Underpinning Science: State of the Art

Non-Cancer Effects, Especially Circulatory Diseases

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Outline of talk

- Introduction
- Circulatory disease
  - A-bomb survivors, occupationally-exposed cohorts
  - Meta-analysis of circulatory disease in moderate+low-dose epidemiological data
- Cataract
- Other non-malignant endpoints
  - Respiratory, digestive
  - Neuro-cognitive
- Conclusions

Dose response for circulatory disease in A-bomb survivors (Shimizu *et al. Br. Med. J.* **340**:b5349;2010)

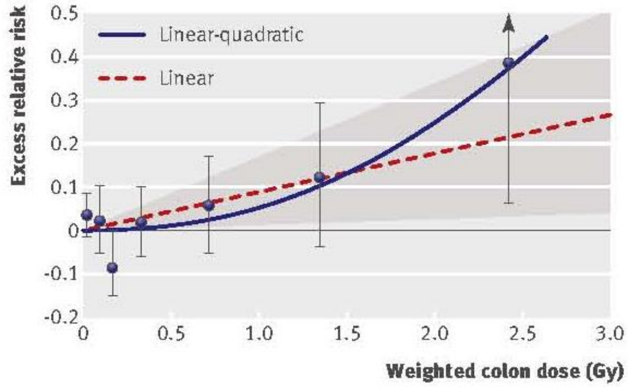


Fig 1 | Radiation dose-response relation (excess relative risk per Gy) for death from stroke, showing linear and linear-quadratic functions. Shaded area is 95% confidence region for fitted linear line. Vertical lines are 95% confidence intervals for specific dose category risks. Point estimates of risk for each dose category are indicated by circles

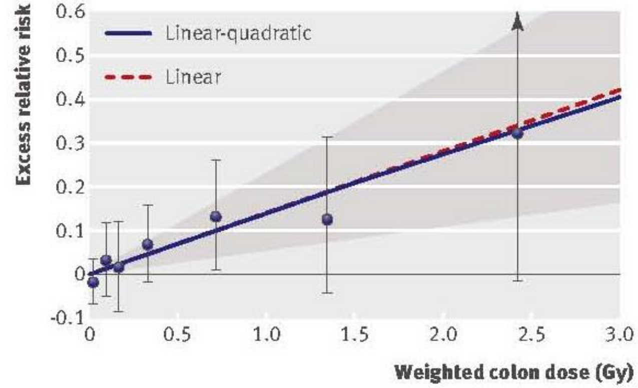


Fig 2 | Radiation dose-response relation (excess relative risk) for death from heart disease, showing linear and linear-quadratic functions. Shaded area is 95% confidence region for fitted linear line. Vertical lines are 95% confidence intervals for specific dose category risks. Point estimates of risk for each dose category are indicated by circles

ERR/Sv heart (ICD9 393-400,402,404,406-429) 0.18 (95% CI 0.11, 0.25)

ERR/Sv stroke (ICD9 430-438) 0.12 (95% CI 0.05, 0.19)

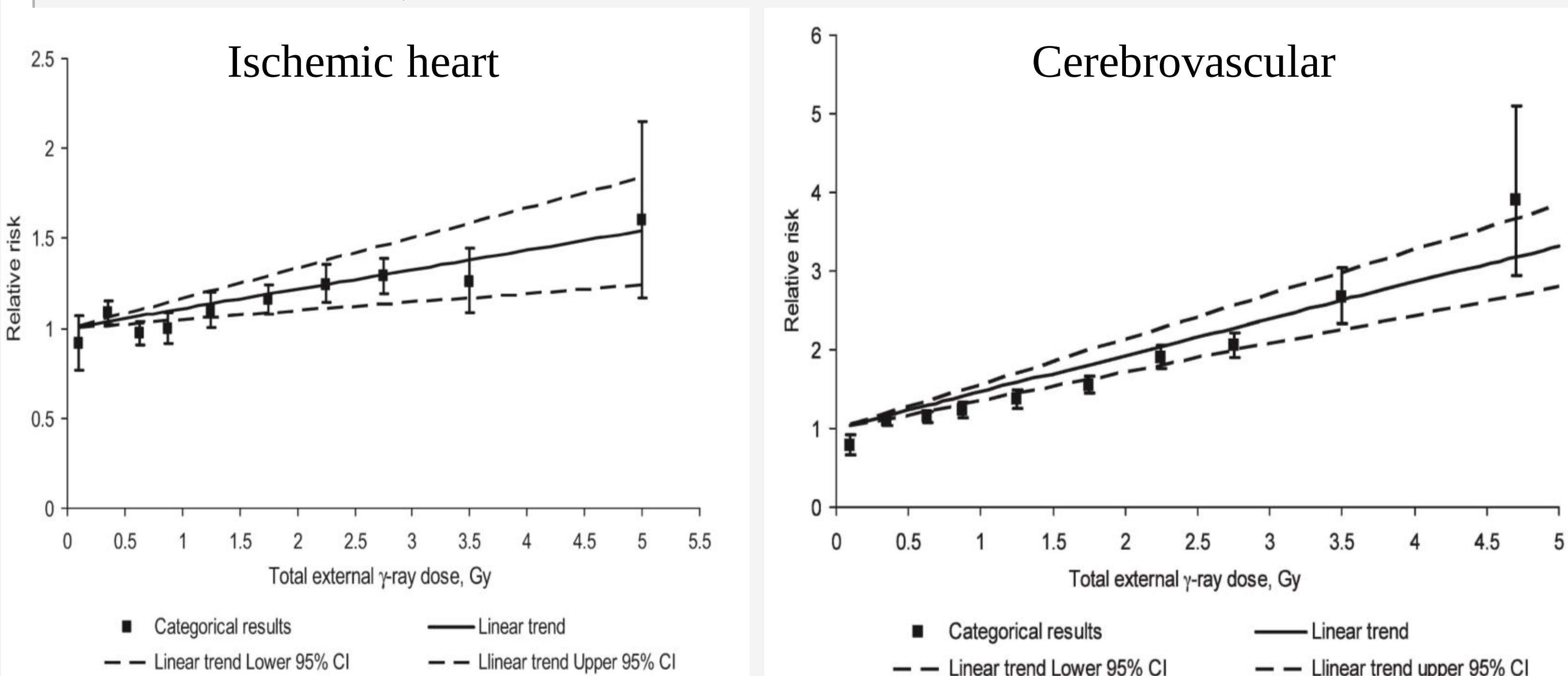
ERR/Sv other circulatory (ICD9 393-459 - above) 0.58 (95% CI 0.45, 0.72)

Significant dose response, but excess risk only clear above ~0.5 Gy

Dose response same if adjusted for smoking, drinking + other CVD risk factors

Shape of dose-response uncertain: weak indications (linear-quadratic vs linear *p*=0.17) of upward curvature for stroke, none (*p*>0.5) for heart disease

Dose response for ischemic heart disease +stroke morbidity in Mayak nuclear workers (Azizova *et al. Radiat. Res.* **174**:155-68; 2010, *Radiat. Res.* **174**:851-64; 2010)



ERR/Gy ischemic heart (ICD9 410-414) 0.119 (95% CI 0.051, 0.186)

ERR/Gy cerebrovascular (ICD9 430-438) 0.449 (95% CI 0.338, 0.559)

Adjustment for smoking and drinking makes almost no difference

Circulatory excess relative risk Sv^{-1} in occupational groups (Little *et al. Radiat. Res.* **169**:99-109;2008, Little *et al. Radiat. Env. Biophys.* **49**:139-153;2010, Little *et al. Env. Health Perspect.* 2012 in press)`

Chernobyl recovery hypertension	0.26 (95% CI -0.04 – 0.56)
Chernobyl recovery ischaemia heart	0.41 (95% CI 0.05 – 0.78)
Chernobyl recovery other heart	-0.26 (95% CI -0.81 – 0.28)
Chernobyl recovery stroke	0.45 (95% CI 0.11 – 0.80)
Mayak ischaemic heart (external γ)	0.11 (95% CI 0.05 – 0.17)
Mayak stroke (external γ)	0.46 (95% CI 0.36 – 0.57)
NRRW-3 circulatory	0.25 (95% CI -0.01 – 0.54)
BNFL circulatory	0.54 (90% CI 0.30 – 0.82)
BNFL ischaemic heart	0.70 (90% CI 0.37 – 1.07)
BNFL stroke	0.66 (90% CI 0.17 – 1.27)
EdF ischemic heart	4.1 (90% CI -2.9 – 13.7)
EdF stroke	17.4 (90% CI 0.2 – 43.9)
Canadian uranium workers ischaemic heart	0.15 (95% CI -0.14 – 0.58)
Canadian uranium workers stroke	-0.29 (95% CI <-0.29 – 0.27)
US Oak Ridge ischaemic heart	-2.86 (95% CI -6.90 – 1.18)
German uranium miner circulatory	-0.26 (95% CI -0.6 – 0.05)

Increased risk in Chernobyl, Mayak, NRRW-3, BNFL, EdF (?)

Most other risks negative, consistent with modest excess risk

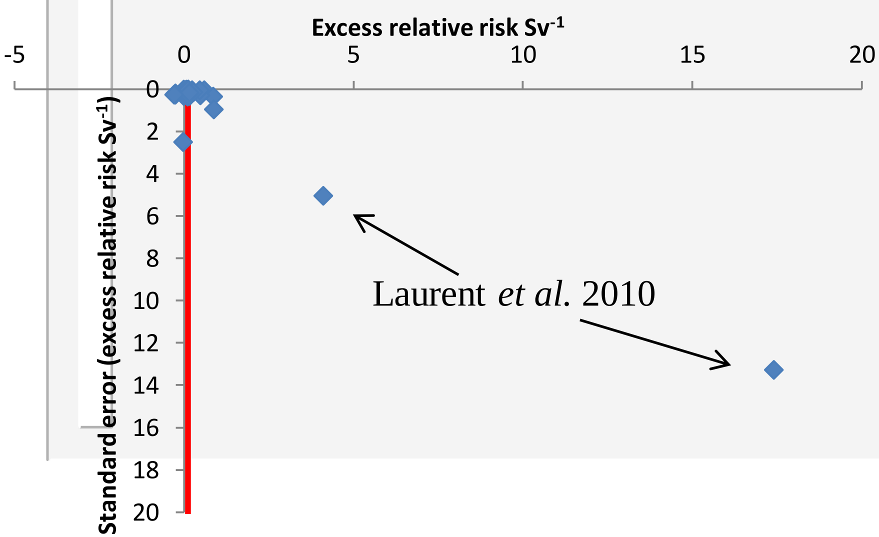
Meta analysis of circulatory disease (Little *et al.* *Env. Health Perspect.* 2012 in press)`

- PubMed + ISI Thompson search using terms "radiation" +"heart" +"disease" or "radiation" +"stroke" or "radiation" +"circulatory" +"disease", published ≥1/1/1990 (search on 14/5/2011 + 17/8/2011)
- Restricted to human data exposed to moderate/low uniform whole body doses (acute mean dose <0.5 Sv – limit suggested by radiobiology, but chronic exposures allowed higher), with good quality dosimetry
- 12 studies identified
- Fixed effect + random effects analysis (random effects needed when significant heterogeneity)

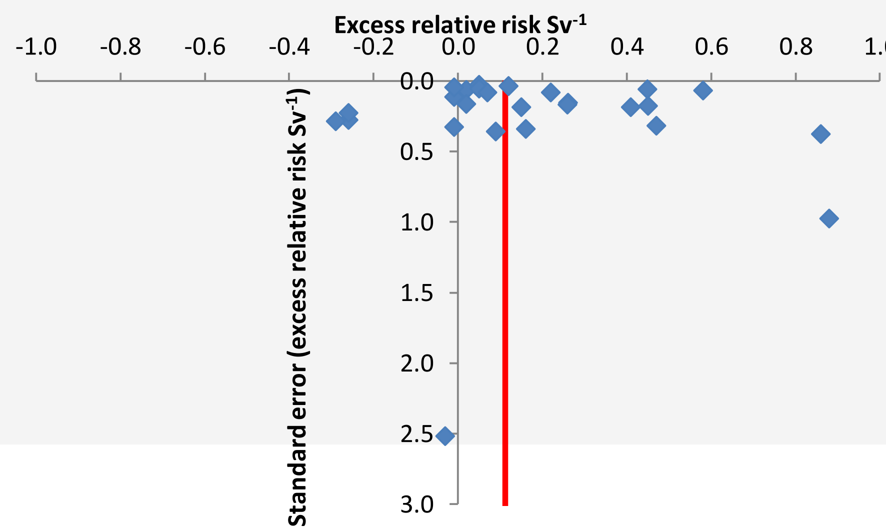
Problems with meta-analysis: publication/selection bias?

- Generally expect bias towards publications with significant results
- Funnel plot (mean *vs* SE) is reasonably symmetric, implying little or no bias (possible slight problem with Laurent *et al.*, but little information in this study)

All data



All data excluding Laurent *et al.* 2010



Test of publication/selection bias, and bias correction (Little *et al.* *Env. Health Perspect.* 2012 in press)

Disease endpoint	Egger *et al.* publication/selection-bias test *p*-value	Random effects ERR Sv^{-1} (and 95% CI), bias-uncorrected	Random effects ERR Sv^{-1} (and 95% CI), corrected using trim-and-fill method of Duval and Tweedie
Ischaemic heart disease	0.322	0.10 (0.04, 0.15)	0.09 (0.02, 0.15)
Other heart disease	0.468	0.08 (-0.12, 0.28)	0.08 (-0.12, 0.28)
Cerebrovascular disease	0.692	0.21 (0.02, 0.39)	0.20 (0.02, 0.39)
Other circulatory disease	0.408	0.19 (-0.00, 0.38)	0.16 (-0.03, 0.35)
All circulatory disease	0.279	0.11 (0.03, 0.19)	0.16 (0.08, 0.24)

Little evidence of publication/selection bias, and bias corrections are minimal

Confounding factors for circulatory disease

- Few studies adequately control for established circulatory risk factors (smoking, diabetes, obesity/inactivity, hypertension, low HDL/high LDL cholesterol)
  - A-bomb morbidity study (Yamada *et al Radiat Res* **161**:622-32;2004) controls for smoking, drinking
  - A-bomb circulatory mortality adjusted for smoking, alcohol intake, education, occupation, obesity (BMI), diabetes mellitus (Shimizu *et al Br Med J* **340**:b5349;2010)
  - Mayak study (Azizova *et al Radiat Res* **174**:155-68,851-64;2010) controls for smoking and drinking
- Many of these risk factors correlated with socioeconomic status (SES): limited adjustment for SES in some occupational studies (IARC 15-country, BNFL, NRRW-3), none in others
- Will they confound (i.e., are they correlated with radiation dose)?
  - No evidence for confounding by these in A-bomb or Mayak studies
  - Lack of associations between radiation dose and smoking-related non-malignant respiratory diseases in occupational studies (IARC 15-country, NRRW-3, EdF) implies that smoking unlikely to confound in these cohorts

Meta-analysis of moderate/low dose circulatory disease: excess relative risk coefficients (Little *et al*. *Env. Health Perspect*. 2012 in press)

Circulatory disease subtype	Studies Included	Fixed-effect ERR / Sv (+95% CI)	Random-effect ERR / Sv (+95% CI)	Heterogeneity *p*
Ischemic heart disease	Yamada *et al.*, Ivanov *et al.*, Vrijheid *et al.* Muirhead *et al.* Azizova *et al.*, Shimizu *et al.*, Laurent *et al.*, Lane *et al.*	0.10 (0.05 to 0.15)	0.10 (0.04 to 0.15)	0.408
Non-ischemic heart disease	Ivanov *et al.*, Vrijheid *et al.*, Shimizu *et al.*	0.12 (-0.01 to 0.25)	0.08 (-0.12 to 0.28)	0.199
Cerebrovascular disease	Yamada *et al.*, Ivanov *et al.*, Kreuzer *et al.*, Vrijheid *et al.*, Azizova *et al.*, Muirhead *et al.*, Shimizu *et al.*, Laurent *et al.* , Lane *et al.*	0.20 (0.14 to 0.25)	0.21 (0.02 to 0.39)	<0.001
Circulatory disease apart from heart disease and stroke	Yamada *et al.*, Ivanov *et al.*, Shimizu *et al.*	0.10 (0.05 to 0.14)	0.19 (-0.00 to 0.38)	<0.001

Random effects model suggests significant excess risk for ischaemic heart disease and stroke

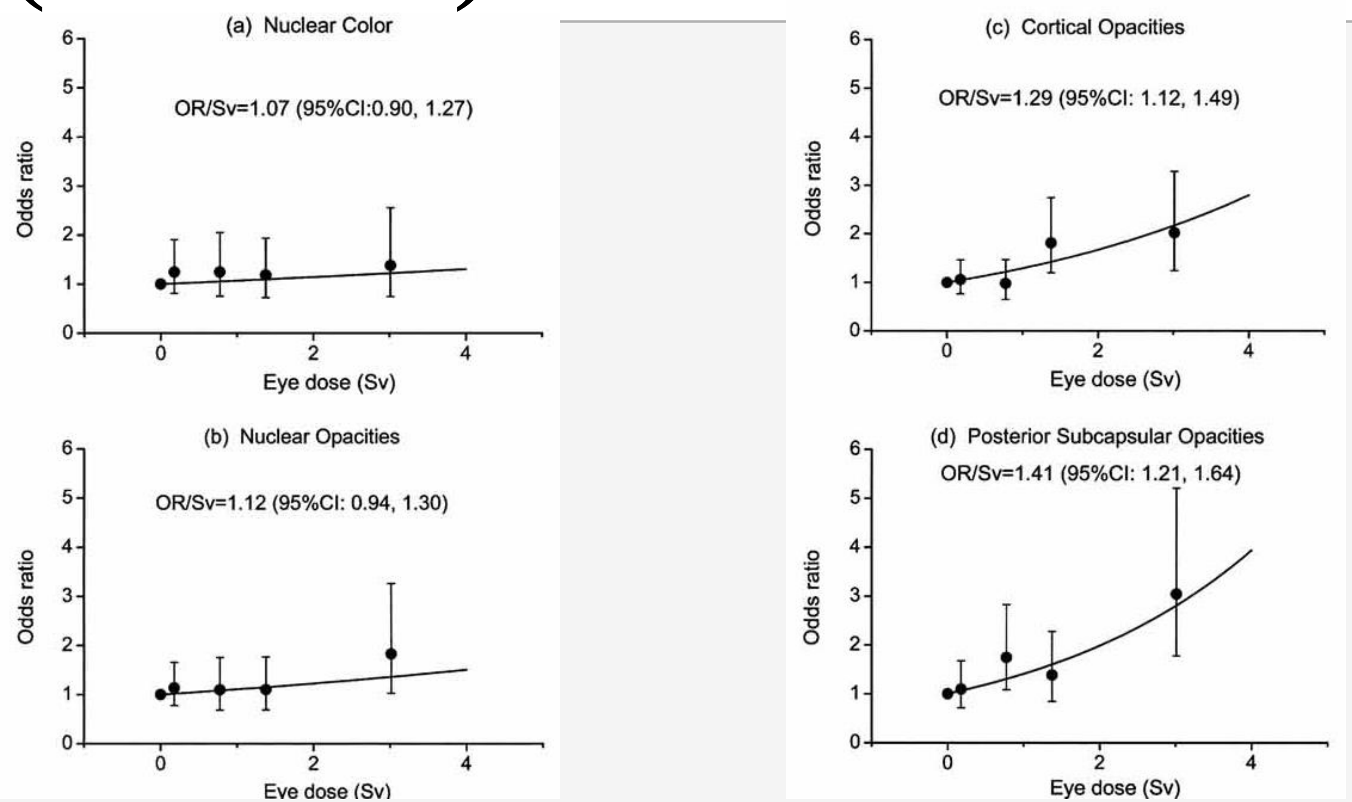
Borderline significant excess risk for circulatory disease apart from heart and stroke

Radiation-Exposure-Induced Death for Various Subtypes of Circulatory Disease, by Country (Little *et al. Env. Health Perspect.* 2012 in press)

Country	Ischaemic heart disease	Other heart disease	Stroke	Other circulatory disease	All circulatory disease	UNSCEAR cancer risks: All solid cancer	UNSCEAR cancer risks: Leukemia excl CLL
China	0.92 (0.41, 1.42)	0.11 (-0.16, 0.37)	4.31 (0.48, 8.14)	1.43 (-0.01, 2.86)	6.76 (2.63, 10.89)	3.95 3.89	0.27 0.42
France	0.50 (0.22, 0.78)	0.54 (-0.85, 1.94)	0.92 (0.10, 1.74)	0.53 (0.00, 1.05)	2.50 (0.77, 4.22)	-	-
Germany	1.71 (0.76, 2.65)	0.97 (-1.52, 3.46)	1.69 (0.19, 3.19)	1.38 (-0.01, 2.76)	5.75 (2.39, 9.10)	-	-
Japan	0.57 (0.25, 0.88)	0.80 (-1.25, 2.85)	2.19 (0.24, 4.14)	0.45 (0.00, 0.91)	4.01 (1.13, 6.89)	4.65 4.90	0.32 0.43
Russia	2.82 (1.26, 4.39)	0.31 (-0.49, 1.11)	4.59 (0.51, 8.66)	0.79 (0.00, 1.57)	8.51 (4.00, 13.02)	-	-
Spain	0.91 (0.41, 1.42)	0.82 (-1.28, 2.52)	1.91 (0.21, 3.60)	0.81 (0.00, 1.63)	4.45 (1.73, 7.17)		
Ukraine	4.14 (1.85, 6.43)	0.20 (-0.31, 0.70)	2.85 (0.31, 5.39)	0.93 (0.00, 1.85)	8.11 (4.53, 11.69)		
UK	1.70 (0.76, 2.64)	0.37 (-0.58, 1.32)	2.24 (0.25, 4.22)	0.76 (0.00, 1.53)	5.07 (2.55, 7.58)	5.15 4.40	0.38 0.43
USA	1.82 (0.81, 2.82)	0.57 (-0.89, 2.03)	1.29 (0.14, 2.44)	0.80 (0.00, 1.61)	4.48 (2.22, 6.74)	4.74 4.41	0.47 0.42

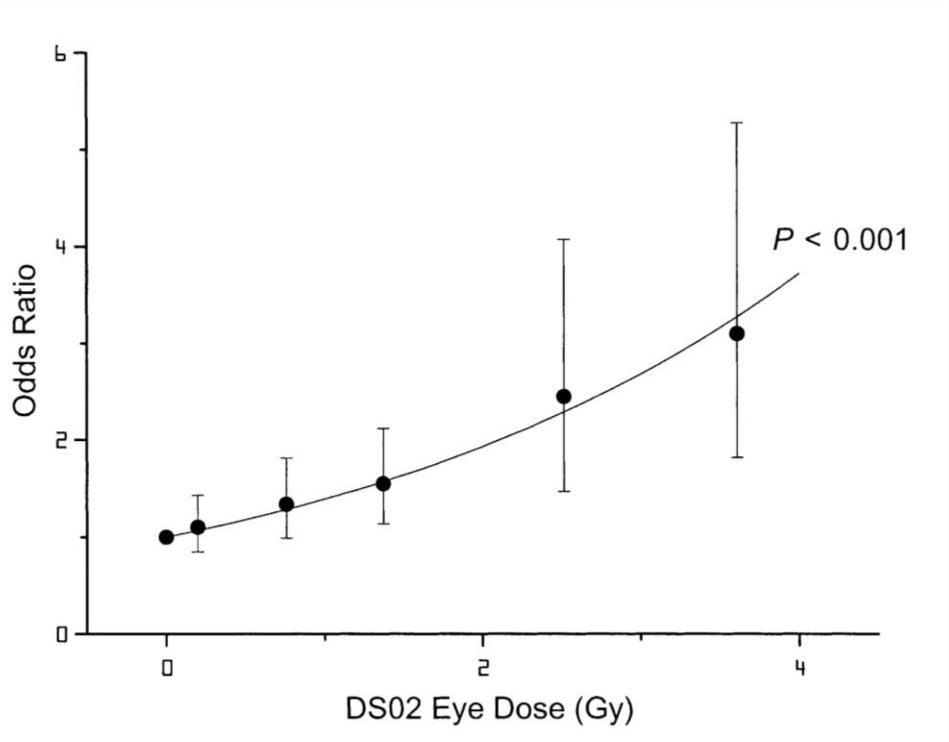
Circulatory disease risk comparable with cancer risk

Cataract in A-bomb survivors: (LOCS II) (Minamoto *et al. IJRB* **80**:339-45; 2004)



Significant increase in cortical and PSC, but nothing significant for nuclear color or opacity

Cataract in A-bomb survivors: (surgical removal) (Neriishi *et al. Radiat. Res.* **168**:404-8; 2007)



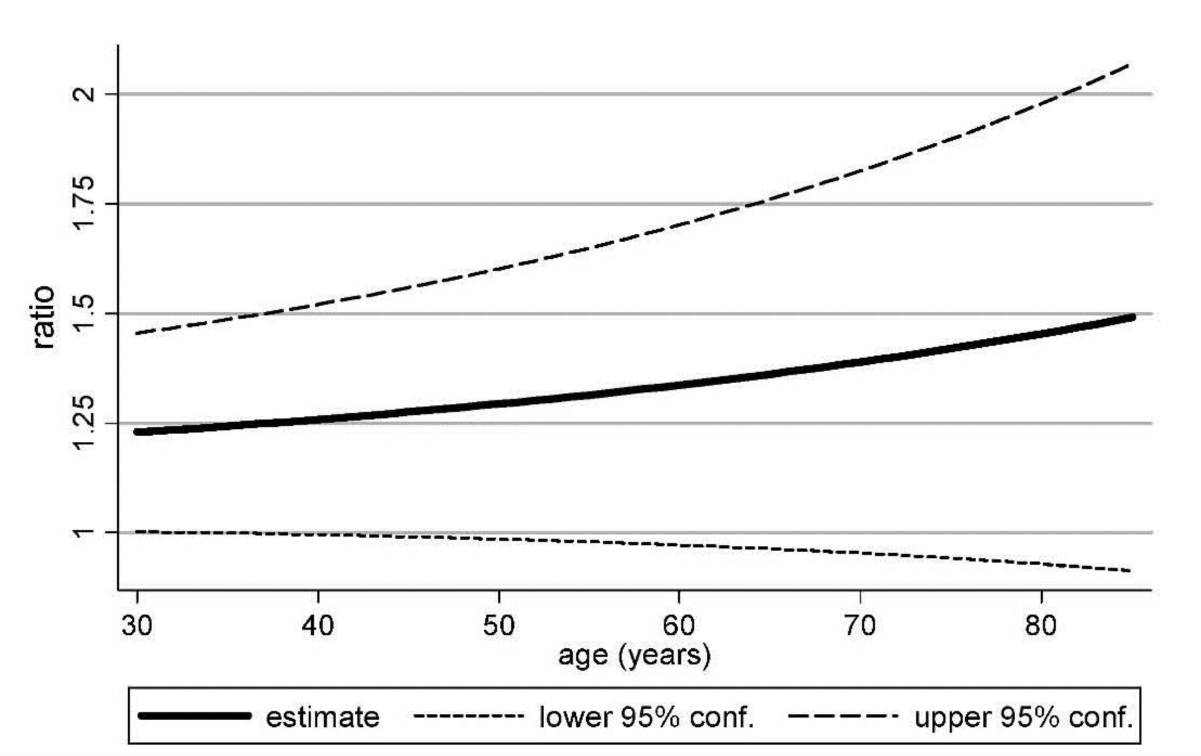
Significant increase in all surgically removed cataract

EOR/Gy = 0.39 (95% CI 0.24, 0.55)

Linear (or linear-quadratic) increase with dose?

Median cortical opacity ratio (exposed *vs* unexposed) in NASA astronauts (LOCS III)

(Chylack *et al. Radiat. Res.* **172**:10-20; 2009)



Significant (*p*=0.017) increase in cortical opacity (parameter σ in skew normal) exposed *vs* unexposed astronauts

No assessment of dose response in this cohort

Threshold dose estimates for cataract

Cohort	Ascertainment	Threshold dose estimates (Gy)	
A-bomb AHS examination (Nakashima *et al. Health Phys.* **90**:154-60; 2006)	LOCS II	Cortical: PSC:	0.6 (90% CI <0, 1.2) 0.7 (90% CI <0, 2.8)
A-bomb AHS cataract surgery (Neriishi *et al. Radiat. Res.* **168**:404-8; 2007)	Surgical removal	All cataract:	0.1 (95% CI <0, 0.8)
Chernobyl recovery worker (Worgul *et al. Radiat. Res.* **167**:233-43; 2007)	Merriam-Focht	Non-nuclear stage 1: PSC stage 1: All cataract stage 1-5:	0.50 (95% CI 0.17, 0.69) 0.35 (95% CI 0.19, 0.66) 0.50 (95% CI 0.17, 0.65)

Thresholds of much more than 0.6 Gy are inconsistent with A-bomb + Chernobyl data

Cataract summary risk estimates

Cohort	Ascertain-ment	Endpoint	Excess odds ratio (EOR) / Gy (95% CI)
Swedish skin haemangioma (Hall *et al Radiat Res* **152**:190-5; 1999)	LOCS I	Cortical: PSC:	0.50 (0.15, 0.95) 0.49 (0.07, 1.08)
A-bomb AHS (Nakashima *et al Health Phys* **90**:154-60; 2006)	LOCS II	Cortical (/Sv): PSC (/Sv): Nuclear opacity (/Sv):	0.30 (0.10, 0.53) 0.44 (0.19, 0.73) 0.07 (-0.11, 0.30)
A-bomb AHS cataract surgery (Neriishi *et al Radiat Res* **168**:404-8; 2007)	Surgical removal	All cataract removal:	0.39 (0.24, 0.55)
Icelandic airline pilots (Rafnsson *et al Arch Opthalmol* **123**:1102-5; 2005)	WHO	Nuclear: Cortical: PSC:	30 (10, 50) <0 (<0, >0) <0 (<0, >0)
Chernobyl recovery worker (Worgul *et al Radiat Res* **167**:233-43; 2007)	Merriam-Focht	Non-nuclear stage 1-5: Nuclear: All cataract stage 1-5:	0.65 (0.18, 1.30) 0.07 (-0.44, 1.04) 0.70 (0.22, 1.38)
US Radiologic technologist (Chodick *et al Am J Epidemiol* **168**:620-31; 2008)	Self-reported removal	All cataract removal:	2.0 (-0.7, 4.7)
Finnish interventional radiologists (Mrena *et al Scand J Work Env Health* **37**:237-43; 2011)	LOCS II	All opacity:	13 (-2, 28)

Endpoint heterogeneity makes comparisons difficult

Evidence of radiation-induced cortical and PSC

Problems with dosimetry in certain cohorts

Non-cancer mortality disease in A-bomb survivors (Ozasa *et al.* *Radiat. Res.* **177**:229-43;2012)

Endpoint	ERR /Sv (95% CI)
Circulatory disease	0.11 (0.05, 0.18)
Respiratory disease	0.23 (0.11, 0.36)
Digestive disease	0.20 (0.05, 0.38)
-*Cirrhosis*	0.11 (-0.07, 0.34)
Genitourinary disease	0.18 (-0.06, 0.46)
Infectious disease	-0.03 (-0.22, 0.23)
Other diseases	0.03 (-0.11, 0.19)
All non-cancer	**0.13 (0.08, 0.18)**
All solid cancer	**0.47 (0.38, 0.56)**

Evidence of excess respiratory and digestive disease (+CVD)

Not seen in any other cohort (uniformity implying possible bias?)

But relative risk distinctly lower than for solid cancer (implying OK? Or due to death certificate misclassification of cancer as non-cancer?)

A-bomb survivor cause of death misclassification (Sposto *et al Biometrics* **48**:605-17;1992)

- Increase in non-cancer mortality due to death certificate misclassification?
- Autopsy study finds 22% of non-cancer deaths misclassified as cancer deaths.
- Statistical adjustment reduces the ERR/Gy for non-cancer mortality from 0.06 to 0.05, but risk coefficient remains statistically significant.

Central nervous system effects

- Many studies of childhood cancer survivors (principally of leukemia) document cognitive impairment associated with high dose cranial irradiation
- Hall *et al.* (*Br. Med. J.* **328**:19;2004) suggested cognitive impairment in Swedish group treated for haemangioma in infancy with much lower doses, with ~50% reduction in high school attendance associated with >100 mGy; similar dose-related reductions in cognitive test performance
- *In utero* exposed A-bomb data also suggest cognitive impairment at high dose (Schull & Otake *Teratology* **59**:222-6;1999), but no cognitive impairment (e.g., reduction in IQ) in 0-100 mGy dose range
- Are low dose studies (A-bomb, Hall *et al.*) consistent (metrics differ)? Is *in utero* same as early childhood?

Conclusions

- Circulatory disease
  - Meta-analysis of moderate+low-dose data suggests significant excess risk for two out of four circulatory disease endpoints (ischaemic heart, stroke), and aggregate risk significant
  - Risk factors from moderate+low-dose cohorts suggest radiation-associated population risks of circulatory disease are similar to radiation-induced cancer
  - Apart from A-bomb + Mayak, few cohorts have information on major lifestyle factors (smoking, drinking, obesity, HDL+LDL cholesterol, hypertension, diabetes), but little indication that these confound in A-bomb or Mayak
- Cataract
  - Evidence that cortical + posterior subcapsular cataract are radiation induced, but not nuclear
  - Thresholds of >0.6 Gy can be ruled out for cataract (but lin/LQ increase with dose?)
- Other non-malignant
  - Significant excess of non-malignant respiratory and digestive disease mortality in A-bomb data, but not seen in any other exposed group (probably not misclassification?)
  - Possibly inconsistent evidence for neuro-cognitive effects after exposure *in utero*, early childhood