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REVIEW

Radiation Cataractogenesis: A Review of Recent Studies

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The lens of the eye is recognized as one of the most radiosensitive tissues in the human body, and it is known that cataracts can be induced by acute doses of less than 2 Gy of low-LET ionizing radiation and less than 5 Gy of protracted radiation. Although much work has been carried out in this area, the exact mechanisms of radiation cataractogenesis are still not fully understood. In particular, the question of the threshold dose for cataract development is not resolved. Cataracts have been classified as a deterministic effect of radiation exposure with a threshold of approximately 2 Gy. Here we review the combined results of recent mechanistic and human studies regarding induction of cataracts by ionizing radiation. These studies indicate that the threshold for cataract development is certainly less than was previously estimated, of the order of 0.5 Gy, or that radiation cataractogenesis may in fact be more accurately described by a linear, no-threshold model.

INTRODUCTION

Cataracts (the opacification of the ocular lens) are the most frequent cause of blindness worldwide (*1*). Besides genetically controlled, congenital cataracts, the prevalence of cataracts increases with age; there are several additional risk factors, including exposure to sunlight, alcohol and nicotine consumption, diabetes and systemic use of corticosteroids (*2–5*). The etiology of cataracts is not fully understood but most likely is multifactorial. Based upon the clinical appearance, three main types can be defined: nuclear, cortical and posterior-subcapsular cataracts (*5, 6*). It is well established that exposure to ionizing radiation leads to the formation of cataracts (*7*). It is generally accepted that radiation damages the dividing cells; the differentiation and migration of the damaged cells to the posterior pole then leads to opacities (*8*). The latent period and the severity of the effects are dependent on age and gender and, with regard to induction by ionizing radiation, are dependent on dose, dose rate and fractionation. After radiation exposure, changes are known to take many years to manifest as visible cataracts (*9*). Moreover, not all changes become clinically relevant. The recent literature suggests that time required for radiation-induced cataract development is approximately inversely proportional to the radiation dose, although it is not always clear whether this reflects improved ability to detect increased risks at higher doses rather than a true difference in the minimum latent period. However, the latent period is also dependent on division and migration rates for epithelial cells. The estimated minimum doses of radiation that are required to cause cataracts vary with study design and methodology. Ionizing radiation is generally (but not exclusively) associated with cortical and posterior subcapsular opacities, with the latter being particularly dependent on dose[2] (*10, 11*). However, it should be noted that, although cortical and posterior cataracts are less common than nuclear cataract, these types of cataracts are also known to occur after treatment with steroids (*12*), and they are observed in the general population (*13*).

The results of several longitudinal studies have led to the conclusion that radiation-induced cataracts are a deterministic, late effect (*14*). In 1996, the UK National Radiological Protection Board (NRPB) published a document regarding the risk from deterministic effects of ionizing radiation in general. Based on the work of Merriam and colleagues in the 1950s (*15*), the minimum

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[2] N. J. Kleiman, L. B. Smilenov, D. J. Brenner and E. J. Hall, Low dose radiation cataract. Presented at the DOE/BER Low Dose Radiation Research Investigators Workshop VII, Washington, DC, January 21, 2008.

dose to produce opacities was estimated to be of the order of 1.3 Gy for acute exposures. Although the document included advice on cataract induction, it was aimed at detailing severe deterministic effects for the purposes of evaluating the consequences of radiation accidents. As such, the document contained a warning that any numbers quoted were given for guidance only (*16*). Similarly, the German Radiation Protection Board (SSK) published a document in 2007 that ranked the tolerance dose for radiation cataracts in the range of 2 Gy but again indicated that this value might be overestimated (*17*). The International Commission on Radiological Protection (ICRP) has also classified cataracts as a deterministic effect, with a threshold of 2 Gy for acute radiation exposure, 4 Gy for fractionated doses, and even higher for long-term exposures (*18, 19*).

However, in recent years, a number of studies have been published that contain evidence that conflicts with the current advice, particularly regarding the tolerance doses and the stated deterministic nature of cataracts. It has been suggested by a number of authors that there was previously too little data regarding cataract development at low doses to form complete judgments (*20*), and that, given the recognized length of the latent period for cataract development, early epidemiological studies were carried out too soon after irradiation for any low-dose effect to be detected.[2] In its most recent recommendations, ICRP (*19*) noted that the lens of the eye may be more radiosensitive than previously thought and that revised judgments may be required. In this paper, we review a number of predominantly recent studies of radiation cataractogenesis that are relevant to this issue and consider their implications.

RECENT PUBLICATIONS

Mechanistic Studies

In 2006, Malmström and Kroger demonstrated that laboratory rodents and primates have similar anatomical characteristics of the eye and thus many of the mechanistic models for cataract development are based on experimental animal studies (*21*). Most of the more recent mechanistic studies have focused on the genetic basis of cataract development. The *ATM*, *RAD9* and *BRCA1* genes are known to be critical to pathways controlling DNA damage response signaling, repair or apoptosis. There is evidence that those with heterozygous mutations of these genes are at increased risk of certain health effects; for instance, they have elevated tissue responses to ionizing radiation and are more susceptible to cancers. Heterozygosity of the *ATM* gene, for example, is estimated to occur in 0.5–1% of the Western population (*22*).

In 2002, Worgul *et al.* investigated the sensitivity of *Atm*-deficient mice exposed to 0.5 to 4 Gy of X rays (*23*). Cataract development was strongly dependent on radiation dose. Opacities were observed earliest in *Atm* homozygotes, but cataracts also developed earlier in heterozygotes compared to wild-type mice for all doses. The severity and latent period were directly related to the number of genomically damaged cells attempting differentiation. Because *Atm* is involved in cell cycle control and pathways to apoptosis, this would indicate that cataracts may be due to defective control of these pathways in response to DNA damage. These results indicate genetic predisposition to cataract development for *Atm* heterozygotes.

Kleiman *et al.* investigated the impact on cataractogenesis of heterozygosity of the mouse *Rad9* and *Atm* genes (*24*). The right eyes of mice were exposed to 0.5 Gy of X rays. Posterior subcapsular opacities were found to develop earlier in X-irradiated double heterozygotes ($Atm^{+/-}/Rad9^{+/-}$) than either of the single heterozygotes, which again developed earlier than in wild-type mice. Interestingly, this trend was mirrored in the unirradiated eyes. Smilenov *et al.* investigated individual genetic susceptibility of cataracts in mice heterozygous for the *Atm*, *Brca1* and *Rad9* genes.[3] Exposure to 0.5 Gy of 250 kVp X rays led to elevated cataract development in double-heterozygote combinations, and cataracts appeared earlier in double heterozygotes. Heterozygosity of the *Atm* and *Brca1* genes resulted in increased resistance to apoptosis and heterozygosity of the *Atm* and *Rad9* genes led to increased resistance to apoptosis and sensitivity to radiation. The above results indicate that the stress response, DNA repair pathways and radiation sensitivity are dependent on genotype and give strong support to a genetic component contributing to cataract development. Furthermore, the above results can all be interpreted to suggest that a stochastic mechanism contributes to cataract development.

Radiation exposures are known to be much higher in space than on the ground, due to the increased complexity of the radiation environment. Worgul *et al.* showed that *Atm* heterozygous mice are also more sensitive to heavy-ion exposure (*25*). Mice were exposed to 325 mGy of 1 GeV/nucleon ^{56}Fe ions. After 35 weeks, 40% of the heterozygotes had developed stage 3 cataracts compared to 5% of wild-type mice. In 2008, Kleiman *et al.* reported that as well as 325 mGy ^{56}Fe ions, exposures as low as 100 mGy X rays led to a statistically significant increase in cataract development in rodents.[2]

With regard to time scale, Wolf *et al.* recently reported that for mice exposed to 11 Gy X rays to the head, cataracts initially developed over a delayed period, 5–11 months, but then matured within a very short time scale,

[3] L. B. Smilenov, N. J. Kleiman, H. B. Lieberman, G. Zhou and E. J. Hall, Individual genetic susceptibility. Presented at the DOE/BER Low Dose Radiation Research Investigators Workshop VII, Washington, DC, January 21, 2008.

of the order of 30 days (*28*). Descendents of the damaged (and superficially repaired) lens epithelial cells were found to differentiate and migrate abnormally. It was postulated that this resulted in critical uptake of environmental oxygen to the lens. This leads to a buildup of reactive oxygen species, overwhelming the resident antioxidant protection and causing the coagulation of lens proteins, and thus cataract formation. The findings of this study suggest that irradiation of the lens leads to premature development of cataracts that would otherwise be seen in old age.

Human Studies

In recent years, it has been suggested that the minimum dose required for cataract formation could be much less than the 1.3- or 2-Gy thresholds given by NRPB (*16*), SSK (*17*) and ICRP (*18, 19*). The data used to make the previous estimates were principally from the Hiroshima and Nagasaki atomic bomb survivors, highly exposed workers, and radiotherapy patients. Difficulties in dose estimation in these cases have been attributed to inadequate data (*20*). Subsequently, more accurate estimations of dose have been carried out. A number of reanalyses dealing with this point are detailed in this review.

Figure 1 gives the Odds Ratio (OR) or Relative Risk (RR) estimated at 1 Gy or 1 Sv for each of seven recent studies investigating longitudinal risk of cataract development for three exposure groups: those undergoing diagnostic radiography or radiation therapy in a clinical setting, the Chernobyl liquidators and the atomic bomb survivors, and occupational exposures. Additionally, two studies are included in Fig. 1 for which odds ratios or relative risks were calculated based on comparisons of exposed and unexposed groups [Chodick *et al.* (*11*) and Rafnsson *et al.* (*38*)], rather than specifically at 1 Gy or 1 Sv. These two studies were included to allow comparisons between the calculated risks for the large atomic bomb survivor data set and exposure due to clinical X rays (*11*) and for pilots (*38*), for which there are few data. The studies included in Fig. 1 are discussed individually below. Table 1 gives further details of these studies, including the cataract type, classification scheme, and details of the study subjects.

1. Clinical exposure

In 1999, Hall *et al.* looked at the prevalence of lenticular opacities in individuals in Sweden exposed to ionizing radiation in childhood as treatment for skin hemangioma and examined correlations with dose and other factors (*27*). A total of 484 exposed subjects and 89 controls, all aged 36–54 when the survey took place, were included in the study. Radiation doses were estimated using individual treatment records and measurements in a phantom (*28*). There was an increased prevalence of lens opacities in subjects who had

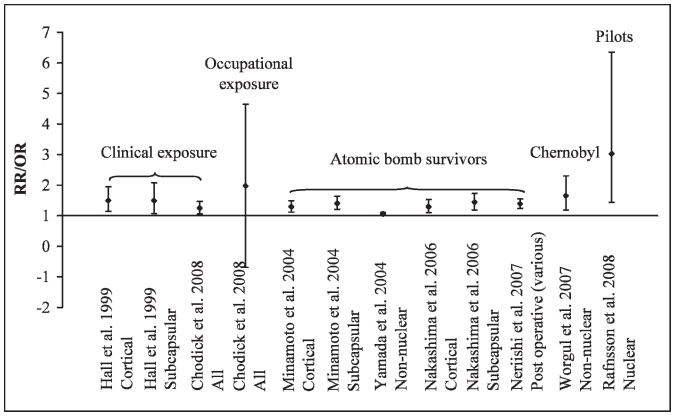

FIG. 1. Odds ratio or relative risk for cataract development at 1 Gy or 1 Sv or for comparisons of exposed and unexposed groups (see text for details), by study, cataract type and exposure group.

undergone radiotherapy as children: 37% compared to 20% of controls; this result was statistically significant ($P << 0.001$). For posterior and subcapsular cataracts, 10% of the 178 control lenses showed cataracts. There were 748 lenses with exposures <0.5 Gy; 12% of these lenses had cataracts. The numbers in exposure categories 0.5 to 1 Gy and >1 Gy were 17% of the 115 exposed and 22% of the 89 exposed, respectively. Of these, only the number of cataracts for the category >1 Gy was statistically significantly different from the control value (t test $P = 0.025$). No distinction was made between types of radiation exposure, and no details of fractionation schedule were available. There was some indication of a combination of age-at-exposure and dose effects. When corrected for age at examination, the OR for 1 Gy was calculated as 1.50 [95% confidence interval (CI): 1.15 to 1.95][4] for posterior cortical cataracts and 1.49 (1.07 to 2.08) for subcapsular cataracts.

Within a separate group of skin hemangioma patients in Sweden, Wilde and Sjostrand investigated the occurrence of posterior subcapsular and cortical cataracts in response to irradiation of the lens (*9*). The cohort consisted of 20 adults who were treated as infants (mean age 6 months) for skin hemangioma in the eyelid or surrounding tissue with ^{226}Ra. Times since irradiation were between 30 and 45 years. The authors found a higher than expected sensitivity of untreated lenses, with subcapsular opacities observed for estimated doses in the region of 0.1 Gy.

Several studies have looked at cataracts in relation to diagnostic radiation exposures. Most recently, Chodick *et al.* explored the risk of cataracts from personal diagnostic radiation for a group of U.S. Radiation Technologists (*11*). A cohort of 35,705 people was followed over an average of 19.2 years. The risk of cataract was found to increase by 15% per year. There

[4] Henceforth 95% confidence intervals are given in parentheses after the OR/RR.

TABLE 1
Individual Study Details for the Eight Studies that Estimated Odds Ratios or Relative Risks for Cataract Development at 1 Gy or 1 Sv, or Comparisons of Exposed and Unexposed Groups

	Study details		
Paper	Cataract type	Classification scheme	Exposure type
Hall *et al.*, 1999 (*27*)	Cortical Subcapsular	LOCS	Clinical; mean lens dose 0.4 Gy, range 0 to 8.4 Gy
Chodick *et al.*, 2008 (*11*)	All	Self reported	Clinical; ≥3 Gy X rays Occupational; 0 to ~60 mGy
Minamoto *et al.*, 2004 (*32*)	Cortical Subcapsular	LOCS	Atomic bomb survivors; DS86 dose estimates: 0 to 2 Gy
Yamada *et al.*, 2004 (*33*)	Non-nuclear	'Cataract' ICD code from AHS database	Atomic bomb survivors; DS86 dose estimates: 0 to 3+ Gy
Nakashima *et al.*, 2006 (*10*)	Cortical Subcapsular	LOCS	Atomic bomb survivors; DS02 mean dose 0.522 Sv, range 0 to 4.940 Sv
Neriishi *et al.*, 2007 (*34*)	All	Post operative	Atomic bomb survivors; DS02 dose estimates: 0 to 3+ Gy
Worgul *et al.*, 2007 (*36*)	Non-nuclear	Stages 1 (discrete opacity) to 5 (mature cataract)	Chernobyl liquidators; 0 to 1 Gy
Rafnsson *et al.*, 2005 (*38*)	Nuclear	WHO (*48*)	Occupational; calculated dose ranges: 0 to 0.48 Sv

Notes. OR = odds ratio; RR = relative risk; LCL = lower 95% confidence limit; UCL = upper 95% confidence limit; LOCS = lens opacities classification scheme (*47*); ICD = International Classification of Diseases; AHS = Adult Health Study.
[a] Hazard ratio.
[b] Excess relative risk.

was a statistically significantly elevated occurrence of cataracts for subjects who had undergone a large number of clinical X rays (>25) compared to less than five X rays, with an OR of 1.4 (1.2 to 1.7). Three or more X rays to the face and neck region also carried an elevated risk [OR 1.3 (1.1 to 1.5)]. However, the analyses were based on self-reported questionnaires with no clinical confirmation, and no information was given regarding X-ray dose or type of opacity. The linear excess relative risk per gray for occupational exposure was calculated to be 1.98, but this was not statistically significant (−0.7 to 4.7).

Smaller studies that examined cataract in relation to self-reported exposures from CT scans have shown either no association (*21*) or an association for posterior subcapsular cataracts at relatively low doses of the order of 0.1 to 0.3 Gy (*30, 31*). However, the potential bias due to the use of self-reported exposures in these studies needs to be considered.

2. Atomic bomb survivors

In 2004, two studies were published looking at the Japanese A-bomb survivors. Minamoto *et al.* carried out eye examinations on survivors who were <13 years old at exposure, 55 years after exposure (*32*). They used a grading system to assist in the standardization of classification of cataracts. Data for 873 adults from Hiroshima and Nagasaki were investigated with a model taking account of age, sex, city, radiation dose and smoking status. Of these survivors, 451 were exposed to <0.005 Gy, 190 to 0.005 to 0.5 Gy; 89 to 0.5 to 1 Gy, and 52 to 1 to 2 Gy. For cortical and subcapsular cataracts, the corresponding ORs at 1 Gy were 1.29 (1.22 to 1.49) and 1.41 (1.21 to 1.64), respectively. The authors found no association for nuclear cataracts [OR at 1 Gy = 1.1 (0.9 to 1.3)]. Yamada *et al.* looked at a large range of non-cancer diseases in A-bomb survivors, based on long-term follow-up over the period 1958–1998 (*33*). A total of 975 males and 2509 females were investigated for cataracts. The results were given as incidence rates, standardized to the Japanese population of 1985. The authors found a statistically significant positive dose response for cataracts ($P = 0.026$). At 1 Gy, the average excess disease rate was 7.98 (0.95 to 15.16) per 10,000 persons per year. The corresponding RR was 1.06 (1.01 to 1.11). The RR decreased to a statistically significant extent with increasing age at examination ($P < 0.001$) and possibly with increasing time since exposure ($P = 0.09$). The RR at 1 Gy was increased to 1.08 for the most recent decade. There was less evidence of a trend in the RR with age at exposure. The authors found no evidence of a dose threshold. The contrasting nature of these results to previous cataract findings was attributed to the length of time cataracts take to develop.

Nakashima *et al.* published a reanalysis of the A-bomb cataract data in 2006 (*10*). The authors tested the fit of the threshold model in an updated data set using the most recent DS02 dosimetry system and found a statistically significant dose effect that decreased with increasing age. The odds ratios per Sv were 1.44 (1.19 to 1.73) for posterior subcapsular opacities and 1.30 (1.10 to 1.53) for cortical opacities after exposure at 10 years of age. No statistically significant effects were found for nuclear opacities. Odds

TABLE 1
Extended

Study details					
Age at exposure	Sample size	Time since exposure	OR/RR	LCL	UCL
Childhood (<18 months)	573 total, 484 exposed	Various between 36 and 54 years	1.50	1.15	1.95
			1.49	1.07	2.08
Adulthood	Cohort of 35,705	Cohort followed for an average of 19.2 years	1.25[a]	1.06	1.47
			1.98[b]	−0.69	4.65
Childhood (<13 years)	873 cases	~55 years	1.29	1.12	1.49
			1.41	1.21	1.64
Not specified	3,484 cases	~40 years	1.06	1.01	1.11
Childhood (<13 years)	873 cases	~55 years	1.30	1.10	1.53
			1.44	1.19	1.73
Range 0–20+	3,282 controls, 479 cases	~55 years	1.39	1.24	1.55
Adulthood	8,607 total	12 to 14 years	1.65	1.18	2.30
Adulthood	445 total, 71 cases	Working life (age 50+ at study onset)	3.02	1.44	6.35

ratios increased with increasing dose for both posterior subcapsular and cortical opacities. The threshold dose was estimated to be 0.6 Sv. However, this result was not statistically incompatible with a threshold of 0 Sv.

In 2007, Neriishi *et al.* published a study investigating dose response for clinically significant cataracts (*34*). A total of 3761 A-bomb survivors and 479 postoperative cataract cases were included, with the data corrected for city, age, sex and diabetes. There was evidence for a linear, but not linear-quadratic, dose response. The OR for postoperative cataracts was 1.39 (1.24 to 1.55) at 1 Gy. The authors observed no statistically significant increase at <0.5 Gy and attributed the lack of statistically significant findings to the lack of subjects in this exposure category. Threshold analysis was carried out, and the estimated threshold dose was 0.1 Gy. The data were not compatible with a threshold dose above 0.8 Gy and were statistically compatible with the lack of a threshold.

3. Chernobyl

In 1995, Day *et al.* published an analysis of the prevalence of lens changes in children residing in the Chernobyl area (*35*). A group of 1787 children was included in the study, 996 of whom were classified as exposed. Small but statistically significant excesses of subclinical posterior subcapsular lens changes ($P = 0.0005$) and posterior subcapsular lens opacities ($P = 0.005$) were recorded. The results were strongly suggestive of a normal distribution of severity of effects around a threshold. Because the pediatric lens is known to be more sensitive than the adult lens, the authors concluded that this threshold should be smaller than the threshold of <1 Gy that had been suggested in the literature for adults.

Worgul *et al.* recently published an analysis of cataract prevalence in a cohort of Ukrainian Chernobyl liquidators (clean-up workers) who were assessed between 12 and 14 years after exposure (*36*). A total of 8607 subjects were included in the study, with age at exposure, age at examination, gender, dose in 50-mGy intervals, smoking status, diabetes and a number of other potentially confounding factors included in the model. Cataracts were split into a number of stages to standardize classification. There were statistically significant increases for non-nuclear (posterior subcapsular and cortical) stage "1 to 5" cataracts: the OR for 1 Gy was 1.65 (1.18 to 2.30), and the dose threshold for these cataracts was calculated to be 0.50 (0.17 to 0.65) Gy. The authors found that the data were incompatible with a dose threshold >0.70 Gy.

4. Occupational exposure

Jacobsen investigated cataract occurrence in 97 retired workers in the U.S. who had been exposed to actinides (*37*). Posterior subcapsular cataracts were reported in 37.5% of workers who had recorded lifetime doses of between 200 and 600 mSv, in contrast to 15% with recorded lifetime doses of less than 200 mSv. Logistic regression was used to calculate an odds ratio for posterior subcapsular cataracts of approximately 1.4 per 100 mSv and a doubling dose of 250 mSv (100 to 500 mSv). Some other studies of occupational exposure are considered later.

5. Commercial and space flight

In addition to the above, there is a body of research exploring the incidence of lens opacities in commercial airline pilots and astronauts. Pilots have increased ionizing radiation exposure from solar particle events and galactic cosmic radiation as well as the secondary events associated with these (*38*). Space radiation has

somewhat different characteristics from those of terrestrial radiation; astronauts are exposed to a mixture of high-energy protons and heavy ions as well as secondary particles produced in collisions with the craft and the astronauts themselves.

In 2001, Cucinotta *et al.* investigated the risk of cataract development amongst NASA astronauts (*39*). For 222 astronauts who had had one or more flights, 48 cases of lens opacification were recorded. The authors found that there was an increased risk of cataracts amongst astronauts. Number of flights (2 or more compared to 0 or 1), age and inclination of flight (relevant because of a higher flux of heavy ions at higher inclinations) were all statistically significant factors. Hazard ratios for ages 60 and 65 years were calculated to be 2.35 (1.01 to 5.51) and 2.44 (1.20 to 4.98), respectively, for lens dose from space radiation only. Doses from personal thermoluminescence dosimeters were used to lead to the assertion that the threshold for cataract development is of the order of 8 mSv; however, no formal threshold analysis was carried out. UV radiation was identified as a potential confounder. While most of the cataracts recorded in this study were not clinically significant, the authors pointed out that early cataracts increase the risk of development of more severe cataracts at a later stage. Some discussion also considered the possible increase in the effects of heavy-ion radiation due to fractionation of the type experienced by astronauts carrying out multiple missions.

In 2005, Rafnsson *et al.* investigated whether employment as a commercial airline pilot was associated with an increased incidence of lens opacities, based on a case-control study of Icelandic pilots (*38*). Controls were those with no opacity or with other types of cataract. Employment time, annual hours flown, time-table and flight profile, and cumulative radiation dose calculated from the above information were included in the analysis. Of four cataract types (nuclear, cortical, central optical zone-based and posterior subcapsular), only occurrence of nuclear cataracts was found to be statistically significantly increased for ever-pilots compared to those who had never been pilots, with an OR of 3.02 (1.44–6.35). Age was found to be a statistically significant factor [OR 1.17 (1.12–1.22)], with cumulative dose up to age 40 and up to age 50 both being statistically significant factors. The results suggest that pilots develop cataracts at a younger age than non-pilots. There was also some evidence of a dose–response relationship, but the numbers of cases in each dose quartile were very low. Interestingly, UV-radiation exposure during flight was not discussed as a potential risk factor. However, recent work suggests that there is a connection between nuclear cataract and UVA radiation (*40*).

Jones *et al.* investigated cataract incidence among astronauts and U.S. Air Force and Navy pilots (*41*). The authors found that U.S. Air Force and Navy flight personnel develop cataracts at a statistically significantly younger age than astronauts ($P < 0.005$ and < 0.001, respectively), even when the figures are adjusted for age of entry and time in service. The biophysical, biochemical, physiological and cellular mechanisms of cataract development are discussed in detail in the paper, and the possibility that radiation is a stronger risk factor than either commercial flight altitude and polar aviation route radiation or surface UV radiation is proposed.

6. *Protracted exposure*

Finally, an unusual opportunity for studying chronic exposure to low-dose-rate γ radiation occurred with the incorporation of radiocontaminated steel into residential and civilian buildings in Taiwan in the 1980s. Chen *et al.* examined the occurrence of opacities in 114 members of the exposed population (*8*). Doses were calculated by age group and were of the order of 0–8 mSv. A dose-dependent statistically significant increase in minor focal lens defects (those not likely to impair visual acuity) was recorded for those subjects aged 3–20 years old ($P = 0.027$). Dose dependence was also observed for the other age groups (20–40 years and 42–65 years), but the results were not statistically significant. The results suggest that chronic low-dose irradiation is an independent risk factor for minor lenticular changes, especially in young people. Importantly, the data also indicate that protraction of the exposure over long periods does not substantially increase the threshold dose. This is in line with the findings of Chodick *et al.* (*11*).

DISCUSSION AND CONCLUSIONS

The most recent mechanistic studies of radiation-induced cataract have concentrated on the genetic components of DNA damage response and repair pathways. There is demonstrable evidence for a genetic component of cataract development, for instance in heterozygosity of the *Atm*, *Rad9* and *Brca1* genes (e.g. *23*). Although the majority of the studies summarized here involved mice, the fact that heterozygosity of some of these genes is observed in humans indicates that a subsection of the population could be genetically predisposed to cataract formation. This is supported by differences in cataract formation in populations with different ethnic backgrounds, e.g. Asian and European (*42, 43*) or European and African (*44*). The mechanistic studies also indicate that low doses of heavy ions may initiate cataract formation; work is ongoing in this area (e.g. *6*). Finally, there is evidence from the animal studies that exposing the lens to ionizing radiation leads to premature development of cataracts that would otherwise be seen in old age (*26*).

With regard to the epidemiological studies, there are difficulties in the literature with the methods of classifi-

cation of cataracts; for instance, several authors differentiated between posterior subcapsular and cortical opacities, Worgul *et al.* (*36*) defined stages of cataracts, whereas Neriishi *et al.* simply defined a clinically significant cataract as one that was removed surgically (*34*). In the past, the LOCS system in its various versions has been widely used by ophthalmologists; however, it needs further standardization to achieve interobserver agreement (*45*). Pei and colleagues (*46*) published details of the Pentacam Scheimpflug system, which provides a quantitative and objective method for classification of lens opacities, because the results are independent of the observer. It is suggested that in future studies, a single classification scheme such as this one should be used universally for studies of radiation-induced cataracts. This would allow investigators in the clinical and epidemiological settings to overcome existing difficulties arising from the variation in classification schemes. Validation of the existing data should also be carried out.

Several studies analyzed the prevalence of cataracts at a single time after irradiation, whereas to study incidence, it would be necessary to monitor the population over time. Furthermore, the study designs vary, and it is difficult to know whether there might have been any selective reporting of results, in particular, whether an absence of increased cataract risks might not have been reported in some small studies. However, Fig. 1 and Table 1 illustrate that, from the studies summarized here, most of the recent analyses had an OR/RR greater than 1. This would appear to indicate that there is a strong likelihood of an association between exposure to ionizing radiation of the order of 1 Gy and initiation or development of the various different types of cataracts and in each of the exposure situations. For the studies investigating lower doses, only Cucinotta *et al.* (*39*) *a*nd Chen *et al.* (*8*) found statistically significant associations with doses less than 0.5 Gy. With regard to the A-bomb survivors and Chernobyl data, the difficulties in finding statistically significant associations with doses of the order of 1 Gy or less may be attributed to insufficient data. For instance, in 2007, Chumak *et al.* (*47*) carried out Monte Carlo analyses of estimated dose for a cohort of 8607 Chernobyl clean-up workers. The authors estimated that only 4.4% of workers received exposures greater than 0.5 Gy and the median lens dose was 123 mGy.

The concept of threshold has been cited as critical to many of the theories regarding the mechanisms of cataract development (*6*). The threshold level may be particularly important for exposure during early childhood. The importance of age at exposure is evident in a number of the studies considered here, and in particular for posterior subcapsular opacities, Hall *et al.* (*27*) found an increased risk of the order of 50% for 1 Gy exposure to the lens during childhood, and Nakashima *et al.* (*10*) calculated an odds ratio of 1.44 at 1 Sv for exposure at 10 years, which decreased to a statistically significant extent with increasing age at exposure ($P = 0.022$).

In recent years there has been an apparent reversal in the consensus in the literature regarding the development of cataracts in response to exposure to ionizing radiation. In much of the recently published literature, the estimated threshold for cataract development has tended to decrease with increasing times from irradiation for the cases in the major epidemiological data set: the A-bomb survivors. Authors have attributed this reversal to the extended period of latency that is common for cataracts: Studies with short follow-up periods may still be within the latent period and thus fail to identify early lens defects, thus recording incorrect rates of cataract development.[2] However, it may also be the case that, with the longer follow-up and identification of larger numbers of cases, the statistical precision to detect raised risks at lower doses has increased. Three recent studies have carried out formal threshold analyses: Nakashima *et al.* (*10*) calculated a threshold of 0.6 Sv for atomic bomb survivors, Neriishi *et al.* (*34*) calculated a threshold of the order of 0.1 Gy and $\leq$0.8 Gy for a similar data set, and Worgul *et al.* (*36*) calculated a threshold of $\leq$0.7 Gy for Chernobyl liquidators. Although calculation methods varied by author and data set, none of these studies found estimated thresholds greater than 1 Gy, and all formal calculations produced results that were statistically compatible with the complete lack of a threshold. Cucinotta *et al.* (*39*) and Chen *et al.* (*8*) found statistically significant increases of opacities associated with very low doses, of the order of 8 mSv; however, these studies did not include formal threshold analyses. All the above estimates are considerably lower than the previous NRPB (*16*), SSK (*17*) and ICRP (*18, 19*) respective recommendations for thresholds of 1.3 and 2 Gy of acute radiation. Furthermore, the protraction of doses in occupationally and environmentally exposed cohorts does not appear to affect risk to a statistically significant extent (e.g. *8, 11*). These results, coupled with the mechanistic studies demonstrating that mice carry defects in DNA damage response genes, suggest that cataracts may in fact develop through a process that conforms with a linear, no-threshold type model.

In conclusion, much of the science is contradictory, and it is therefore very difficult to reach a firm conclusion between a threshold and a no-threshold dose response for cataract formation, which is likely to be a multifactorial process. Values of threshold doses are subject to statistical uncertainty and depend on the severity or stage of the cataract and also on the cataract type. From the more recent data, the threshold dose for cataract formation may be judged to be in the region of 0.5 Gy of low-LET radiation. It is also possible that cataract induction could be treated as a non-threshold phenomenon, with a doubling dose that may be of the order of $\sim$2 Gy. A

precise figure would need to be determined by formal calculations, which are beyond the scope of this current work. It should be noted that threshold and doubling dose figures may be dependent on a number of factors, including variation in background levels of cataract development with genetic background, age, gender, lifestyle, latent period, time since diagnosis and dose rate and/or fractionation. It is clear that more work is required to verify the findings and judgments presented here and the biological implications of the linear, no-threshold response. This could be achieved by implementation of a systematic screening program for people exposed occupationally to ionizing radiation. Perhaps the most important requirement is to obtain more evidence from mechanistic studies concerning the existence of a threshold. At present, while DNA damage responses have been identified as important, it is not clear whether a mutational mechanism, or one based on lens cell function, differentiation, cell killing and/or mode of death, is operating. The former would suggest a no-threshold approach, while the latter would likely favor a judgment of a relatively low threshold. It is suggested that mechanistic studies should now focus on the identification of animal strain-dependent differences and additional mouse mutants. Where possible, reanalyses of the previous data should also be carried out using the more sophisticated methods that have been developed and in the light of recent work.

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