on this point are clearly needed, because the precision of existing studies is limited.

A secondary question about this end point is whether radiation-associated minor opacities progress to become vision-impairing cataracts. Most of the data on this question are anecdotal, with a suggestion that a fraction of them progress and earlier high-dose studies suggesting that the rate of progression may be dose-related (*39*).

As to the more consequential cataracts causing visual impairment, there is no informative study available of such risk after highly fractionated or protracted exposure, which reflects an important gap in the scientific evidence. The A-bomb study, with a brief exposure, has addressed vision-impairing cataracts by analyzing the prevalence of cataract surgeries in the clinical AHS subcohort. The result, after adjusting for age and other variables, was a dose-threshold estimate of 0.1 Gy (CI: <0, 0.8 Gy) (*33*). A preliminary analysis of cataract surgery incidence in the AHS yielded a similar dose-threshold upper bound (Nakashima and Neriishi, unpublished, 2009). One uncertainty with the A-bomb data comes from basing the analysis on a weighted Gy (γ-ray + 10 $\times$ neutron) dose metric; if the true neutron RBE for cataract were 20 or 30, this could alter the estimated dose threshold but probably not greatly since neutrons constitute only a small fraction of the dose. Based largely on experimental data, the ICRP has tentatively concluded that the RBE for neutron induction of cataracts is in the range 2–20 (*40*).

Another question of import for radiation protection purposes is the degree to which the risk of radiation-associated opacities is modified by age at exposure. Several different studies reported that exposure at an early age confers more risk per unit dose than exposure at a later age (*26, 30, 32, 41*), although other human data have not provided support for this (*33*). Most data sets, however, have had only a limited age range, so arriving at a broad-based answer is difficult.

Although PSC opacities have been considered the classical sentinel effect of radiation on the lens, there are now several studies showing radiation effects for cortical opacities as well (*21, 25, 26, 29*). Various studies, however, have found that nuclear cataracts are not associated with radiation exposure (*21, 25, 26, 29*), with one possible exception being a study of airline pilots (*42*).

Ultimately one would like to ask what biological mechanisms mediate the development of radiation cataracts. This question is beyond the scope of this review, but mention should be made that a lens tissue bank of extracted cataracts from A-bomb survivors has been initiated at the RERF (K. Neriishi, principal investigator) in anticipation of collaborations with various radiobiologists to study mechanistic questions. Environmental co-exposures (e.g. smoking) or genetic factors may affect susceptibility to cataract induction by radiation. For example, a study has shown that

haploinsufficiency of the mrad9 and atm genes confers added susceptibility to radiation cataractogenesis in mice (*43*). It will be of interest to determine whether heterozygous mutations in those or other human genes are involved in radiation cataract susceptibility.

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