

IRSN

INSTITUT
DE RADIOPROTECTION
ET DE SÛRETÉ NUCLÉAIRE

Faire avancer la sûreté nucléaire

Risk of radiation-induced cataract and lens opacities : results from epidemiological studies

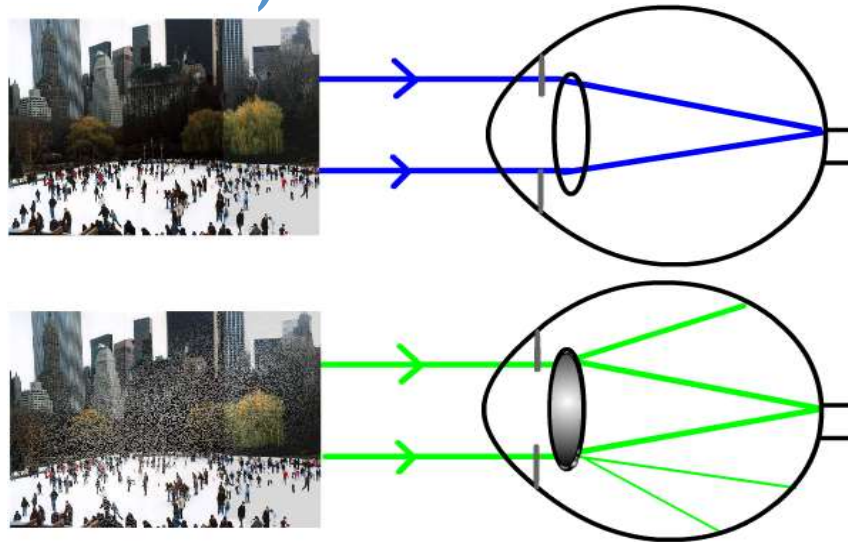
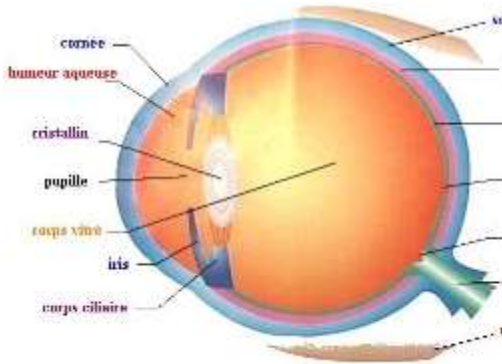
Sophie Jacob

Laboratory of Epidemiology. IRSN. France

13th EURADOS Winter School
Firenze. January 30. 2020

Cataract

➤ From few opacities in the eye lens (vision loss) to cataract surgery (blindness)



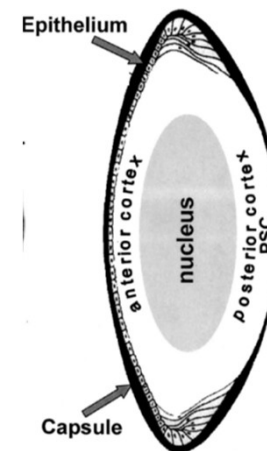
Cataract

➤ First cause of vision loss in the world

- Increasing with aging
- Prevalence : 50% in the population aged 65 years and 70% in those older than 85 years in industrialized countries

➤ Several types

- Cortical
- Nuclear
- Subcapsular posterior (SCP)



➤ Risk factors

- Solar ultraviolet radiation exposure, diabetes, high BMI, smoking, corticosteroid use, ocular trauma
- Ionizing radiation

Cataract

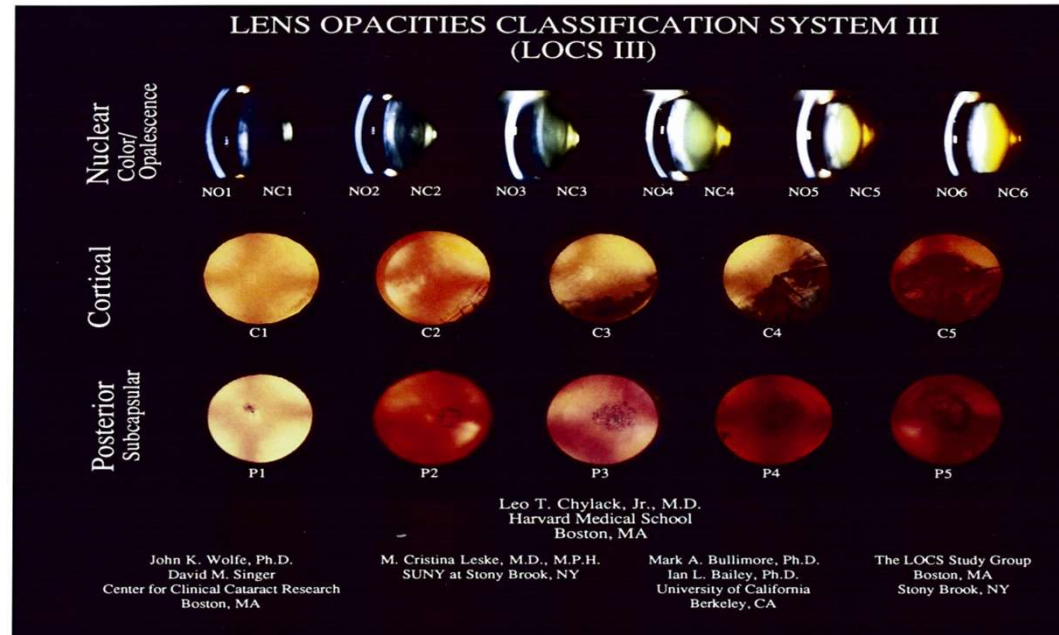
➔ Diagnosis

Ophthalmologic examination

Slit lamp+ pupillary dilatation

Coding : according to the type and the stage

⚠ different classifications (Merriam-Focht. LOCS. WHO. ...)



Radiation-induced cataract since 2011

- Threshold has been decrease. based on results from epidemiological studies



INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION

Statement on Tissue Reactions

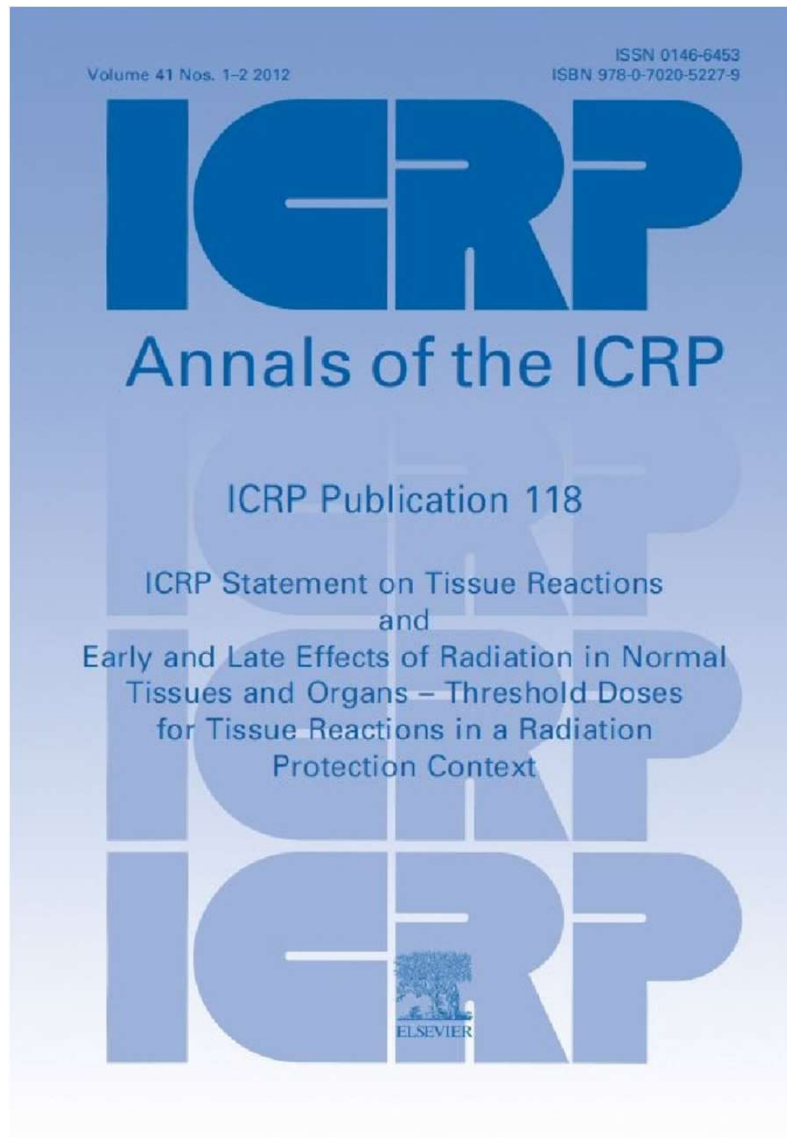
Approved by the Commission on April 21, 2011

(2) The Commission has now reviewed recent epidemiological evidence suggesting that there are some tissue reaction effects, particularly those with very late manifestation, where threshold doses are or might be lower than previously considered. For the lens of the eye, the threshold in absorbed dose is now considered to be 0.5 Gy.

0.5 Gy

(3) For occupational exposure in planned exposure situations the Commission now recommends an equivalent dose limit for the lens of the eye of 20 mSv in a year, averaged over defined periods of 5 years, with no single year exceeding 50 mSv.

20 mSv/an
instead of
150
mSv/year



For cataracts in the lens of the eye induced by **acute exposures**, recent studies, where formal estimates of threshold doses have been made after long follow-up periods, indicate **values of approximately 0.5 Gy with 90–95% confidence intervals including zero dose**. This is lower by a factor of 10 than deduced in earlier studies.

...

For **fractionated and protracted exposures**, values of approximately **0.5 Gy** have been similarly deduced from recent studies. However, the evidence pertaining to the latter exposures mainly refers to **opacities rather than cataracts impairing vision because the follow-up times are shorter** in those studies.

...

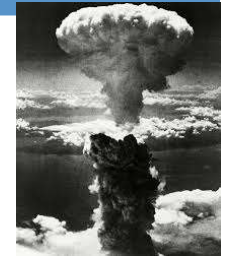
For **chronic exposure** over several to many years, much of the evidence refers to **minor lens opacities**. Nonetheless, there is **no indication that threshold accumulated doses are higher** in this scenario.

Epidemiological studies

- **Environmental exposure**
 - *Hiroshima/Nagasaki*
 - *Children living close to Tchernobyl*
 - *Contaminated buildings in Taiwan*
- **Medical exposure**
 - *Diagnostic examinations*
- **Occupational exposure**
 - *Chernobyl clean-up workers*
 - *Airline Pilots/Astronauts*
 - *Industry radiographers*
 - *Radiological technologists*
 - *Interventional radiologists and cardiologists*

➤ Hiroshima Nagasaki survivors

Nakashima et al 2005:



- 730 subjects
 - Ophthalmic examination. LOCS II classification
 - Median age at exposure: 10.5 yrs
 - Median age at examination: 66.6 yrs
 - Lens doses: <1 Sv for 79% of the population

- PSC :
 - OR/1 Sv= 1.44 (95% CI=1.19-1.73)
 - Threshold: 0.7 Sv (<0; 2.8)

- Cortical:
 - OR/1 Sv=1.3 (95% CI=1.10-1.53)
 - Threshold: 0.6 Sv (<0; 1.2)

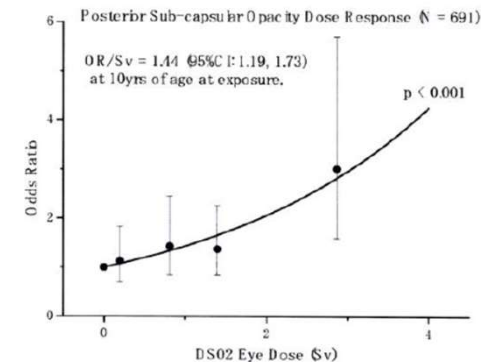


Fig. 4. Dose response of posterior sub-capsular opacity (PS).

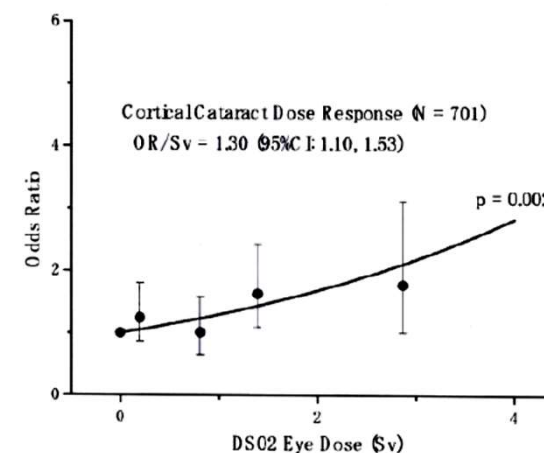
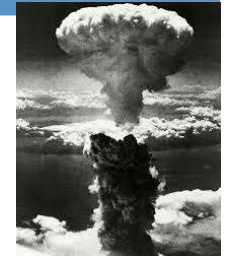


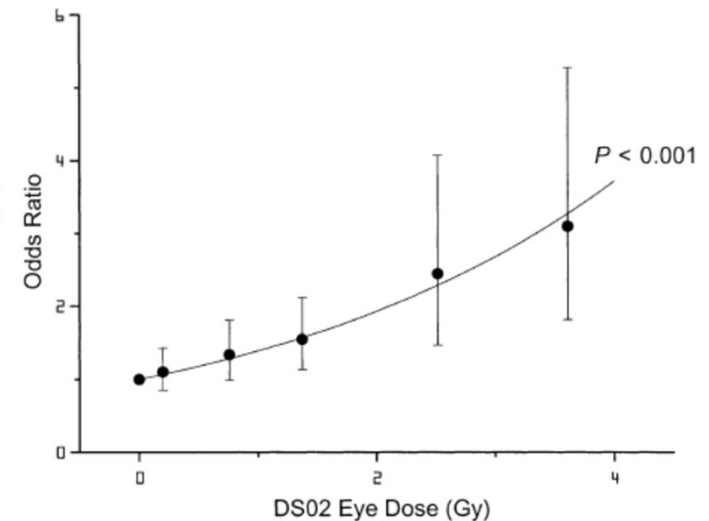
Fig. 3. Dose response of cortical cataract (CC).

➤ Hiroshima Nagasaki



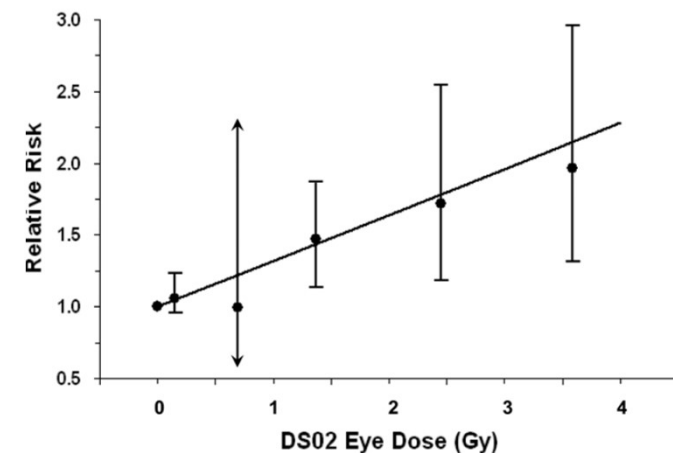
Neriishi et al 2007:

- 3800 subjects (age at exposure: 0-37.9 yrs)
 - **Surgery for cataract 1986- 2005**
 - Prevalence study (no consideration of time)
 - OR/Gy = 1.39 (95% CI.1.24-1.55)
 - Threshold=0.1Gy (<0; 0.8) Gy



Neriishi et al 2012:

- 6006 subjects (age at exposure: 0-54yrs)
 - **Surgery for cataract 1986- 2005**
 - Incidence study (consideration of time)
 - **ERR/1 Gy = 0.32(0.2-0.47)**
 - Threshold=0.5Gy (0.1 Gy. 0.95) Gy



➤ Chernobyl

Day et al. 1995:

- 996 children exposed/ 791 not exposed
 - **Ophthalmic examination. LOCS III**
 - Age at examination: 5-17 yrs
 - 3.6% PSC exposed/ 1.1% PSC non exposed ($p < 0.0005$)



➤ Contaminated buildings Co60 / Taiwan

Chen et al. 2001:

- 114 subjects with **LOCS III and FLD classification**. in 1998
- Mean age at examination: 24.8 yrs
- Increased frequency of lens opacities in those <20 yrs in function of the dose ($p = 0.027$) but not for older

Hsieh et al. 2010:

- 73 subjects (<20 years). 100 controls with LOCS III and FLD classification. in 2004
- FLD score increased



➤ Diagnostic imaging : Head and neck CTs



Klein et al.1993

- Beaver Dam Eye Study; 4.926 adults
- Only CT scan associated with lens opacities
- OR PSC= 1.45 (CI 95%. 1.08-1.95)
- OR Nuclear=1.26 (CI 95%. 1.02-1.61)
- OR cortical= 1.17(CI 95%. 0.88-1.55)

TABLE 2—Age- and Sex-Adjusted Odds Ratios for Lens Opacities

X-ray Type	Posterior Subcapsular Opacity		Nuclear Sclerotic Opacity		Cortical Opacity	
	OR	95% CI	OR	95% CI	OR	95% CI
Abdomen	1.18	0.89, 1.55	1.04	0.85, 1.28	1.04	0.84, 1.29
Chest	1.74	0.74, 4.07	1.36	0.77, 2.42	1.16	0.62, 2.16
Head	1.27	0.98, 1.68	1.13	0.93, 1.38	0.87	0.71, 1.07
CAT scan	1.45	1.08, 1.95	1.26	1.02, 1.61	1.17	0.88, 1.55
Other	1.20	0.93, 1.55	0.90	0.61, 1.15	0.94	0.70, 1.19

Note: Odds ratios (ORs) are from multiple logistic regression with age and sex included in the models. CI = confidence interval; CAT = computerized axial tomography.

Yuan et al.2013

- 2776 patients exposed to head CT/ 27 761 non exposed (based on Taiwan registry 1995-2009) (1 CT = 50mSv to the lens)
- HR E/non E= 1.76 (95%CI. 1.2-2.6)

TABLE 2: Association Between Radiation Exposure From CT and Cataract Incidence

No. of CT Studies	Cataract Incidence, No. (%)	Crude Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI) ^a
0 (n = 27,761)	201 (0.72)	1 (referent)	1 (referent)
1–2 (n = 1512)	12 (0.79)	1.40 (0.78–2.50)	1.61 (0.90–2.88)
3–4 (n = 645)	6 (0.93)	1.71 (0.76–3.85)	1.64 (0.73–3.69)
≥ 5 (n = 619)	9 (1.45)	2.23 (1.14–4.35)	2.12 (1.09–4.14)

Note—*p* for trend = 0.001.

^aAdjusted for age, sex, history of hypertension, diabetes mellitus, and coronary artery disease.

➤ Chernobyl clean-up workers

Worgul et al 2007



Nb of subjects	8607
Mean age at exposure	32.7 yrs
Mean age at examination	44.9-47 yrs (Merriam Focht classification)
Median dose to the lens	123 mGy (94% < 400 mGy)
Results	OR/1Gy=1.70 (95% CI. 1.22-2.38) all types Threshold: 0.34 Gy (0.19 - 0.68)
	OR/1Gy=1.42 (95% CI. 1.01-2.0) PSC Threshold: 0.35 Gy (0.19 - 0.66)

➤ Astronauts

	Cucinotta. 2001	Rastegar. 2005	Chylack. 2009
Nb of subjects	295	21 E/395 NE	171 E/ 247 NE
Lens dose	0.2-91 mSv		15.1-129 mSv
Results	HR=3.73 p=0.012 for PSC and N at 60 yrs	Increase of C and PSC opacities	Increase of C opacities (p=0.015)



➤ Airline Pilots

Rafnsson et al 2005:

- Nested case control study in a cohort of pilots
- 205 cases: 71 N. 102 C . 32 PSC /374 controls
- WHO cataract classification
- Mean age cases=75yrs. controls=66 yrs;
- lens doses: 0-48mSv
- Nuclear cataracts OR=4.19 (95% CI. 1.04-16.86)

Table 2. Age-Adjusted Odds of Nuclear Cataract Risk According to Cumulative Radiation Dose Sustained Before the Age of 40 Years, Divided into Quartiles

Variable	Controls (n = 374)*	Cases (n = 71)*	Odds Ratio (95% Confidence Interval)
Age, y	NA	NA	1.16 (1.11-1.21)
Cumulative radiation dose			
Not exposed†	310	56	1.00
First quartile (1-7 mSv)	13	6	2.82 (0.95-8.41)
Second quartile (8-15 mSv)	18	3	2.60 (0.67-10.11)
Third quartile (16-21 mSv)	18	3	2.48 (0.64-9.70)
Fourth quartile (22-48 mSv)	15	3	4.19 (1.04-16.86)

➤ Industry radiographers

Lian et al 2015

- 1401 Chinese radiographers/1878 unexposed. followed for 12 years;
- Lens doses: based on individual monitoring: mean dose 38.8 mGy
- Eyes examination

Table 2 Incidence rates, HRs and 95% CIs of cataract compared with unexposed group

Cataract subtype	Industry radiographer		Unexposed group		HR*	95% CI
	n (%)	Rate per 10 000 person-years	n (%)	Rate per 10 000 person-years		
Nuclear cataract	42 (3.00)	26.98	27 (1.44)	12.39	0.93	0.78 to 1.11
Cortical cataract	42 (3.00)	26.30	12 (0.64)	5.51	2.58	1.36 to 3.82
PSC cataract	29 (2.07)	18.16	13 (0.69)	5.97	3.57	1.27 to 4.79
Mixed cataract	10 (0.71)	6.26	5 (0.27)	2.30	3.25	1.20 to 6.78
Cortical or PSC or mixed cataract	81 (5.78)	50.72	30 (1.60)	13.77	3.64	1.78 to 5.52

*Adjusting for sex, education, age at exposure, hypertension, hypercholesterolaemia, diabetes mellitus, myocardial infarction, smoking, body mass index and oral or injected corticosteroid use.
PSC, posterior subcapsular.

Table 4 Cox regression HR and 95% CI of cortical, PSC or mixed cataract among industrial radiographers according to demographic factors, radiation dose and cataract risk factors

Covariate	Cataract cases/total participants	Analysis with basic covariates*		Analysis with adjustment†	
		HR	95% CI	HR	95% CI
Cumulative recorded radiation dose					
>0–48.4	12/350	1.0		1.0	
48.4–66.1	18/350	0.76	0.36 to 1.57	0.83	0.22 to 1.82
66.1–88.6	20/350	1.02	0.44 to 1.11	1.03	0.14 to 1.32
88.6–146.1	31/351	1.12	0.88 to 1.79	1.15	0.73 to 1.64

Increased risk of cortical and PSC cataracts. **No dose effect relationship**

➤ Medical workers: radiological technologists

Little et al 2018 (US cohort of technologists)



- **67246** technologists. mean follow-up : 12 years;
- Lens doses: based on work history and badge monitoring: mean dose 55.7 mGy
- Cataract assessment: [self report](#)

Eye-lens absorbed dose (mGy)	Cataract history			Cataract surgery		
	Cases	Person years	Hazard ratio ^a	Cases	Person years	Hazard ratio ^a
< 10.0	415	43,386	1 (reference)	174	45,096	1 (reference)
10.0–19.9	948	125,145	1.09 (0.97, 1.22)	345	129,319	1.00 (0.83, 1.20)
20.0–49.9	3874	363,712	1.11 (1.00, 1.23)	1566	381,068	1.11 (0.95, 1.30)
50.0–99.9	4027	217,756	1.15 (1.04, 1.27)	1853	237,159	1.22 (1.05, 1.43)
100.0–199.9	2302	71,356	1.15 (1.03, 1.27)	1212	82,074	1.27 (1.08, 1.49)
200.0–499.9	722	10,774	1.32 (1.17, 1.50)	347	13,231	1.17 (0.97, 1.41)
≥ 500.0	48	350	1.76 (1.29, 2.40)	12	473	0.61 (0.33, 1.10)

Dose range	Endpoint	Cases	EHR/mGy × 10 ³ (+ 95% CI)	p value
0–100 mGy	Cataract history	9264	1.16 (0.11, 2.31)	0.030
	Cataract surgery	3938	0.39 (– 1.15, 2.22)	0.638
0–200 mGy	Cataract history	11,566	1.07 (0.47, 1.72)	< 0.001
	Cataract surgery	5150	0.17 (– 0.59, 1.05)	0.675
Unrestricted	Cataract history	12,336	0.69 (0.27, 1.16)	< 0.001
	Cataract surgery	5509	0.34 (– 0.19, 0.97)	0.221

➤ Medical workers: radiological technologists

Bernier et al 2017 (US cohort of technologists)

- 42545 technologists. including 12 964 (30%) technologists working with Nuclear Medicine procedures;
- Cataract assessment: [self report](#)



Table 2

Cataract Frequency and Surgery in U.S. Radiologic Technologists according to NM Work History Characteristics (n = 42545)

Parameter	Cataract Diagnosis		Cataract Surgery	
	No. of Cases*	HR†	No. of Cases‡	HR†
Ever worked with NM procedures				
No (n = 25 827)	3965	1.00 (Ref)	1316	1.00 (Ref)
Yes (n = 12 964)	2458	1.08 (1.03, 1.14)	850	1.09 (1.00, 10.18)
Missing (n = 3754)	714	...	306	...
Ever worked with diagnostic NM procedures				
No (n = 27 415)	4281	1.00 (Ref)	1425	1.00 (Ref)
Yes (n = 10 967)	2060	1.07 (1.01, 1.12) [§]	711	1.07 (0.98, 1.17)
Missing (n = 4163)	796	...	336	...
Ever worked with therapeutic NM procedures				
No (n = 30 403)	4713	1.00 (Ref)	1569	1.00 (Ref)
Yes (n = 7005)	1436	1.10 (1.04, 1.17) [§]	489	1.07 (0.96, 1.18)
Missing (n = 5137)	998	...	414	...

- Increased risk of cataract associated with Nuclear Medicine diagnostic and therapeutic procedures
- No association with radiation protection techniques

➤ Medical workers: radiologists and interventional cardiologists



Study	Year	Lens scoring system	Lens areas assessed	Sample size (n)	Prevalence of lens changes
Junk et al. [17]	2004	Scheimpflug	PSC	59 interventional radiologists	22/59 (37%) had precataract PSC changes; 5/59 (8%) had frank PSC opacities
Ciraj-Bjelac et al. [18]	2010	MF	PSC	67 exposed (56 ICs and 11 nurses) and 22 controls	34/67 (51%) exposed had PSC lens changes vs. 2/22 (9%) controls; 3 ICs (5%) had PSC grade >1.0
Vassileva et al. [19]	2010	MF	PSC	42 exposed (18 ICs, 24 staff)	14/42 (33%) exposed had PSC lens changes vs. 2/24 (8%) controls
Vano et al. [20]	2010	MF	PSC	116 exposed (58 ICs, 58 staff) and 93 controls	22/58 (38%) ICs had PSC lens changes vs. 12/58 (21%) technicians/nurses vs. 11/93 (12%) controls
Mrena et al. [21]	2011	LOCS II	All	57 exposed (40 radiologists, 16 cardiologists, 1 surgeon)	24/57 (42%) had lens changes
Ciraj-Bjelac et al. [22]	2012	MF	PSC	52 exposed (30 ICs, 22 nurses and technicians) and 34 controls	16/30 (53%) ICs had PSC lens changes vs. 10/22 (45%) nurses/technicians (26/52 [50%] exposed overall) vs. 7/34 (20%) controls
Jacob et al. [23]	2013	LOCS III	All	106 ICs and 99 controls	Cortical: 23% ICs vs. 29% controls Nuclear: 61% ICs vs. 69% controls PSC: 17% ICs vs. 5% controls
Vano et al. [24]	2013	MF	PSC	127 exposed (54 ICs, 4 surgeons, 69 nurses and technicians), 91 controls	27/54 (50%) ICs had PSC lens changes vs. 29/69 (42%) staff vs. 10% controls
Rajabi et al. [25]	2015	LOCS III	All	81 exposed (44 ICs, 37 technicians), 14 controls	64/81 (79.0%) exposed had lens opacities vs. 1/14 (7.1%) controls
Andreassi et al. [26]	2016	Survey	-	466 exposed (218 ICs, 191 nurses, 57 technicians), 280 controls	22/466 (4.7%) exposed reported cataract vs. 2/280 (0.7%) controls

Results in favor of an increased risk of early PSC cataracts

➤ European project EURALOC



- 11 countries involved (2014-2017)
- 393 interventional cardiologists / 243 non exposed
- LOCS III classification
- Median lens doses: 151 mSv (max 2815 mSv) for left eye

EURALOC

- Prevalence of **Posterior Subcapsular (PSC)** lens opacities

	All participants N=553		Interventional Cardiologists N=318		Unexposed group N=235		p-val.	OR (95% CI) Adjusted on Age		
Posterior Subcapsular	N	%	N	%	N	%		OR	95% CI	
PSC uni or bilateral	52	9.40	39	<u>12.2</u>	13	<u>5.53</u>	0.004	2.39	1.35	5.08
PSC Left	40	7.23	29	9.12	11	4.68	0.031	2.04	1.08	4.59
PSC Right	43	7.78	33	10.3	10	4.26	0.006	2.61	1.35	5.87
PSC bilateral	31	5.61	23	7.23	8	3.40	0.042	2.21	1.03	5.41

EURALOC

- Dose-response analysis for **Posterior Subcapsular (PSC)** lens opacities

Model	Parameters	Estimates	95% CI		p-value	AIC
Linear non threshold (LNT)	α_1	-5.265	-6.515	-4.015	0.000	439.331
	α_2	-5.662	-8.101	-3.224	0.000	
	α (Gy^{-1}) (ERR)	1.308	0.127	3.320	0.025	
	ρ (Age^{-1})	0.023	0.002	0.045	0.031	
Linear Threshold	α_1	-5.258	-6.415	-4.090	0.000	441.33
	α_2	-5.650	-8.081	-3.221	0.000	
	α (Gy^{-1})	1.327	0.134	3.334	0.023	
	ρ (Age^{-1})	0.023	0.002	0.046	0.030	
	Threshold (Gy)	0.039	undefined	0.769	0.730	

➤ Threshold or not threshold?

Few epidemiological studies provide estimates of threshold

Table 1
Comparison of estimated dose-response thresholds in lens opacity studies.

Study and Opacity Characterization	Data Acquisition Method; Opacity Grade	Dose-response Estimated Threshold, Gy (95% CI)
A-bomb, PSC [34,35]	Screening ^a ; PSC "defect"	1.5 (0.2, 1.8) ^b
A-bomb, PSC [36]	Screening; "axial opacity"	0.5 (n.a.) ^{c,d}
A-bomb, PSC opacity [33]	Screening; LOCS-II, analysis of ordinal opacity grades	0.7 (<0, 2.8) ^e
A-bomb, Cortical opacity [33]	Screening; LOCS-II, analysis of ordinal opacity grades	0.6 (<0, 1.2) ^e
A-bomb, Cataract surgery [32]	Incidence; extracted cataracts	0.5 (0.1, 1.0) ^f
Chernobyl clean-up workers, PSC [24]	Screening; Stage 1 (M-F grade) ^g	0.4 (0.2, 0.7) ^h
Chernobyl clean-up workers, Posterior cortical [24]	Screening; Stage 1 (M-F grade)	0.3 (0.2, 0.5) ^h
Chernobyl clean-up workers, All non-nuclear cataracts [24]	Screening; Stages 1-5 (M-F grade)	0.5 (0.2, 0.7) ^h

From Shore. Mutation Research 2016

- Range from 0.3 to 1.5 Gy
- Wide intervals
- Caution needed : dosimetric uncertainties. methodological discrepancies (outcomes. length of follow-up. age at exposure)

➤ Progression of lens opacities to true cataract?

- Results largely based on small lens opacities assessment
- Sparse results on follow-up of small opacities (AHS), cataract surgery not always reliable surrogate of cataract incidence

- Epidemiological studies are in favour of radiation induced cataract at low dose
 - Acute and protracted low doses appear to be associated with increased risk of cataract

- However, evidence and level of a threshold is still debated
 - Few studies calculating threshold
 - Large confidence intervals

- Dosimetric issues and epidemiological limits should be taken into account in new studies



Thank you for your attention