Radiation-induced Cataracts

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The eye lens: a radiosensitive tissue

Therefore:

ICRP regulations 1990 und 2007:

Detectable opacities: 0.5-2 Gy (total dose received in a single exposure)

5 Gy (total dose received in fractionated exposure)

>0.1 Gy/y (annual dose per year, fractionated exp.)

Visual impairment (cataract) 5 Gy (total dose received in a single exposure)

>8 Gy (total dose received in fractionated exposure)

>0.15 Gy/y (annual dose per year, fractionated exp.)

Are these thresholds acceptable?
I. The lens

II. General aspects of (human) cataracts

III. Radiation-induced cataracts in human

IV. Radiation-induced cataracts in mice

V. Elements of future studies
The Lens (2)

**Early eye development and maturation:**

in mice: E9.5 – E12.5

eye opening 2 weeks after birth

in humans: week 5 – 7

eye opening in 7th month of gestation

Cataracts – congenital and age-related

a) congenital: mutation in \textit{CRYBB2} gene

\textbf{frequency:} \(~1:10.000\) (dominant disorder)

b) age-related cataract

Posterior-subcapsular cataract

granular opacities in the posterior pole of cortex adjacent to the posterior capsule.

\textbf{Risk increased by:}

intraocular inflammation, steroid administration, vitreo-retinal surgery, trauma, \textbf{irradiation}, diabetes.
Cataracts:
Increase by age
Induction by environmental factors:
No „all-or-nothing“
Rather: earlier than later
Validated Cataracts in the KORA Eye Study:

- Validated Lens Opacities (101 cases)
  - nuclear cataract 34
  - cortical cataract 27
  - subcapsular cataract 12
  - posterior cataract 11
  - anterior cataract 4
  - total cataract 2
  - No detailed diagnosis 33

(multiple answers possible)

Graw et al., in prep.
The Lens Opacity Classification System (LOCS-III)

Fig 5.—The LOCS III standards. This set of standards is prepared as a set of slides for grading standardized photographic images of opacity. The five or six individual standard slides for the cataract type or nuclear color being graded are projected at the same size as the slides of unknown opacity. NO1 to NO6 and NC1 to NC6 are the standards for nuclear opalescence and nuclear color, respectively. C1 to C5 are the standards for cortical cataract, and P1 to P5 are the standards for posterior subcapsular cataract.

Chylack et al., 1993
Risk factors for cataract:

- age
- female sex
- diabetes
- UV-radiation
- ionizing radiation
- smoking?
- alcohol?
- diet? vitamins?
- Genetic predisposition?
- Ethnic background?
Cataract therapy: Surgery

Side effect: 20-40% of cataract surgery develop postoperative cataract within 2-5 years

Avasti et al., 2009)
Radiation-induced cataracts in humans
Nefzger et al., 1969: “posterior subcapsular changes in the lens have been a consistent finding in A-bomb survivors”

Otake and Schull, 1996

FIG. 2. Occurrence rate of cataracts by DS86 mean equivalent dose and 35% random-dose error based upon an assumed neutron RBE of 10.

FIG. 5. Relative risk of cataracts and two thresholds for the epilation group and the no-epilation group based on DS86 eye organ equivalent dose (RBE = 10) and 35% random-dose error, using 1105 individual exposed in Japanese houses.

Questions: Age-distributions of cataracts? Population control?
Posterior subcapsular opacity dose response (n = 691)

OR/Sv = 1.44 at 10 yrs of age at exposure

Posterior subcapsular opacity (n = 691)

OR/Sv vs age at exposure

Cortical cataract dose response (n = 701)

OR/Sv = 1.30

No threshold !!

Differences to previous work:
- including cataract surgery
- including diabetics
- including higher age at examination
- different dose assessment

Question again: Population control?
Chernobyl Liquidators

8607 Persons
90% younger than 55 years at 1st examination
(weak age-dependence)

ophthalmic examination:
25% suffer from cataract !!

Adjustment to all major risk factors

Reference group: 0-99 mGy

Worgul et al., 2007
### Chernobyl Liquidators

**Odds ratios for dose ranges**

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR at 1 Gy (reference)</th>
<th>0–99 mGy</th>
<th>100–249 mGy</th>
<th>250–399 mGy</th>
<th>400–599 mGy</th>
<th>600–799 mGy</th>
<th>800+ mGy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early pre-cataract changes</td>
<td>1.15</td>
<td>1.0</td>
<td>1.19</td>
<td>1.12</td>
<td>1.16</td>
<td>0.85</td>
<td>1.07</td>
</tr>
<tr>
<td>Stage 1–5 cataract</td>
<td>1.70</td>
<td>1.0</td>
<td>0.94</td>
<td>1.02</td>
<td>1.07</td>
<td></td>
<td>1.55</td>
</tr>
<tr>
<td>Stage 1 cataract</td>
<td>1.49</td>
<td>1.0</td>
<td>0.92</td>
<td>0.97</td>
<td>0.89</td>
<td></td>
<td>1.46</td>
</tr>
<tr>
<td>Stage 2–5 cataract</td>
<td>1.57</td>
<td>1.0</td>
<td>1.04</td>
<td>1.56</td>
<td>2.37</td>
<td></td>
<td>1.29</td>
</tr>
<tr>
<td>Stage 1–5, non-nuclear cataract</td>
<td>1.65</td>
<td>1.0</td>
<td>0.88</td>
<td>1.00</td>
<td>0.97</td>
<td></td>
<td>1.53</td>
</tr>
<tr>
<td>Stage 1, non-nuclear cataract</td>
<td>1.52</td>
<td>1.0</td>
<td>0.85</td>
<td>0.97</td>
<td>0.89</td>
<td></td>
<td>1.39</td>
</tr>
<tr>
<td>Stage 2–5, non-nuclear cataract</td>
<td>1.82</td>
<td>1.0</td>
<td>1.23</td>
<td>1.80</td>
<td>2.56</td>
<td></td>
<td>1.76</td>
</tr>
<tr>
<td>Early superficial posterior cortical changes</td>
<td>1.17</td>
<td>1.0</td>
<td>1.24</td>
<td>1.13</td>
<td>1.03</td>
<td>0.77</td>
<td>1.24</td>
</tr>
<tr>
<td>Stage 1 superficial posterior cortical changes</td>
<td>1.51</td>
<td>1.0</td>
<td>0.89</td>
<td>1.00</td>
<td>1.07</td>
<td></td>
<td>1.42</td>
</tr>
<tr>
<td>Early posterior subcapsular changes</td>
<td>1.89</td>
<td>1.0</td>
<td>1.28</td>
<td>1.11</td>
<td>1.48</td>
<td>0.91</td>
<td>2.36</td>
</tr>
<tr>
<td>Stage 1 posterior subcapsular cataract</td>
<td>1.42</td>
<td>1.0</td>
<td>0.90</td>
<td>0.93</td>
<td>1.20</td>
<td>1.24</td>
<td>1.72</td>
</tr>
</tbody>
</table>

*Worgul et al., 2007*

**Confidence interval ?**  **Dose-dependence ?**
Radiotherapy in children suffering from skin hemangioma (mainly in the face)

TABLE 4
Total Number of Examined Lenses and Lenses with LOCS Scores ≥1.0 in Relation to Type of Cataract and Lenticular Dose among Children Exposed before the Age of 18 Months

<table>
<thead>
<tr>
<th>Lenticular dose (Gy)</th>
<th>Total no. of lenses possible to evaluate</th>
<th>Operated lenses</th>
<th>No. of lenses with LOCS score ≥1.0 (%)</th>
<th>No. of affected lenses, cortical / subcapsular</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonexposed</td>
<td>178</td>
<td>0 (—)</td>
<td>8 (4)</td>
<td>26 (15)</td>
</tr>
<tr>
<td>&lt;0.5</td>
<td>748*</td>
<td>8 (1)</td>
<td>78 (10)</td>
<td>175 (23)</td>
</tr>
<tr>
<td>0.5–1.0</td>
<td>115</td>
<td>1 (1)</td>
<td>19 (17)</td>
<td>22 (20)</td>
</tr>
<tr>
<td>&gt;1.0</td>
<td>89</td>
<td>1 (1)</td>
<td>14 (16)</td>
<td>23 (25)</td>
</tr>
</tbody>
</table>

*Only 747 and 746 lenses could be examined for cortical and subcapsular opacities, respectively.

Dose-dependence only in Ń cortical / subcapsular, not in nuclear

In parenthesis: % (of total lenses)

Small numbers of controls – related to cases!

Positive family history for cataracts: controls 29%, irradiated: 34%

Hall et al., 1999
Radiotherapy in children suffering from skin hemangioma (mainly in the face)

TABLE 6
Odds Ratios (OR) and 95% Confidence Intervals (CI) Using Logistic Regression for Cortical and Posterior Subcapsular Opacities among Children Exposed\textsuperscript{a} before the Age of 18 Months

<table>
<thead>
<tr>
<th></th>
<th>Cortical</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>OR\textsuperscript{b}</td>
<td>95% CI</td>
<td>OR</td>
<td>95% CI</td>
<td>OR\textsuperscript{b}</td>
</tr>
<tr>
<td>Dose (per Gy)</td>
<td>1.35</td>
<td>1.07–1.69</td>
<td>1.50</td>
<td>1.15–1.95</td>
<td>1.50</td>
<td>1.10–2.05</td>
<td>1.49</td>
</tr>
<tr>
<td>Age at exposure (per month)</td>
<td>1.14</td>
<td>1.06–1.22</td>
<td>1.13</td>
<td>1.07–1.20</td>
<td>0.75</td>
<td>0.62–0.91</td>
<td>0.73</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Internal comparison within the exposed group was used for dose–response estimates.

\textsuperscript{b} OR corrected for age at examination, dose rate and steroid treatment.
Radiologic technologists in the USA

132,454 certified US radiologic technologists

90,305 responded to the baseline questionnaire

23,926 were excluded:
   21,651 were not in the age range of 24–44 years
   1,885 had exceptionally high occupational doses
   390 had never worked as radiologic technologists

66,379 radiologic technologists were eligible

35,870 answered the baseline and two follow-up questionnaires

133 were excluded because of cataract/cataract extraction prior to baseline
32 reported cataract but unknown year of diagnosis

35,705 were available for analysis

Validation of cataracts in questionnaire: 80% (KORA-Eye Study)

Chodick et al., 2008
Radiologic technologists in the USA

adjusted for baseline values of age, sex, body mass index, cigarette smoking, diabetes, hypertension, hypercholesterolemia, alcohol consumption, arthritis etc.

Chodick et al., 2008
Radiologic technologists in Colombia and Uruguay

Vano et al., 2010

Lens examination by slitlamp – better than questionnaire

But:

➢ small numbers

➢ Other types of cataracts?

➢ Dose estimation: questionnaire; 0.05 cSv per procedure for interventional cardiologists and 0.015 cSv per procedure for nurses

Result: Cardiologists: $6.0 \pm 6.6$ Sv (cumulative dose)

Nurses: $1.5 \pm 1.4$ Sv (cumulative dose)

➢ Adjustment for sex and other risk factors? (age: control 20-66 years, cardiologists: 30-69 years)
Radiation-induced cataracts in mice

Hall et al., 1999
Radiation-induced cataracts in mice

LAF₁-Mice

Upton et al., 1956

Lowest dose: 33 rep = 0.3 Gy
Differences in controls = differences among strains!
Radiation-induced cataracts in mice

Mice: Swiss-albino, m/f
age: 10-14 Weeks at irradiation
Very small group size!

<table>
<thead>
<tr>
<th>Exposure (r)</th>
<th>Number of Lenses Stage</th>
<th>Average Degree of Opacification*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>I</td>
</tr>
<tr>
<td>A. 200-kv x-radiation, LD 50 = 575 r</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td>300</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>400</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>450</td>
<td>22</td>
<td>1.0</td>
</tr>
<tr>
<td>500</td>
<td>4</td>
<td>1.0</td>
</tr>
<tr>
<td>600</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>700</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>800</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>900</td>
<td>24</td>
<td>3.0</td>
</tr>
<tr>
<td>1000</td>
<td>18</td>
<td>3.0</td>
</tr>
<tr>
<td>1100</td>
<td>14</td>
<td>3.0</td>
</tr>
<tr>
<td>1200</td>
<td>16</td>
<td>3.0</td>
</tr>
<tr>
<td>B. 250-kv x-radiation, LD 50 = 575 r</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>100</td>
<td>8</td>
<td>0.5</td>
</tr>
<tr>
<td>300</td>
<td>8</td>
<td>1.0</td>
</tr>
<tr>
<td>700</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>800</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>850</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>875</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>900</td>
<td>6</td>
<td>3.0</td>
</tr>
<tr>
<td>1000</td>
<td>14</td>
<td>3.0</td>
</tr>
</tbody>
</table>

* Derivation of average explained in text.
Radiation-induced cataracts in mice

RF-mice: female, 8 weeks old
8 mice/single dose
Slit lamp: % opacity

Darden et al., 1970

Fig. 6. Estimated mean percent opacity as a function of dose at specific postirradiation intervals (A) 150 days: O protons; ● x-rays. (B) 350 days: □ protons; ■ x-rays.

Fig. 5. Fitted curves together with simple means of observed percent opacity plotted as a function of posttreatment interval for 300-kVp x-rays. ● 300 rads; ■ 100 rads; □ unirradiated control.
Mice: A-strain, 5-6 mice per group, 300 R (X-ray), 170 kVp, 42 R/min
Comment:
mitotic index of lens epithelial cells decreases continuously from day 1 -> day 35

Gajewski et al., 1977
Summary: radiation-induced cataracts in mice

Lowest dose: 0.3 Gy (Upton, 1956)
               1 Gy (Riley, 1956)
               1 Gy (Darden, 1970)

Age of irradiation: Difference between very young mice and adult mice
Radiation-induced cataracts in mice: genetics

*Atm*-knockout mice (Ataxia telangiectasia mutated); heterozygous mice seem to be healthy...

- **Irradiation:** 4 weeks, 250 kV, X-ray, 0.5 Gy/min; slit lamp; 10 mice/group
- **Heterozygotes:** cataract ~1 month earlier; difference disappears at higher doses

Worgul et al., 2002, 2005
Radiation-induced cataracts in mice: genetics (II)

*Atm*-knockout Mäuse (Ataxia telangiectasia mutated); *Mrad9* (mouse RAD9 homolog)

\[ Atm^{+/+}; \; Mrad9^{+/+} \quad Atm^{+/-}; \; Mrad9^{+/-} \]

Kleiman et al., et al., 2007

**FIG. 5.** Mean cataract stage as a function of time in unirradiated or irradiated eyes of mice. Genotypes of mice: (panel A) *Atm^{+/+}; Mrad9^{+/+};* (panel B) *Atm^{+/-}; Mrad9^{+/-};* Unirradiated (triangles); exposed to 50 cGy of X rays (diamonds).

Slit lamp; irradiation: 250 kVp age of 4 weeks; statistics?

irradiated: n=57; control: n= 56 (both genotypes)
Summary: radiation-induced cataracts in mice:

Depending on the genetic constitution, cataracts appear earlier or later after irradiation.
Radiation-induced cataracts in mice – mechanism

Wolf et al., 2008

11 Gy (100 kV)

Mice: C57BL/6 (f)

Age: 2 months at irradiation

Control, 7 Mo (1+)
1 Mo after irradiation (0)

3 Mo after irradiation

5 Mo after irradiation (4+)

5 Mo after irradiation (4+)

appearance of x-ray cataracts

Irradiated 11 Gy (100 kV)
Control

Percent

0 20 40 60 80 90

Time Post-Irradiation (months)

Mice: C57BL/6 (f)

Age: 2 months at irradiation

Wolf et al., 2008

HelmholtZentrum münchen

German Research Center for Environmental Health
Strahleninduzierte Katarakte bei Mäusen

Comet-Assay in lens epithelial cells after irradiation
(11 Gy; 100 kV)

Chromsomal aberrations in lens epithelial cells after irradiation

New paper:
Increase of 8-OH-Guanosine in nuclei of lens epithelial cells
Decrease of numbers of lens epithelial cells after irradiation

Effect similar for low dose ??
Ionizing radiation and cataract

Future studies need (more) quantitative data for
Ionizing radiation and cataract

Future studies need (more) quantitative data for

Lens opacities  
Lens doses
Quantification of lens opacities

Scheimpflug Camera in combination with Slit lamp

Rotating measurement principle avoids errors compared to results from horizontal scanning

Area under the curve: quantitative data

Used in epidemiological studies: Pei et al., 2008

Mobile Version of Pentacam used in Irish Nons Eye Study (INES) – Wegener et al., EVER 2010
Pentacam for mouse studies:
Densitometry diagram of O377

Control

O377-/-

Opacification (%)

Opacification (%)

C

I

L

lens area
Ionizing radiation and cataract

Future studies on „numbers“ using quantitative data:

- Again: Liquidators at Chernobyl with Pentacam
- Again: Radiologic technologists, cardiologists with Pentacam and quantitative dosimetry
- 10-years supervision (using Pentacam) of all exposed persons in EU? (or permanent registry?)
- Appropriate population control
- Association with genetics (GWAS); other risk factors!!
- Numbers or life-time distribution: more cataracts at a given age or cataracts earlier in life?
Ionizing radiation and cataract

Future studies (II) on mechanisms:

➢ Animal models (mice, rats …): genetics (strain differences, influence of heterozygous mutations), epigenetics, differentiation (cell cycle control)

➢ Radiation and type of cataract: posterior-subcapsular cataract specific for radiation-induced cataracts?

➢ Co-factors: decreasing and/or increasing risk (e.g. estrogen)