

Ionizing Radiation as a Risk Factor for Cataract: What about Low-Dose Effects?

Sophie Jacob^{1*}, Morgane Michel¹, Antoine P. Brézin², Dominique Laurier¹ and Marie-Odile Bernier¹

¹Institute of radiation protection and nuclear safety (IRSN), DRPH, SRBE, LEPID Laboratory of Epidemiology, Fontenay-aux-Roses, France

²Paris Descartes University APHP Centre Cochin Ambulatoire d'Ophthalmologie, Paris, France

Abstract

Lens opacities are potential serious consequences of eye exposure to ionizing radiation. Several studies have shown with certainty that radiation cataractogenesis has a much lower threshold than the old radiation protection guidelines of the International Commission on Radiological Protection (ICRP), specifically 2 Gy (Grays) for acute exposure and 5 Gy for fractionated exposure. In April 2011, the ICRP revised its eye dose threshold for cataract induction downwards from 2 Gy to 0.5 Gy, and the occupational annual dose limit from 150 mSv to 20 mSv/year. Moreover, based on previous studies the traditional view that posterior subcapsular opacities are the only signature form of radiation cataract may have to be broadened to cortical cataracts.

We present the most recent results on lens opacities and early stages of cataract that were observed for ionizing radiation doses below 1 Gy and which have led the ICRP to decrease the eye lens dose threshold.

Keywords: Ionizing radiation; Cataracts; Lens opacities

Introduction

The radiosensitivity of the ocular lens to high doses of ionizing radiation is well known and posterior subcapsular lens changes are characteristic of radiation exposure [1-3]. However, considerable uncertainty still surrounds the relationship between radiation dose and cataract development, without omitting the baseline knowledge that cataract is an eventual result of aging. Moreover consequences of eye exposure to ionizing radiation in terms of radiation-induced lens opacities are an important concern. In April 2011, the International Commission on Radiological Protection (ICRP) revised its eye dose threshold for cataract induction downwards from 2 Gray (Gy) to 0.5 Gy as well as the maximum occupational annual lens dose of workers exposed to ionizing radiation from 150 milliSievert (mSv) to 20 mSv/year [4] following the results of recent studies which suggest that the lens may be more radiosensitive than previously considered. But the current radioprotection system still considers that radiation-induced cataracts appear only if a dose threshold is exceeded (deterministic effect) whereas several epidemiological and experimental studies suggest a stochastic hypothesis (non-threshold/zero threshold effect). Moreover, some epidemiological studies have reported that both posterior subcapsular and cortical opacities – and possibly nuclear cataracts – were associated with radiation exposure [5-7], broadening the traditional view that posterior subcapsular opacities are the only signature form of radiation cataract.

In this article, we present an overview of the physiopathology of radiation-induced cataracts and a review of the main epidemiological results which have led to question the possible implication of lower doses of ionizing radiation exposure in the early development of cataracts resulting in the decreased ICRP dose threshold.

Genotoxic Basis Mechanism as Main Hypothesis for Radiation-Induced Cataract

The eye is considered to be a relatively radiosensitive organ, mainly because of the development of radiation-induced cataracts. Typically, radiation cataract initially manifests itself as a defect in the transparency of the superficial posterior subcapsular sector of the lens where the accumulation of abnormally differentiated progeny of the germinative

cells of the lens epithelium leads to its development. Proliferation of epithelial cells and migration of the abnormal cells to the posterior part of the lens is responsible for the formation of subcapsular opacities, basis for the early stage of radiation-induced lens opacification. The opacities appear after a latent period, inversely related to the received dose. Their appearance is also correlated with the rate at which damaged lens epithelial cells divide, aberrantly differentiate and migrate to the posterior pole [8].

Although the mechanism of radiation-induced cataract is not precisely known, several hypotheses have been advanced. The main hypothesis considers that the observed cellular modifications of the epithelial cells of the lens are linked to genomic damage. Indeed, genomic damage of the cells resulting in altered cell division, transcription and/or lens fibre cell differentiation is compatible with the well known genotoxicity of the ionizing radiation [9]. Epithelial cells in the germinative zone are the most likely targets for radiation-induced damage to the DNA. Metabolic alterations leading to oxidative stress appear to be one of the earliest events in the pathogenesis of the radiation-induced cataract. Unrepaired DNA damage to the lens epithelium due to oxidative stress has been hypothesized to be responsible for the cataract formation process [9]. Apoptotic pathways of epithelial cells linked to radiation are also suspected, but not clearly demonstrated in *in vitro* or *in vivo* studies.

Animal models confirm the impact of ionizing radiation on DNA damage repair. Animals with mutated genes involved in DNA damage

***Corresponding author:** Sophie Jacob, Institute of radiation protection and nuclear safety (IRSN), DRPH, SRBE, LEPID Laboratory of Epidemiology, BP17, 92262, Fontenay-aux-Roses Cedex, France, Tel: +331.58.35.74.27; Fax: +33 1.46.57.03.86; E-mail: sophie.jacob@irsn.fr

Received December 01, 2011; **Accepted** February 29, 2012; **Published** March 05, 2012

Citation: Jacob S, Michel M, Brézin AP, Laurier D, Bernier MO (2012) Ionizing Radiation as a Risk Factor for Cataract: What about Low-Dose Effects? J Clin Exp Ophthalmol S1:005. doi:10.4172/2155-9570.S1-005

Copyright: © 2012 Jacob S, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

repair such as Atm, Brca1 and rad9 were exposed to radiation and those studies observed an enhanced sensitivity of these animals to radiation-induced cataract formation [5,10-12]. The role of these genes in the cell cycle and during DNA repair is consistent with a genotoxic basis for radiation cataractogenesis. The observation of radiation-induced cataracts in rats or mice for doses as low as 100 mGy [11] suggests that the threshold dose for cataract induction could be much lower than expected even in humans, since those animal models mimic closely the human response to radiation.

There is no direct mechanistic evidence that a single damaged cell can give rise to a cataract, which would be the hallmark of a stochastic effect with zero thresholds. However, there is evidence of the importance of cell division and proliferation in the formation of cataracts. It can be speculated that radiation cataract formation could be explained by initial damage to single progenitor epithelial cells in the lens which, upon cell division and differentiation, result in groups of defective lens fibre cells [3]. Future research may elucidate the true mechanism of cataract formation.

Review of Epidemiological Studies

This review focuses on the risk of lens opacities after exposure to low and medium radiation doses (less than 5 Gy), either internal or external. The literature search was conducted from the Medline and Scopus database. The following headings were identified: “lens opacities” “cataract” “radiation effect” “dose-response relationship, radiation”. When several studies concerned the same population, only the most recent was taken into account. The estimation of the dose was based on the absorbed dose to the organ expressed in Gray (Gy) or the equivalent dose expressed in Sievert (Sv), these two units being equivalent for external exposure to β , γ and X-radiation. The exposure could be acute in the case of survivors of Hiroshima-Nagasaki, fractionated for medical exposure or chronic in case of occupational exposure. Estimation of the dose received by the lens varied among the studies. No exact measure with dosimeters recording exposure to the lens was ever carried out, leading to uncertainties in estimating the dose received. Even for populations subjected to radiation monitoring, like nuclear workers or radiologists, the dose to the lens had to be extrapolated from the dose registered by the chest dosimeter or by taking into account the type of occupational exposure. For the survivors

of Hiroshima and Nagasaki, the dose estimation was mostly based on a subject’s distance to the source of radiation (DS 86). In the medical field, the exposure was approximated by the number of examinations carried out or reconstituted with dosimetric phantoms. In some cases, no quantification of exposure was available. Depending on the design of the studies, results on the risk of lens opacities were expressed with either Odds Ratio (OR) or Relative Risk (RR) or Hazard Ratio (HR), which are comparable criteria to quantify risk.

Environmental exposure

Hiroshima and Nagasaki survivors: Several studies were conducted on cataract prevalence and threshold in atomic-bomb survivors, using the Adult Health Study cohort as a reference sample for people exposed in Hiroshima and Nagasaki (see Table 1).

Otake and Schull [13] first evaluated the relationship of γ rays and neutrons to the occurrence of posterior lenticular opacities. They used the DS86 dosimetry to evaluate the doses, which allowed them to make an estimation of the eye organ dose. 1,983 subjects were included in their study, focusing especially on the 71 cases of posterior subcapsular opacities diagnosed in 1963-1964. Other types of lens opacity were not taken into account and the children exposed *in utero* were excluded from the analysis. The subjects’ mean age at exposure was 29.3 years in Hiroshima and 23.4 years in Nagasaki. The DS86 eye organ dose ranged from <0.01 to >6 Gy, with 66.9% and 72.8% of the subjects exposed to less than 1 Gy in Hiroshima and Nagasaki respectively. They used no known classification to grade lens modification, choosing to score them as ‘equivocal’, ‘minimal’, ‘small’, ‘moderate’ and ‘large’. Their analysis found an estimated γ threshold of 0.73 Gy and an estimated neutron threshold of 0.06 Gy. The 95% upper bound of the confidence interval was 1.39 Gy for γ rays.

The Adult Health Study cohort was re-examined between 2000 and 2002, providing new information on that population 55 years after exposure. Minamoto et al. [14] used those examinations to study the relationship between lens changes and radiation dose in A-bomb survivors. They also assessed the effect of various cataract risk factors on radiation-induced cataract (including other ophthalmological findings, environmental and host factors and laboratory tests identifying potentially relevant conditions) and searched for intermediate risk factors for lens opacities. Out of the 4,058 people still alive in 1999, 913

Hiroshima & Nagasaki	Minamoto et al. 2004 [14]	Nakashima et al. 2006 [15]
Number of subjects	873 (143 exposed in utero)	730
Mean age at exposure	8.8 years	10.5 years (median)
Mean age at eye examination	64.8 years	66.6 years (median)
Time lag since exposure	55 years	55 years
Eye lens dose	<0.05 Gy to >2 Gy (84% < 1Gy)	79% < 1Gy
Results	OR/1Gy=1.41 (1.21-1.64) (PSC) OR/1Gy=1.29 (1.12-1.49) (CC) Not significant for others	OR/1Gy=1.44 (PSC) OR/1Gy=1.3 (CC) thresholds=0.7 (PSC) and 0.6 Gy(CC) not significantly different from 0 Risk of PSC decreases with increasing age at exposure
Tchernobyl / Taiwan	Day et al. 1996 [16]– Children in contaminated territories of Chernobyl	Chen et al. 2001 [17] – Populations exposed to contaminated building in Taiwan
Number of subjects	E=996,NE=791	114
Mean age at eye examination	5-17 years	24.8 years
Cumulated dose	-	161.9 mSv
Results	3.6% of PS ocities for E vs. 1.1% for NE (p<0.0005) Boys 12-17 years ++, absorption of local vegetables	Significant increase of lens opacities, dose-response relationship for < 20 years subjects (p=0.027)

PSC: posterior subcapsular cataract; CC: Cortical cataract; E: exposed; NE: Not exposed

Table 1: Studies on environmental exposure.

agreed to participate and 873 were analyzed in the study. The subjects were examined by an ophthalmologist who graded lens modifications according to the Lens Opacities Classification System II (LOCS II) which details nuclear opacities, nuclear colour, cortical opacities and posterior subcapsular opacities. Age at the time of the bombing ranged from -0.8 (exposition *in utero*) to 37.9 (mean = 8.8 years), while age at the time of the examination ranged from 54.3 to 94.4 (mean = 64.8 years). The DS86 eye dose (or the dose to the mother's uterus for the 143 subjects exposed *in utero*) varied from < 0.005 to 2 Sv (mean = 0.405 Sv). ORs at 1 Sv associated with the distribution of cases were statistically significant for cortical opacities (1.29, CI 95% = 1.12 – 1.4) and posterior subcapsular opacities (1.41, CI 95% = 1.21 – 1.64). Regression analysis adjusted on other risk factors showed that ORs at 1 Sv in cortical and posterior subcapsular opacities were still significant and 1.34 and 1.36 respectively.

Nakashima et al. [15] then reanalyzed Minamoto's data to try and establish threshold radiation doses for cortical and posterior subcapsular opacities since they were the only ones for which the dose main effects were significant. They used the same subjects as in the previous study, focusing on the 730 who had been exposed after birth and separating them from the 143 who had been exposed *in utero*. The median ages at the time of the exposure and examination were 10.5 and 66.6 years respectively. The photographs taken during Minamoto's study were re-diagnosed by a single ophthalmologist using LOCS II. The mean radiation dose was 0.522 Sv, ranging from 0 to 4.94 Sv. The authors found a threshold dose point of 0.6 Sv for cortical cataracts and 0.7 Sv for posterior subcapsular cataracts. Neither differed significantly from 0. They both showed a significant dose effect with an OR per Sv of 1.3 for cortical cataract, which had no dose-effect modifiers. On the other hand, the dose effect for posterior subcapsular cataract decreased significantly with increasing age at exposure with an OR per Sv of 1.64 for those exposed between 0 and 10 years, 1.32 Sv for the 10-20 years group and non-significant for those over 20 years old. They observed no dose response for the *in utero* survivors.

Chernobyl children: A study conducted by Day et al. [16] investigated the prevalence of lens changes between exposed children in contaminated territories of Chernobyl and non-exposed children. The study was carried out in 1992 in 2 contaminated territories and in 1 non-contaminated territory. 996 exposed children and 791 non-exposed children between 5 and 17 years of age were examined by several trained ophthalmologists who classified the lesions according to the LOCS III classification. A slit lamp examination on dilated eyes was performed. Lens and retinal photographs were taken when lesions were observed. Minor lens changes such as vacuoles, flakes or dots were observed in more than three quarters of the children, both exposed and non-exposed. Many of these lesions were below the scoring threshold of the LOCS III standards. A greater frequency of PSC opacities at both the category 1 and ≥ 2 levels was observed in the exposed group compared to the non-exposed group (2.8 % vs 1.0 %, $p = 0.0048$). Lens modifications tended to occur more frequently in older boys and in children who consumed locally grown and contaminated mushrooms on a regular basis. The study is in favour of an association between PSC lens changes and exposure to ionizing radiation. Nevertheless, this study was not able to separate the effect linked to the acute exposure to ionizing radiation during the days or weeks immediately following the accident from long term exposure secondary to living in contaminated territories. The unexpected excess of minor lens changes observed in both exposed and non-exposed children may be the result of secondary environmental exposure (diet, pollution, pesticides) that are common to rural farming areas of Ukraine.

Contaminated buildings: Chen et al. [17] studied the effect of chronic low-dose gamma radiation on populations exposed to buildings contaminated with ⁶⁰Co in their daily living. 114 individuals were included in the cohort, with a mean age of 24.8 years. Each was examined by an ophthalmologist who was blinded to the dose received. Lenticular opacities were graded using both the LOCS III and the Focal Lens Defect System (FLD, for minor, subclinical lenticular changes in the cortical and/or nuclear portion of the lens). The dose-equivalent exposure was reconstructed based on living history and field measurements taken in the living environments of the subjects. That dose was deemed representative of dose-equivalent levels to the eye lens for people living in apartments with high radiation levels. The mean cumulative dose was 161.9 mSv. They analysed the data by age group: those under 20 years old, those between 20 and 40 and those older than 40 years old. The potential confounding factors considered were steroid treatment, history of diabetes mellitus or previous eye disorder, and long-term outdoor sunlight exposure. They found that LOCSIII was not sensitive enough to address a dose-related lenticular change because up to 100% of the younger subjects presented a clinically undetectable change. However, when using the FLD System they found a significant dose-response relationship for those under 20 years of age ($p=0.027$). The results were non-significant in the other two groups ($p=0.825$ and 0.868). Those results suggest that chronic low-dose gamma irradiation is an independent risk factor for minor lenticular changes in young subjects and the radiation-associated effect is much milder in populations older than 20 years old.

Medical exposure

Treatment of benign diseases: Two separate Sweden studies have investigated the relationship between irradiation of the skull during infancy in case of skin haemangioma located on the head and cataract formation. The main study by Hall et al. [18] concerned a cohort of roughly 16,500 children younger than 18 months of age, treated for 89% of them by radiotherapy. From the initial cohort, 483 individuals treated by radiotherapy for a facial haemangioma and 89 controls not treated by radiotherapy were subjected to an ophthalmologic examination more than 30 years after treatment, which means the age at the time of the examination ranged from 36 to 54 years. Lens opacities were scored according to the LOCS. Dose to the lens was calculated using distance, prescribed dose and fractionation, taking a shielding factor into consideration. The mean age at exposure was 5 months and the mean dose 0.4 Gy (0-8.4). There was a significant increase of lens opacities in the treated group (37%) compared to the control group (20%). When adjusting for age at examination, dose rate and steroid treatment, children exposed to a lenticular dose of 1 Gy had a 50% increased risk (odds ratio = 1.49, 95% CI = 1.07-2.08) of developing a posterior subcapsular (PSC) opacity. A significant increased risk was also observed in case of cortical opacities (odds ratio = 1.50, 95% CI = 1.15-1.95). An interaction between age at treatment and dose was suggested only for PSC opacities, where the prevalence increased with dose only among those less than 4 months old at the time of treatment (see Table 2).

The second study dealt with a cohort of 20 adults, treated before the age of 6 months by radium irradiation for skin haemangioma of the eyelid [19]. A high prevalence of light to moderate PSC and cortical cataract formation was found in the lenses on the treated side irradiated with a mean dose ranging from approximately 1 to 8 Gy. The cataract formation increased as a function of dose. They also noted the presence of subcapsular punctate opacities and vacuoles in the lenses on the untreated side which had received an estimated dose around 0.1 Gy.

Therapeutic purpose - Radiotherapy for skin hemangioma	Wilde et al. 1997 [19]	Hall et al. 1999 [18]
Number of patients	20	E=484; NE=89
Median age at exposure	6 months	< 18 months
Mean age at eye examination	31-46 years	E=46 years; NE=42 years
Eye lens dose	0.02 – 0.12 Gy (non treated side)	0.4 Gy (90% < 1Gy)
Results	13 cases with lens opacities, increase of prevalence with increasing doses	37% of lens opacities E vs. 20% for NE OR/1Gy=1.49 (1.07-2.08) (PSC) OR/1Gy=1.50 (1.15-1.95) (CC)
Diagnostic purpose – Examinations involving X-rays	Klein et al. 1993 [20]	
Number of subjects	4926 adults	
Mean age at eye examination	43-84 years	
Results	Brain scan and PSC: OR=1.45 (1.08-1.95) Brain scan and NC: OR=1.28 (1.02-1.61)	

PSC: posterior subcapsular cataract; CC: Cortical cataract; NC: Nuclear cataract; E: exposed; NE: Not exposed

Table 2: Studies on medical exposure.

Diagnostic examinations: A study was carried out in the Beaver Dam Eye Study to investigate the relationship between X-ray exposure and the incidence of lens opacities [20]. 4,926 adults between the age of 43 and 84 years old at the time of the ophthalmic examination were questioned as to whether they had ever had diagnostic X-ray exposure. The assessment of lens opacities was carried out through photographs of the lens performed after dilatation of the pupils. Any cortical opacity was considered to be positive for this lesion while only PSC cataract involving more than 5% of that lens area was taken into account. No dosimetric quantification of the lens irradiation was performed. X-ray exposure was assessed through a questionnaire at the time of the examination. After adjusting for age and sex, PSC opacity was significantly associated with a history of head CT scan (OR = 1.45, 95% CI = 1.08-1.95). No other type of X-ray examination was associated with an increased risk. However, the fact that they also found that nuclear opacities were associated with head CT scan (OR = 1.28, 95% CI = 1.02-1.61) raises the question of a potential confounder, nuclear cataract not being usually associated with radiation exposure.

Occupational exposure

Nuclear workers – chernobyl liquidators: A cohort of 8,607 Ukrainian Chernobyl clean-up workers was assessed for cataract 12 and 14 years after exposure [12]. They had been exposed between April '86 and December '87. Two separate ophthalmologic examinations were performed after pupil dilatation and the ophthalmologists were blinded as to lens doses. Lens changes were classified according to the semi-quantitative scoring technique developed by Merriam and Focht [21]. In early lens changes were included the appearance of a “polychromatic sheen” or “beaten brass”, dots or vacuoles located either in the PSC region or anywhere in the superficial cortex. Lens β and γ particle doses were estimated from several sources: individual recorded doses, group doses, calculated doses for a given work detail and estimates derived from tooth enamel electron paramagnetic resonance for a set of 104 workers [22]. The mean ages at exposure and at first and second examination were respectively 32.7, 44.9 and 47 years. More than 80% of the studied population was under 40 years at the time of exposure. The median estimated lens dose was 0.12 Gy, ranging from 0 to 0.8 Gy. More than 90% of the population has doses less than 0.4 Gy. Posterior subcapsular or cortical opacities were present in 25% of the subjects. Odds ratios were calculated according to the category of dose. They were adjusted on age at exposure, age at first examination, clinic performing the examination, sex, smoking status, diabetes mellitus, corticoid or phenothiazine use, other chemical occupational exposure, ionizing radiation (other than Chernobyl), infrared and ultraviolet

radiation. Subjects exposed to a lenticular dose of 1 Gy had a 70% increased risk (odds ratio = 1.70, 95% CI = 1.22-2.38) of developing a cataract, mostly stage 1 cataract (odds ratio = 1.49, 95% CI = 1.08-2.06). Early PSC changes and stage 1 PSC cataract were also increased at 1 Gy (odds ratio = 1.89, 95% CI = 1.25-2.84 and 1.42, 95% CI = 1.01-2.00, respectively). Nuclear cataracts which are not thought to be associated with radiation exposure were not increased (OR = 1.07, 95% CI = 0.56-2.04). According to the dose category, both PSC and cortical cataracts showed suggestive or significant increases in risk from 0.5 Gy. Significant increased risks in the category of smaller doses, i.e. 0.1 to 0.249 Gy, were observed for both PSC (OR = 1.28 95% CI = 1.1-1.5) and posterior capsular early changes (OR = 1.24 95% CI = 1.1-1.4). Maximum likelihood estimates of the dose-effect threshold ranged from 0.34 to 0.50 depending on the type of cataract, with all confidence interval excluding values of dose greater than 0.7 Gy (see Table 3).

Astronauts and pilots: A cohort of 295 NASA astronauts was analyzed by Cucinotta et al. [23]. It included all past and present astronauts since 1977 and followed them for 30 years at mean and aged from 35 to 70 years old. To assess exposure, personal-badge doses and lens equivalent doses were used. Depending on the missions, average lens dose due to cosmic radiation ranged from 0.2 mSv to 91 mSv. Among the 295 astronauts, 48 developed cataracts of different types, in particular 20 cortical, 8 nuclear and 5 posterior subcapsular cataracts were diagnosed. The comparison of the <8 mSv group (mean=3.6 mSv) to the > 8 mSv group (mean=45 mSv) showed a higher risk for the most exposed group (HR = 2.44 95% CI=1.2-5.0 for any type of cataract). Increased number of nuclear cataracts and posterior subcapsular/nuclear and mixed cataracts were also observed in the higher exposure group (HR = 3.44 CI95%=1.1-11.1 and HR=3.37 CI95%=1.3-9.1 respectively). Moreover, posterior subcapsular cataracts presented a high hazard ratio (HR=5.76 95%CI=1.0-34.2) even if it did not reach statistical significance.

Another small German study was performed on 21 former astronaut volunteers for whom the Scheimpflug technique was applied in order to assess minor opacities in the posterior capsule [24]. Age ranged from 40 to 69 years, half of the population being more than 50 years old. A cohort of 395 German Air force employees (both pilots and ground personnel) aged 81 years old at maximum was considered as reference group. The results indicated that most opacities values for posterior cortex region were above the average values of the reference cohort in most of the astronauts (ref).

The NASCA study (NASA study of cataract in astronaut) included

Chernoby liquidators	Worgul et al. 2007 [12]		
Number of subjects	8607		
Mean age at exposure	32.7 years		
Mean age at eye examination	44.9 years then 47 years		
Time lag since exposure	12 and 14 years		
Median eye lens dose	123 mGy (94%<400 mGy)		
Results	OR/1Gy=1.70 (1.22-2.38) (any type) OR/1Gy=1.42 (PSC) Not significant for CC Increased risk above 0.5 Gy Threshold: 0.34 to 0.5 Gy according to the type, maximum 0.7 Gy		
Astronauts	Cucinotta et al. 2001 [23]	Chylack et al. 2009 [25]	Rastegar et al. 2005 [24]
Number of subjects	295	171 (control group=247)	21 (control group=395)
Eye lens dose	0.2-91 mSv	15.1-129.3 mSv	-
Results	HR=3.73 (p=0.012) high doses Vs. low doses for PSC, NC or mixed at 60 yrs. HR=3.44 for NC alone at 65 yrs.	Significant increase of CC (p=0.015)	OR=3.02 (1.44-6.35) for NC
Airline pilots	Rafnsson et al. 2005 [26]		
Number of subjects	79 pilots; 366 non pilots		
Cumulated dose	0 - 48 mSv		
Results	Association with NC, not with tobacco or UVB; no eye lens dose; doses>50 years not considered		
Radiology technicians	Chodick et al. 2008 [27]		
Number of subjects	35,705		
Mean age at exposure	24-44 years at inclusion		
Mean age at eye examination	Followed for 20 years		
Median eye lens dose	28.1 mGy		
Results	ERR/1Gy=1.98 (ns) HR high doses (60mGy) vs. low doses (5mGy) =1.18 (0.99-1.4)		
Interventional cardiologists	Vano et al. 2010 [29]	Ciraj-Bjelac et al. 2010 [30]	
Number of subjects	58 IC; 93 NE	56 IC; 22 NE	
Mean age at eye examination	IC=46 years; NE=41 years	IC=42 years; NE=44 years	
Range eye lens dose	0.1-27 Gy	0.02-43 Gy	
Results	OR for PSC=3.2 (38%vs 12%)	OR for PSC=5.7 (52% vs. 9%)	

PSC: posterior subcapsular cataract; CC: Cortical cataract; NC: Nuclear cataract; E: exposed; NE: Not exposed; IC: Interventional cardiologists

Table 3: Studies on occupational exposure.

171 astronauts having flown at least once compared to 247 individuals (astronauts without flight in space, ground personnel) [25]. Data was collected between 2004 and 2006. Nearly half of the astronauts had a cumulative space lens dose above 10 mSv. Eye examination combined LOCS III and Nidek EAS 1000 digitized images and allowed for continuous measure of nuclear, cortical and PSC lens opacities. The result indicated a significant higher risk of PSC for astronauts exposed to higher space radiation doses (OR = 2.23 95%CI=1.2-4.3). Results were less clear for cortical opacities and no association was found between space radiation and nuclear cataracts.

Only one case-control study was performed on pilots by Rafnsson et al. [26]. It included 71 cases aged 74.6 years at mean and 374 controls aged 66.1 years at mean of the population in Reykjavik. All the participants had an eye examination and lens opacities were graded with the World Health Organisation (WHO) classification. There were 21% of pilots in the case group as compared to 17%. Nuclear, cortical and posterior subcapsular lens opacities were considered. No eye lens dose was available, but the effective radiation dose for pilots was obtained from a detailed employment questionnaire and eyes lens dose was then calculated with specific software. This study found an association between cumulative exposure and the risk of nuclear cataract (OR = 1.02 95%CI = 1.00-1.03) but no association with cortical or posterior subcapsular cataract. These results remain isolated and controversial because of the advanced mean age of the case group compared to the control one.

Radiology technicians: Chodick et al. [27] analyzed a cohort of 35,705 US radiology technologists aged between 24 and 44 years and followed between 1983 and 2004. No specific eye examination was performed and each participant had to declare diagnosis of cataract. During the study period, 2,382 cataracts and 647 cataract extractions were reported by participants. To assess exposure, information on occupational history combined with passive dosimetry (badges) was used. Eye lens doses ranged from 0 to more than 60 mGy and the median dose was estimated to 28.1 mGy. Survival analysis allowed to observe that the risk of cataract was higher in most exposed technicians (mean=60 mGy) compared to less exposed workers (mean=5 mGy) with HR = 1.2 95%CI = 1.0 – 1.4. This result was even more significant if the cataract occurred before 50 years.

Interventional radiologists and cardiologists: Mrena et al. [28] studied the prevalence of lens opacities among 57 physicians from Helsinki, occupationally exposed to radiation (including some interventional radiologists). They all had an eye examination and LOCS 2 was used to grade nuclear, cortical and posterior subcapsular lens opacities. Mean age at eye examination was 58 years. No eye lens dose was available but passive dosimetry was used as an index of eye exposure. At all, 8 individuals had nuclear opacity, 3 had cortical opacity and 2 had posterior subcapsular ones. Considering both cortical and posterior opacities and excluding nuclear opacities, the authors found an association with cumulative dose.

Vano et al. [29] published a study including 58 interventional

cardiologists (mean age=46 years), 58 nurses and technicians (mean age=38 years) from Bogota and Montevideo and 93 unexposed controls (mean age=41 years). All participants had an eye examination during a cardiology conference and Merriam-Focht classification was used to grade posterior subcapsular lens opacities. Eye lens dose for exposed individuals was assessed retrospectively using occupational questionnaire and doses per procedure. Compared to the unexposed group, interventional cardiologists presented a high risk of cataract (38% vs. 12%, RR = 3.2 95%CI = 1.7-6.1) whereas the result was not significant for nurses (21% vs. 12%, RR = 1.7 95%CI = 0.8-3.7).

Another study with the same design as Vano's was published by Ciraj-Bjelac et al. [30]. They included 56 Malaysian interventional cardiologists with a mean age of 42 years, 11 nurses (mean age=38) and 22 unexposed controls (mean age=44). Cumulative eye lens doses were assessed retrospectively and ranged from 0.01 to 43 Gy, with a median value of 1.0 Gy. In this study, a significant excess risk of posterior subcapsular lens opacities was found for both interventional cardiologists and nurses compared with unexposed group (52% vs. 9%, RR=5.7 95%CI=1.5-22, and 45% vs. 9%, RR=5.0 95%CI=1.2-21, respectively). Moreover, when considering cumulative eye dose a strong dose-response relationship was observed.

In France, the multicenter cross-sectional O'CLOC study (Occupational Cataracts and Lens Opacities in interventional Cardiology) was performed between October 2009 and April 2011 [31]. 106 interventional cardiologists and 99 unexposed workers were included. They all had a medical questionnaire to collect information on potential confounders of lens opacities and all had an eye examination including LOCS 3 classification of lens opacities. Cardiologists also had an occupational questionnaire to describe their past and present activity in catheterization laboratory. Preliminary results showed that there was no significant difference between both groups for nuclear and cortical lens opacities. However posterior subcapsular lens opacities were significantly more frequent among interventional cardiologists (17% vs. 5%, $p = 0.006$) [32]. Further analyses still have to be performed, in particular to take into account workload, radiation protection equipments and cumulative eye lens dose.

Discussion

We reviewed 18 studies analyzing the effect of low doses of radiation on the lens. Out of the 17 studying the association between risk of posterior sub-capsular cataract and low doses of radiation, 15 found an association. Out of the 14 discussing the risk of cortical cataract, 4 found a significant association and for the 12 studying nuclear cataract, only 1 found an association. However, the comparison of the risks observed in these studies remains difficult because of methodological issues.

The absence of a uniformed grading system for cataract is a first difficulty. In the various publications, the diagnosis of lens opacities was made using different methods leading to uncertainties in the assessment of the disease. Otake et al. [13] for example did not use a standard classification for cataract in order to diminish diagnostic error. The very small number of actual cataracts is another limit of this study, as is the fact that this study chose to focus entirely on posterior subcapsular opacities. A comparison with other non radiation-induced cataracts would have been welcomed to eliminate potential confounding factors. In contrast, Minamoto's study [14] used a standardized classification to grade cataract and each type of lens opacity was separated during the statistical analysis. In Nakashima's study [15] they also separated the different types of lens opacities. Moreover, the fact that a single

ophthalmologist reviewed all the diagnoses is one of the study's strong suits. In Day's study [16], reliability of the lesions assessment was not very good between ophthalmologists despite examiner training and other quality-control measures, with strong evidence for a statistically significant incremental linear learning effect across the 3 field sites leading to an under-assessment during the initial phase of the field research. Among interventional cardiologists, only posterior subcapsular lens opacities was previously investigated, which may appear as a limit [29,30]. The use of standard classification as LOCS 2 or 3 for eye lens classification, as it was done in the NASCA study [25] and many others, is nevertheless a good approach to investigate the impact of ionizing radiation on different types of cataracts. However, even if these findings were difficult to compare, our review confirms that posterior subcapsular opacities are characteristic of radiation exposure. Moreover, we observed that cortical cataracts may also be regarded as radiation-induced. Only one case-control study on pilots found an exclusive association with nuclear cataracts [26] and these results remain isolated and controversial because of the advanced mean age of the case group compared to the control one. This study highlighted the difficulty to consider both that cataract is an eventual result of aging and that the individuals with the highest exposure may be older as well.

Previous ocular guidelines presumed that a minimum dose of 2 Gy to the lens in case of a single exposure and 5 Gy for fractioned or protracted exposure was required to produce a detectable cataract [3]. As a consequence, eye lens dosimetry is another important challenge in studies on radiation-induced cataracts. Since no exact measure with dosimeters recording exposure to the lens was carried out in any of these studies, dose uncertainties remain. According to the results of the performed studies, estimation of dose received by the lens markedly varied and in some cases the knowledge of exposure level was not even available as was the case for Chernobyl children [16]. In Otake et al. and Minamoto et al. [13,14], the studies' main advantage was the use of the eye organ dose which allows an estimation of the dose received by the lens. In Worgul et al. [12], uncertainties on the estimated doses remain an important limit of the paper, even if the impact of dose uncertainty on the results was assessed. In medical staff studies, doses were either based on passive dosimetry (chest badge) [28] which may not be a good index for eye lens exposure, especially when radiation protection eyewear is used, or based on description of workload in terms of procedures and mean doses per procedure, which may suffer from memory bias [29-31]. However, radiation-induced cataracts have been globally observed in different exposed populations at lower doses (< 1 Gy) than the expected dose threshold of 2 Gy.

Recent findings also challenge the deterministic model (threshold effect) used for radiation-induced cataract, questioning the presence of a threshold dose and leaning towards a stochastic effect (non threshold effect). Indeed Nakashima et al. found that the threshold dose for cortical and posterior subcapsular cataract was 0.6 and 0.7 Sv respectively, yet neither was statistically different from 0, which led them to wonder whether there was indeed a threshold or not [15]. In any case, if that threshold does exist several arguments seem to indicate that it would probably be under 1 Gy: Worgul reports a significant threshold of 0.35 Gy for posterior sub-capsular cataracts (CI95% = [0.19; 0.66]), which is much lower than the traditional 2 Gy [12]. It also raises new questions as to the radioprotection of the lens for the chronically exposed populations.

Based on these results, the ICRP decided to revise the old thresholds to the new value of 0.5 Gy [4]. Future research from both animal

models and human exposed populations are necessary to ascertain the mechanisms through which radiation induces cataract formation and whether it is stochastic or deterministic.

At a microscopic level, if a minimum number of damaged cells are required before a lens opacity is clinically observed, that would suggest a requirement for a threshold radiation dose and therefore radiation cataract could be classified as a deterministic effect. On the other hand, radiation cataract formation could be explained by initial damage to single lens epithelial cells, which upon cell division and differentiation result in groups of defective lens fibre cells, all of which are progeny of a single damaged progenitor lens epithelial cell. In this case, radiation cataract development would be stochastic [3]. Support for the stochastic theory of radiation cataract development is provided by a number of epidemiological and experimental studies presented here.

Conclusion

Several studies have assessed with certainty that radiation cataractogenesis has a much lower threshold than the old radiation protection guidelines, specifically 2 Gy for acute exposure and 5 Gy for fractionated exposure. Lens opacities or early stages of cataract have been observed for doses less than 1 Gy, which in turn has led the ICRP to decrease the threshold to 0.5 Gy. Further studies focused on populations at risk such as children subjected to head CT scans or interventional radiology practitioners have to be developed in order to assess the impact of low to moderate doses of radiation.

References

1. ICRP (1991) The 1991 Recommendations of International Commission on Radiological Protection. In: ICRP Publication 60. Oxford: Pergamon Press.
2. UNSCEAR (2006) United Nations Scientific Committee on the Effects of Atomic Radiation - Volume I: Report to the General Assembly, Scientific - Annexes A and B.
3. ICRP (2007) The 2007 Recommendations of International Commission on Radiological Protection. In: ICRP Publication 103. Oxford: Elsevier.
4. ICRP (2011) International Commission on Radiological Protection - Statement on tissue reaction. In: ICRP ref 4825-3093-1464.
5. Kleiman N (2007) Euratom, Radiation protection 145 - New insights in radiation risk and basic safety standards. *Radiation cataract* 81-95.
6. Ainsbury EA, Bouffler SD, Dorr W, Graw J, Muirhead CR, et al. (2009) Radiation cataractogenesis: a review of recent studies. *Radiat Res* 172: 1-9.
7. Shore RE, Neriishi K, Nakashima E (2010) Epidemiological Studies of Cataract Risk at Low to Moderate Radiation Doses: (Not) Seeing is Believing. *Radiat Res* 174: 889-894.
8. Worgul BV, Merriam GR, Szechter A, Srinivasan D (1976) Lens epithelium and radiation cataract. I. Preliminary studies. *Arch Ophthalmol* 94: 996-999.
9. Worgul BV, Merriam GR Jr, Medvedovsky C (1989) Cortical cataract development—an expression of primary damage to the lens epithelium. *Lens Eye Toxic Res* 6: 559-571.
10. Worgul BV, Smilenov L, Brenner DJ, Junk A, Zhou W, et al. (2002) Atm heterozygous mice are more sensitive to radiation-induced cataracts than are their wild-type counterparts. *Proc Natl Acad Sci U S A* 99: 9836-9839.
11. Worgul BV, Smilenov L, Brenner DJ, Vazquez M, Hall EJ (2005) Mice heterozygous for the ATM gene are more sensitive to both X-ray and heavy ion exposure than are wildtypes. *Adv Space Res* 35: 254-259.
12. Worgul BV, Kundiyeve YI, Sergiyenko NM, Chumak VV, Vitte PM, et al. (2007) Cataracts among Chernobyl clean-up workers: implications regarding permissible eye exposures. *Radiat Res* 167: 233-243.
13. Otake M, Schull WJ (1990) Radiation-related posterior lenticular opacities in Hiroshima and Nagasaki atomic bomb survivors based on the DS86 dosimetry system. *Radiat Res* 121: 3-13.
14. Minamoto A, Taniguchi H, Yoshitani N, Mukai S, Yokoyama T, et al. (2004) Cataract in atomic bomb survivors. *Int J Radiat Biol* 80: 339-345.
15. Nakashima E, Neriishi K, Minamoto A (2006) A reanalysis of atomic-bomb cataract data, 2000-2002: a threshold analysis. *Health Phys* 90: 154-160.
16. Day R, Gorin MB, Eller AW (1995) Prevalence of lens changes in Ukrainian children residing around Chernobyl. *Health Phys* 68: 632-642.
17. Chen WL, Hwang JS, Hu TH, Chen MS, Chang WP (2001) Lenticular opacities in populations exposed to chronic low-dose-rate gamma radiation from radiocontaminated buildings in Taiwan. *Radiat Res*, 156: 71-77.
18. Hall P, Granath F, Lundell M, Olsson K, Holm LE (1999) Lenticular opacities in individuals exposed to ionizing radiation in infancy. *Radiat Res* 152: 190-195.
19. Wilde G, Sjostrand J (1997) A clinical study of radiation cataract formation in adult life following gamma irradiation of the lens in early childhood. *Br J Ophthalmol* 81: 261-266.
20. Klein BE, Klein R, Linton KL, Franke T (1993) Diagnostic x-ray exposure and lens opacities: the Beaver Dam Eye Study. *Am J Public Health* 83: 588-590.
21. Merriam GR Jr, Focht EF (1962) A clinical and experimental study of the effect of single and divided doses of radiation on cataract production. *Trans Am Ophthalmol Soc* 60: 35-52.
22. Chumak VV, Worgul BV, Kundiyeve YI, Sergiyenko NM, Vitte PM, et al. (2007) Dosimetry for a study of low-dose radiation cataracts among Chernobyl clean-up workers. *Radiat Res* 167: 606-614.
23. Cucinotta FA, Manuel FK, Jones J, Iszard G, Murrey J, et al. (2001) Space radiation and cataracts in astronauts. *Radiat Res* 156: 460-466.
24. Rastegar N, Eckart P, Mertz M (2002) Radiation-induced cataract in astronauts and cosmonauts. *Graefes Arch Clin Exp Ophthalmol* 240: 543-547.
25. Chylack LT Jr, Peterson LE, Feiveson AH, Wear ML, Manuel FK, et al. (2009) 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* 172: 10-20.
26. Rafnsson V, Olafsdottir E, Hrafnkelsson J, Sasaki H, Arnarsson A, et al. (2005) Cosmic radiation increases the risk of nuclear cataract in airline pilots: a population-based case-control study. *Arch Ophthalmol* 123: 1102-1105.
27. Chodick G, Bekiroglu N, Hauptmann M, Alexander BH, Freedman DM, et al. (2008) Risk of cataract after exposure to low doses of ionizing radiation: a 20-year prospective cohort study among US radiologic technologists. *Am J Epidemiol* 168: 620-631.
28. Mrena S, Kivela T, Kurttio P, Auvinen A (2011) Lens opacities among physicians occupationally exposed to ionizing radiation—a pilot study in Finland. *Scand J Work Environ Health* 37: 237-243.
29. Vano E, Kleiman NJ, Duran A, Rehani MM, Echeverri D, et al. (2010) Radiation cataract risk in interventional cardiology personnel. *Radiat Res* 174: 490-495.
30. Ciraj-Bjelac O, Rehani MM, Sim KH, Liew HB, Vano E, et al. (2010) Risk for radiation induced cataract for staff in interventional cardiology: Is there reason for concern? *Catheter Cardiovasc Interv*. *Catheter Cardiovasc Interv* 76: 826-834.
31. Jacob S, Michel M, Spaulding C, Boveda S, Bar O, et al. (2010) Occupational cataracts and lens opacities in interventional cardiology (O'CLOC study): are X-Rays involved? Radiation-induced cataracts and lens opacities. *BMC Public Health* 10: 537.
32. Jacob S, Laurier D, Bernier MO (2011) Occupational cataracts and lens opacities in interventional cardiology (O'CLOC study). *Acta Ophthalmol* 89: 0 (abstract).

This article was originally published in a special issue, **Cataract** handled by Editor(s). Dr. Line Kessel, University of Copenhagen, Denmark