Radiation and risk of non-cancer diseases

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DCEG Radiation Epidemiology and Dosimetry Course 2019

Overview

- Introduction
- Circulatory diseases
  - A-bomb survivors
  - Occupational low-dose studies
  - Radiotherapy studies
- Eye lens opacities (cataract)
  - A-bomb survivors
  - Occupational low-dose studies
  - Radiotherapy studies

Non-cancer diseases

- Everything but cancer
- International Classification of Diseases ICD-11
  - Infectious diseases, Neoplasms, Hematological, Immune, Endocrine, Mental/Behavioral, Sleep, Neurological, Visual, Ear, Circulatory, Respiratory, Digestive, Skin, Musculoskeletal, Genitourinary, Sexual, Pregnancy/Childbirth, Perinatal, Developmental, Signs/Symptoms, Injury/External causes
- Not covering tissue reactions (a.k.a. deterministic effects)
  - Not a topic addressed by epidemiology

What are non-cancer effects of radiation?

- Other than tissues reactions (deterministic effects)
  - Vascular disease
  - Cataract (eye lens opacities)
  - Endocrine effects
  - Nervous system effects
  - Immunological effects
  - Respiratory disease
  - Kidney disease

Radiation and circulatory disease

Three systematic reviews

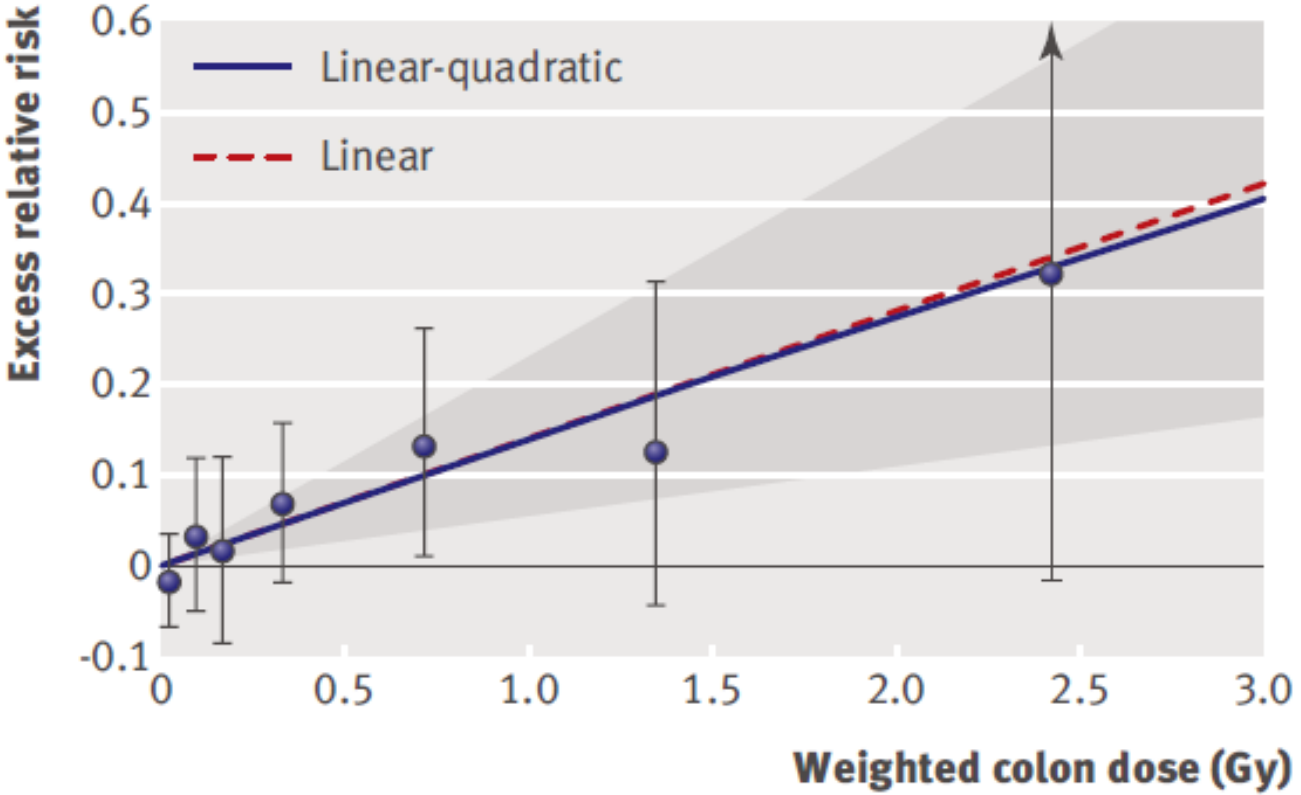
- 2005 McGale & Darby: Epidemiological data do not at present provide clear evidence of a risk of circulatory diseases at doses of ionising radiation in the range 0-4 Gt
  - 26 studies, occupational and medical exposures
- 2012 Little et al: Our review supports an association between circulatory disease mortality and low and moderate doses of ionising radiation…limited by heterogeneity…if confirmed
  - 10 studies (A-bomb survivors and occupational cohorts)
- 2016 Little: The review provides strong evidence in support of a causal association between both low and high dose radiation and most types of circulatory disease
  - 20 studies (A-bomb, occupational, medical, environmental)

Paradigm change

- Earlier regarded as a high-dose phenomenon only
  - Tissue damage to the heart
- Recognised initially in radiotherapy
- Observations among A-bomb survivors a game changer
- Subsequent findings also in chronic low-dose exposure in occupational setting

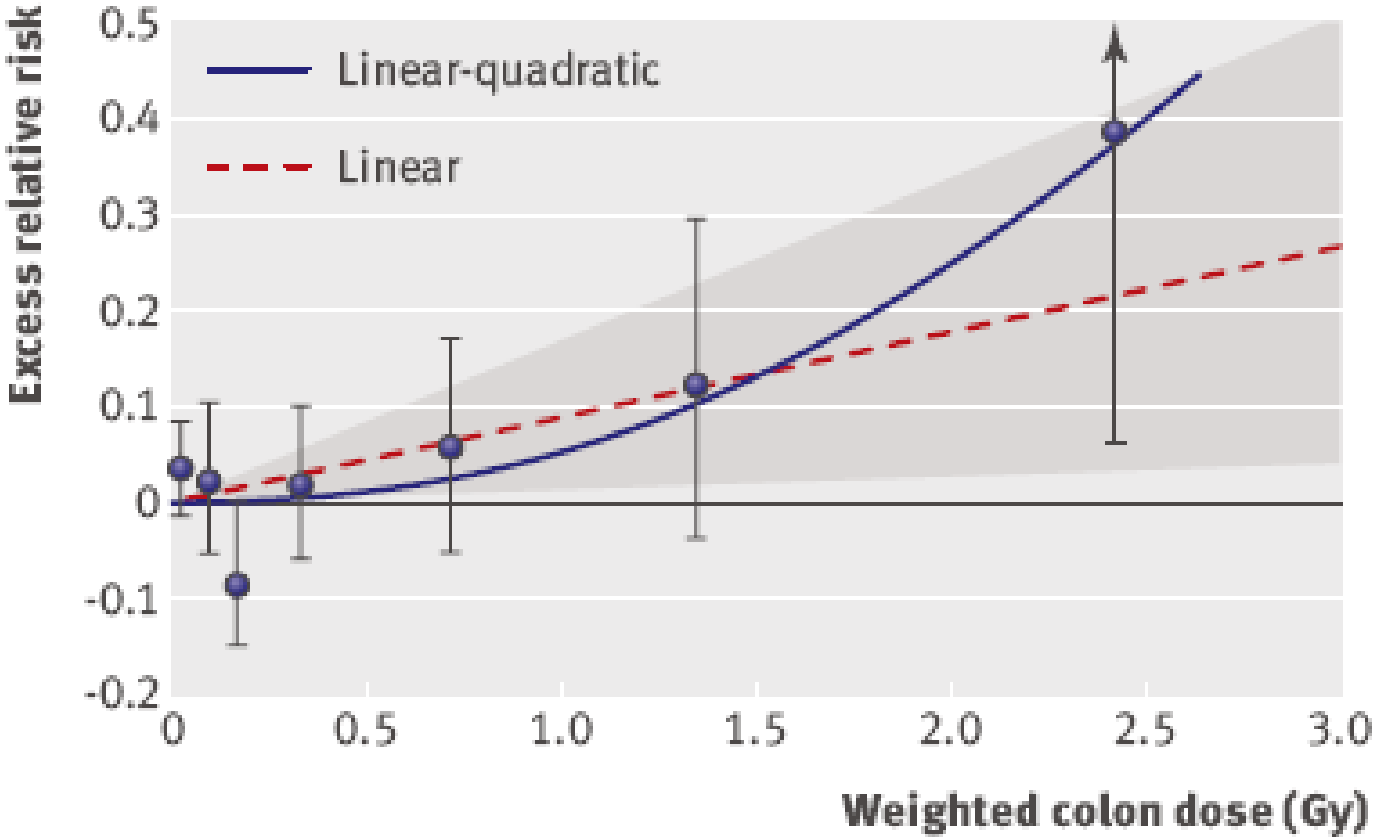
Atomic bomb survivors

Dose-response for heart disease mortality (1950-2003)



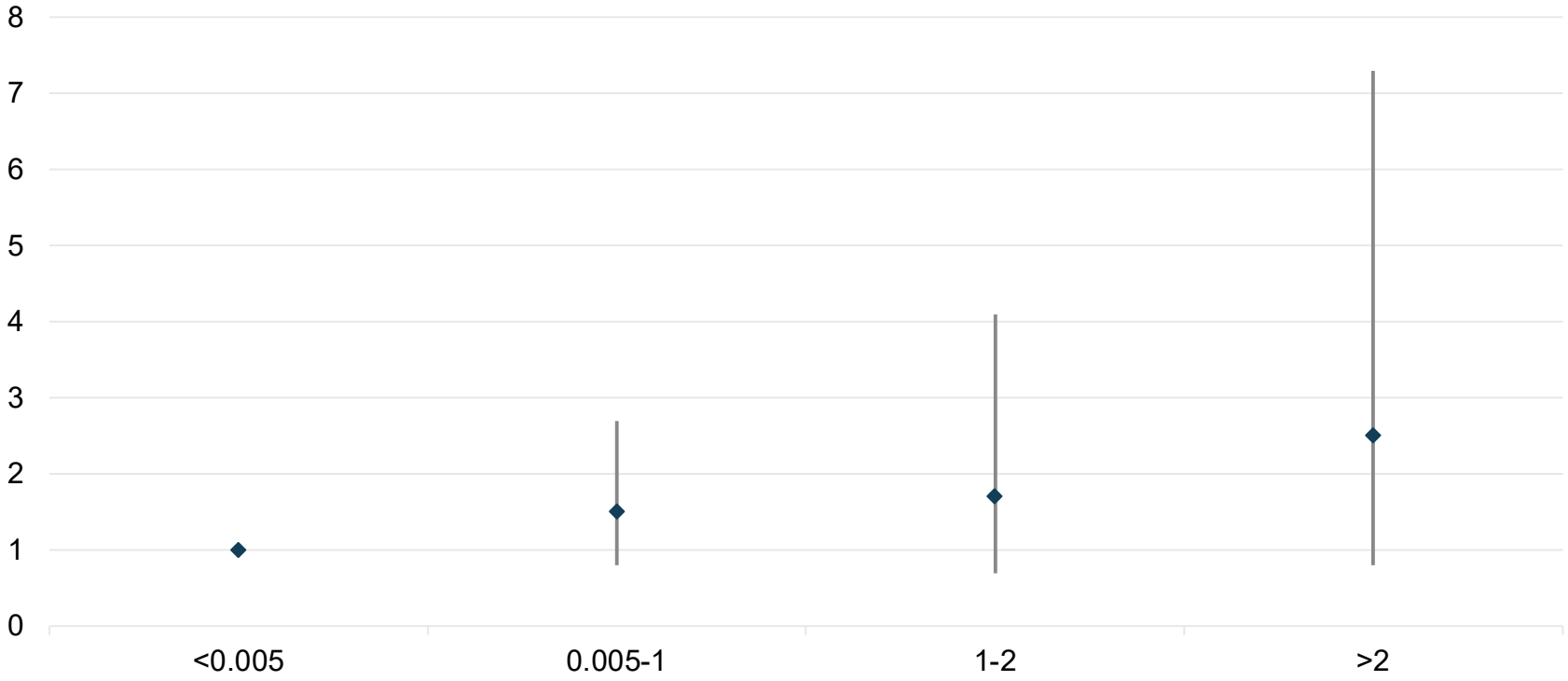
Shimizu *BMJ* 2010

Dose-response for stroke mortality (1950-2003)



Shimizu *BMJ* 2010

Dose-response for hemorrhagic stroke incidence (1980-2003)



Takahashi et al. *BMJopen* 2012

LSS mortality from non-cancer diseases

Non-neoplastic diseases and other causes		
Blood diseases	1.70 (0.96, 2.70)	238
Circulatory diseases	0.11 (0.05, 0.17)	19,054
Respiratory diseases	0.21 (0.10, 0.33)	5,119
Digestive diseases	0.11 (-0.01, 0.24)	3,394
Genitourinary diseases	0.14 (-0.06, 0.38)	1,309
Infectious diseases	-0.02 (-0.15, 0.13)	1,962
Other diseases	0.01 (-0.1, 0.12)	4,847
External causes	-0.11 (-0.21, 0.02)	2,432

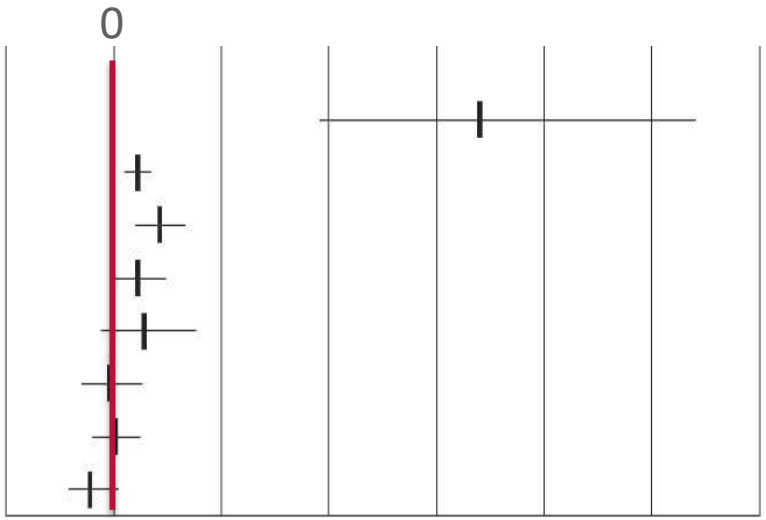
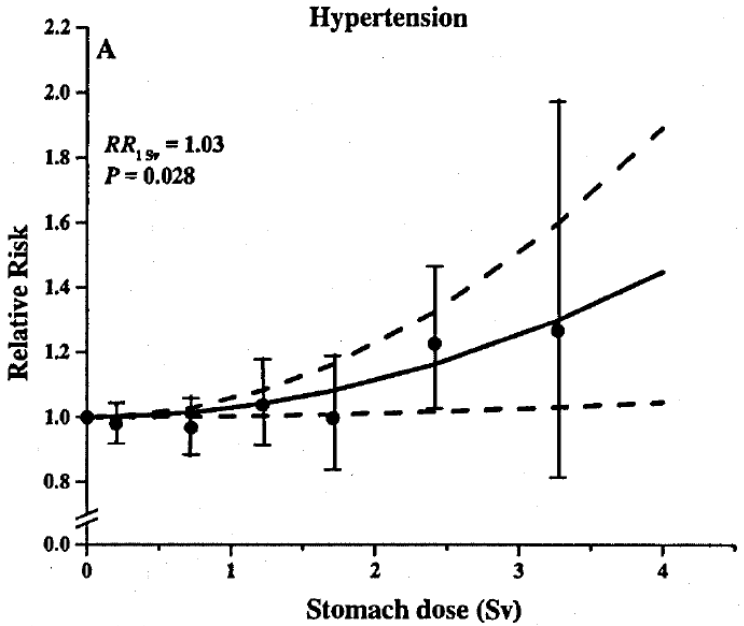
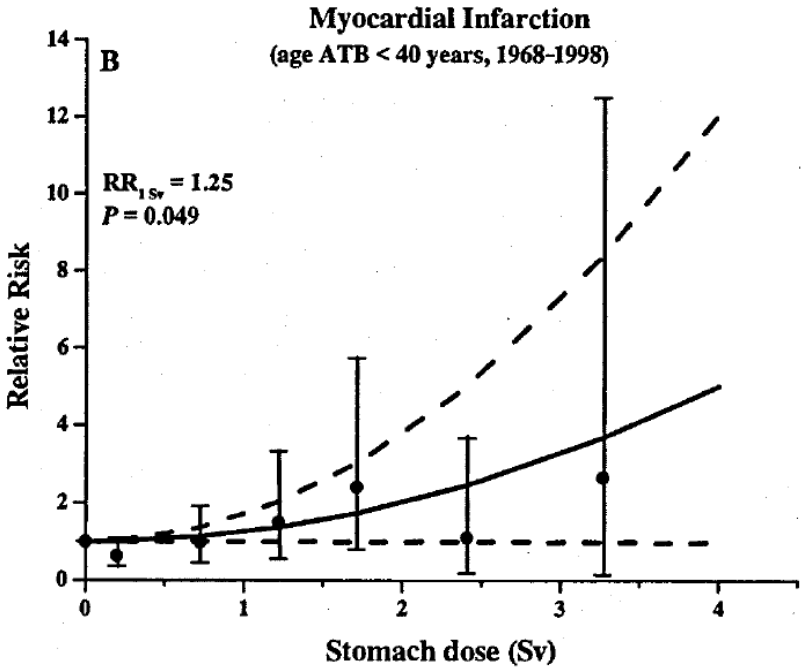


FIG. 1. Estimates of excess relative risk (ERR) per Gy and 95% CI for major causes of death. [a] ERR was estimated using the linear dose model, in which city, sex, age at exposure, and attained age were included in the background rates, but not allowing radiation effect modification by those factors. [b] Confidence interval. Horizontal bars show 95% confidence intervals. [c] The size of plots for site-specific cancers was proportional to the number of cases. [d] ERR (95% CI) of leukemia was 3.1 (1.8, 4.3) at 1 Gy and 0.15 (−0.01, 0.31) at 0.1 Gy based on a linear-quadratic model with 318 cases (not displayed in the figure). [e] The lower limit of 95% CI was lower than zero, but not specified by calculation.

Ozasa et al. *Radiat Res* 2012

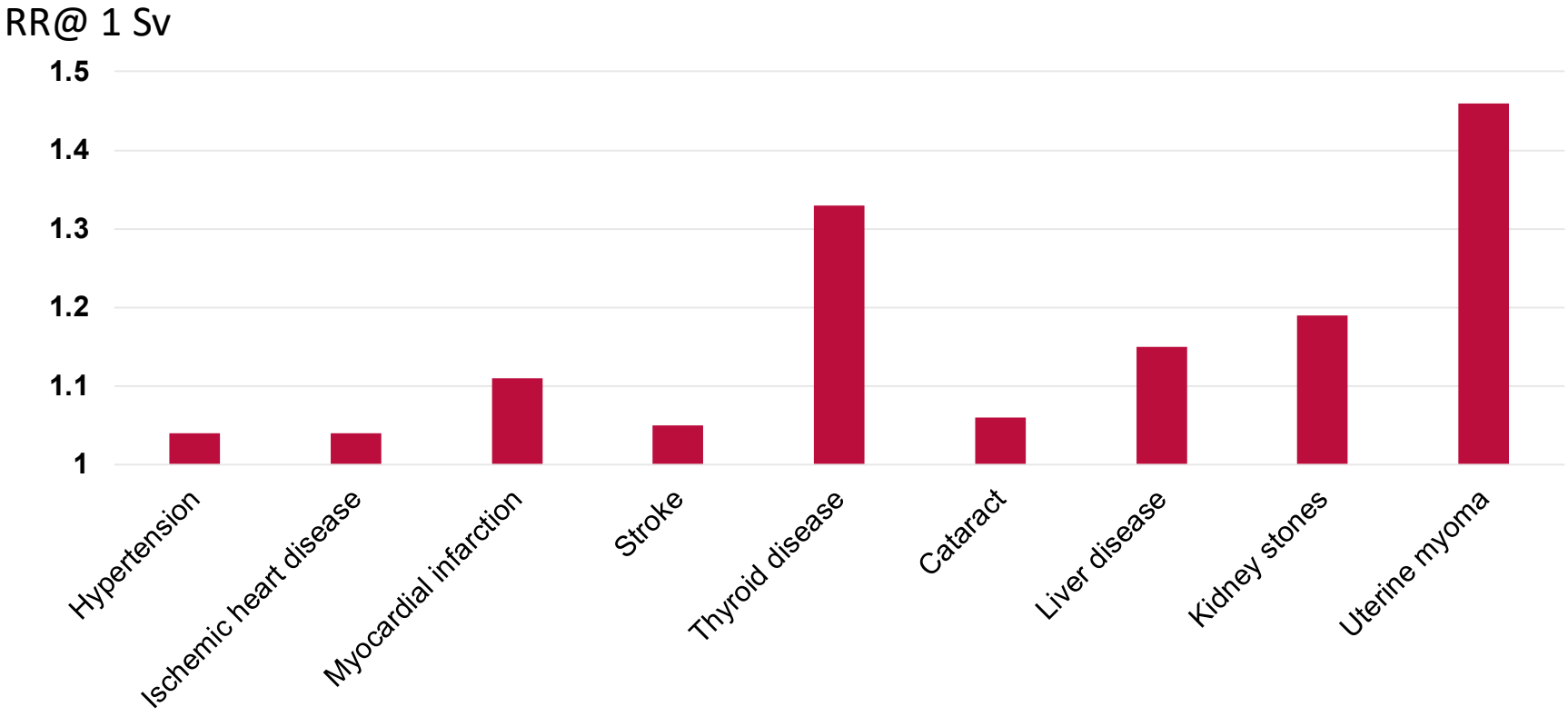
Dose-response for vascular disease





Yamada et al. Radiat Res 2004

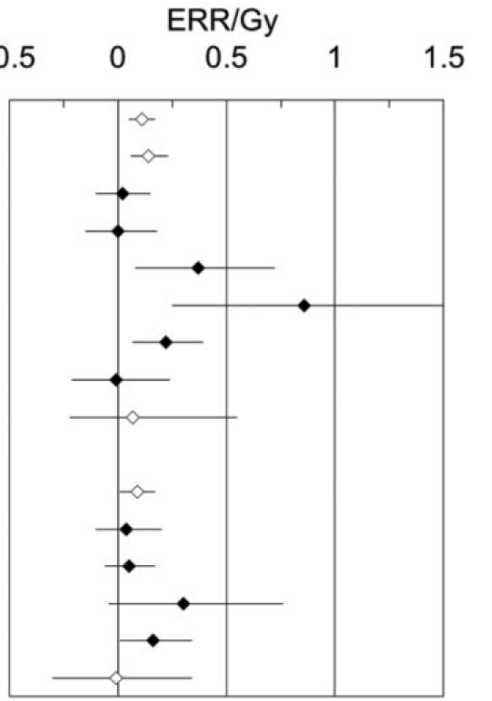
Risk coefficient per dose unit, by dg (incidence)



Yamada et al. *Radiat Res* 2004

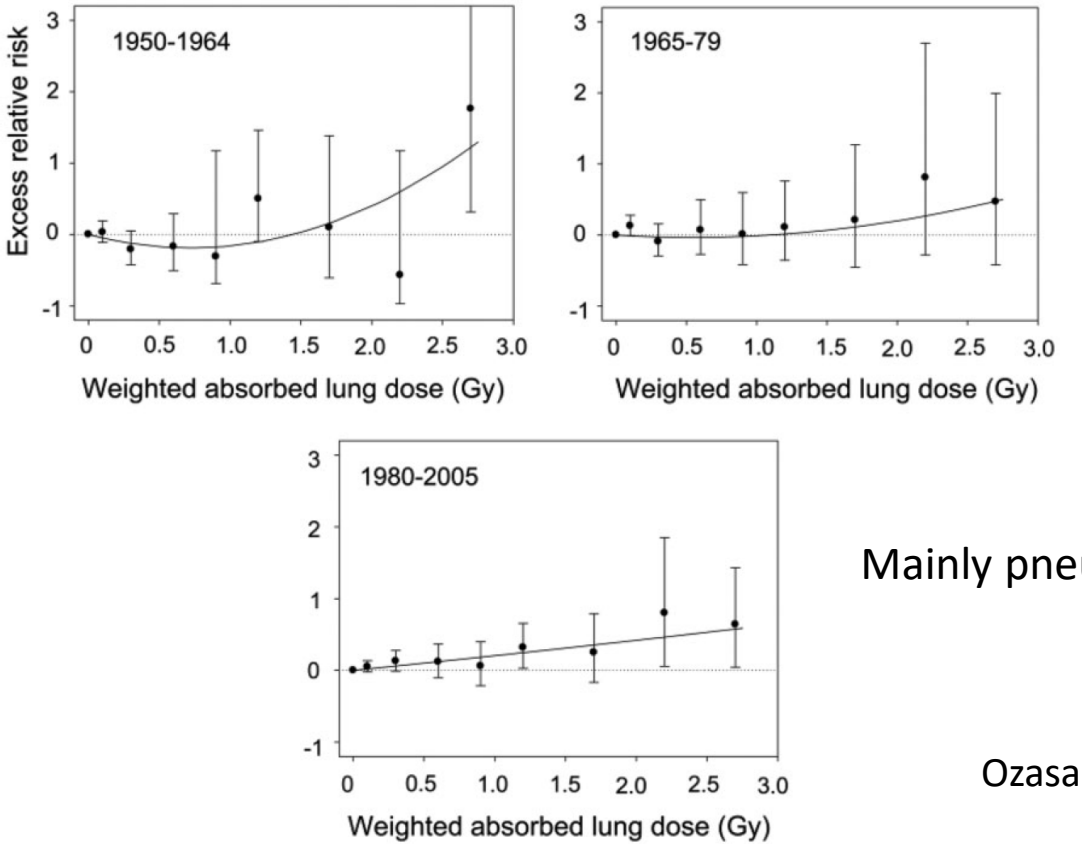
ERR/Gy for vascular diseases (1950-2003)

Disease category (ICD-9 code)	No of deaths
Circulatory disease (390-459)	19,054
Heart disease (390-398, 402, 404, 410-429)	8,463
Ischemic heart disease (410-414)	3,252
Myocardial infarction (410)	1,735
Hypertensive heart disease (402, 404)	922
Rheumatic heart disease (393-398)	242
Heart failure (428)	2,983
Other heart diseases	1,064
Hypertensive disease without heart diseases (401, 403, 405)	411
Stroke (430-438)	9,622
Cerebral infarction (433, 434)	2,659
Cerebral hemorrhage (431)	4,060
Subarachnoid hemorrhage (430)	461
Others or unspecified	2,442
Other circulatory disease	558



Ozasa et al. *Ann ICRP* 2015

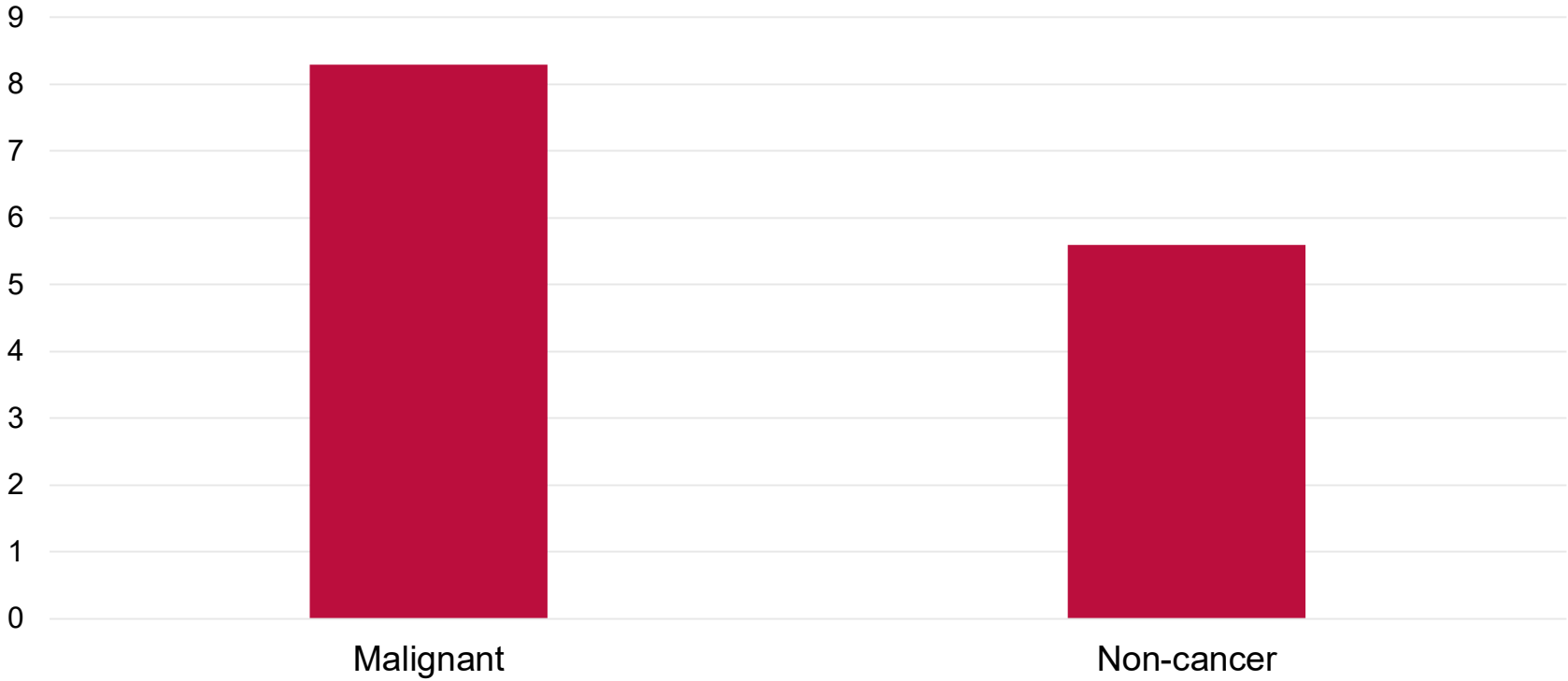
Dose and respiratory disease mortality by period



Mainly pneumonia and influenza

Ozasa et al. *Ann ICRP* 2015

Population attributable risk (% of deaths)



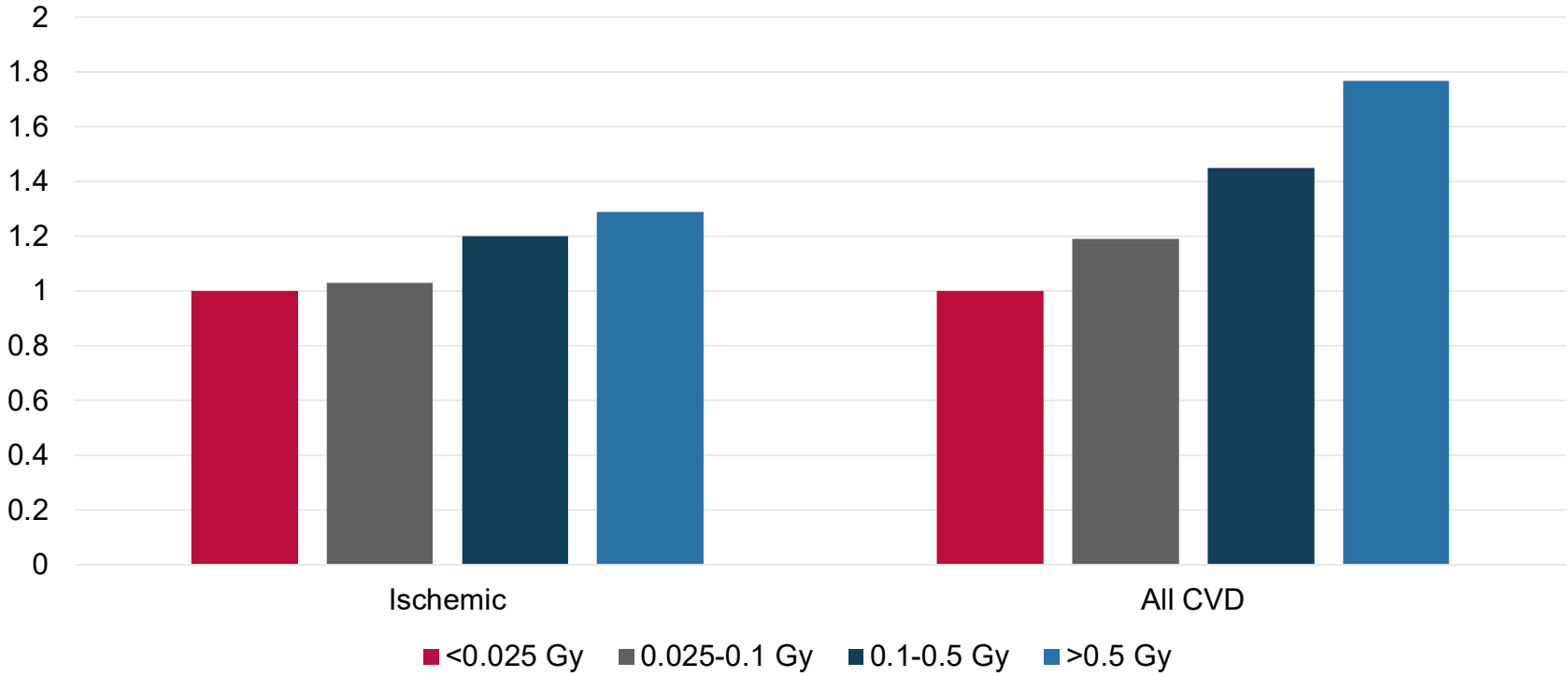
Ozasa et al. *Radiat Res* 2012

Occupational studies

Mayak workers

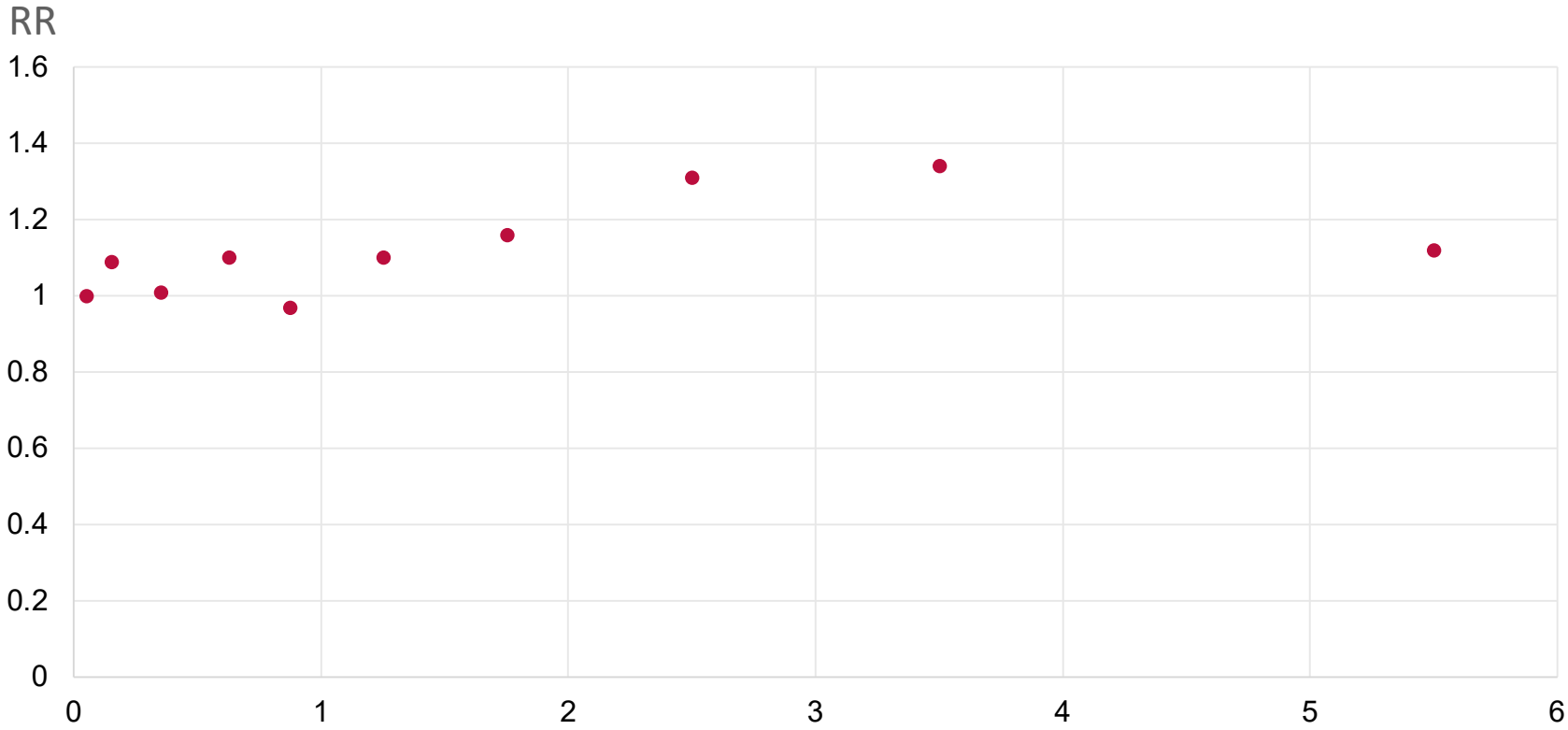
- Moseeva *Radiat Environ Biophys* 2014, Azizova *Br J Radiol* 2015
- 22,377 workers
- Mean dose 0.51 Gy for external gamma
  - Mean alpha dose form plutonium to the liver 0.29 Gy
- Follow-up mean 20 years for incidence, 37 years for mortality
  - 5% loss to follow-up, 4% unknown cause of death
  - Ischemic heart disease 7225 incident cases and 2848 deaths
    - 5098 & 2127 cases, 2304 & 544 deaths in men and women

Heart disease incidence in Mayak workers



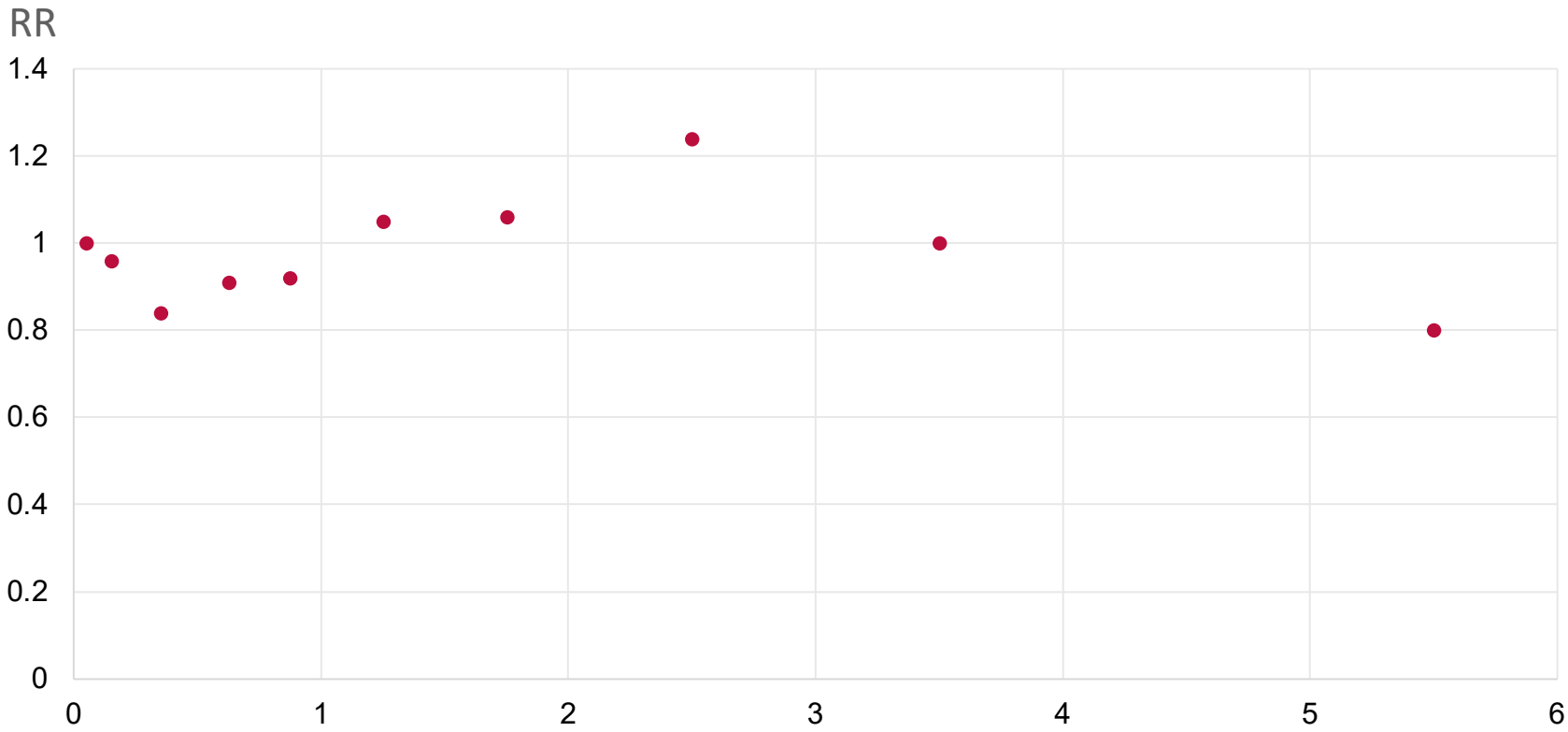
Moseeva 2014

Ischemic heart disease incidence: Dose-response



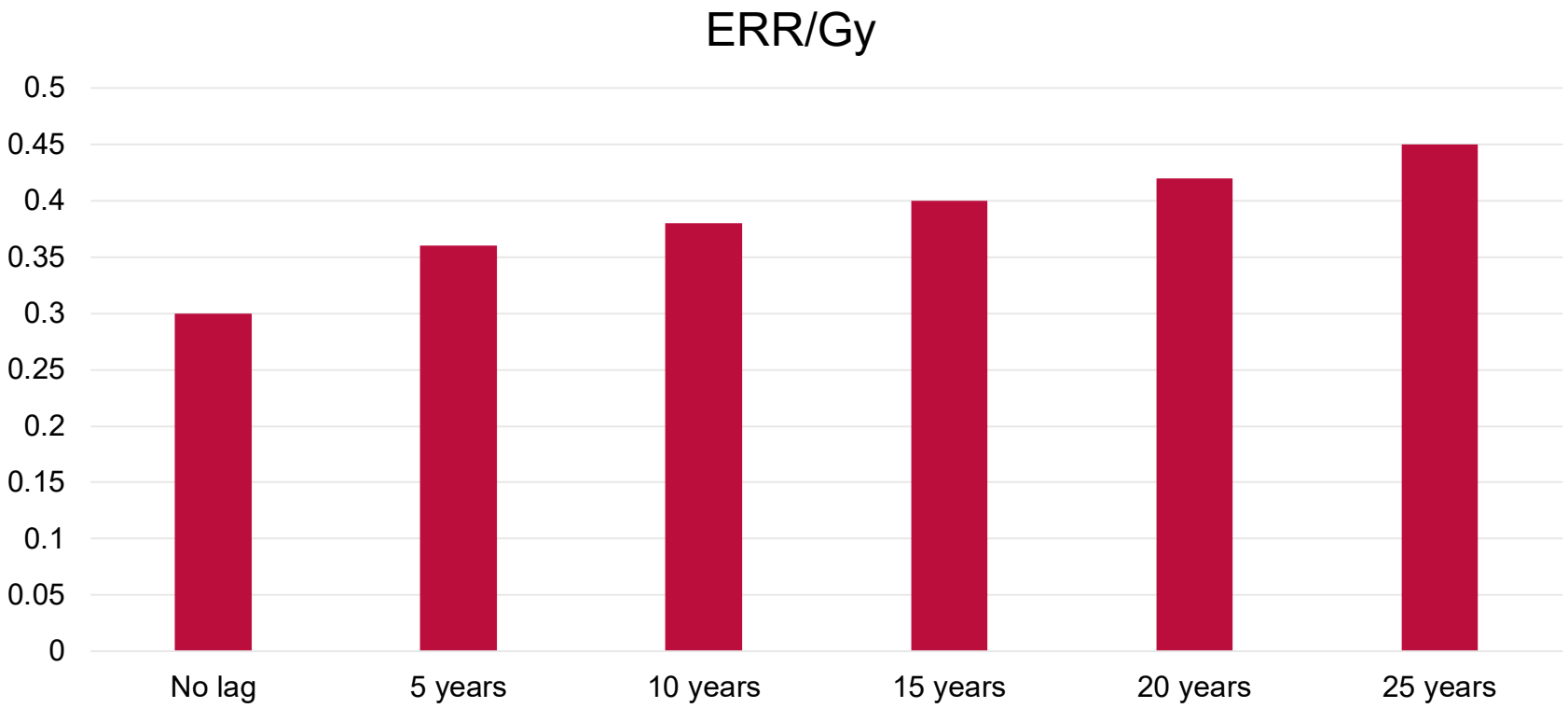
Azizova et al. 2015

Ischemic heart disease mortality: Dose-response



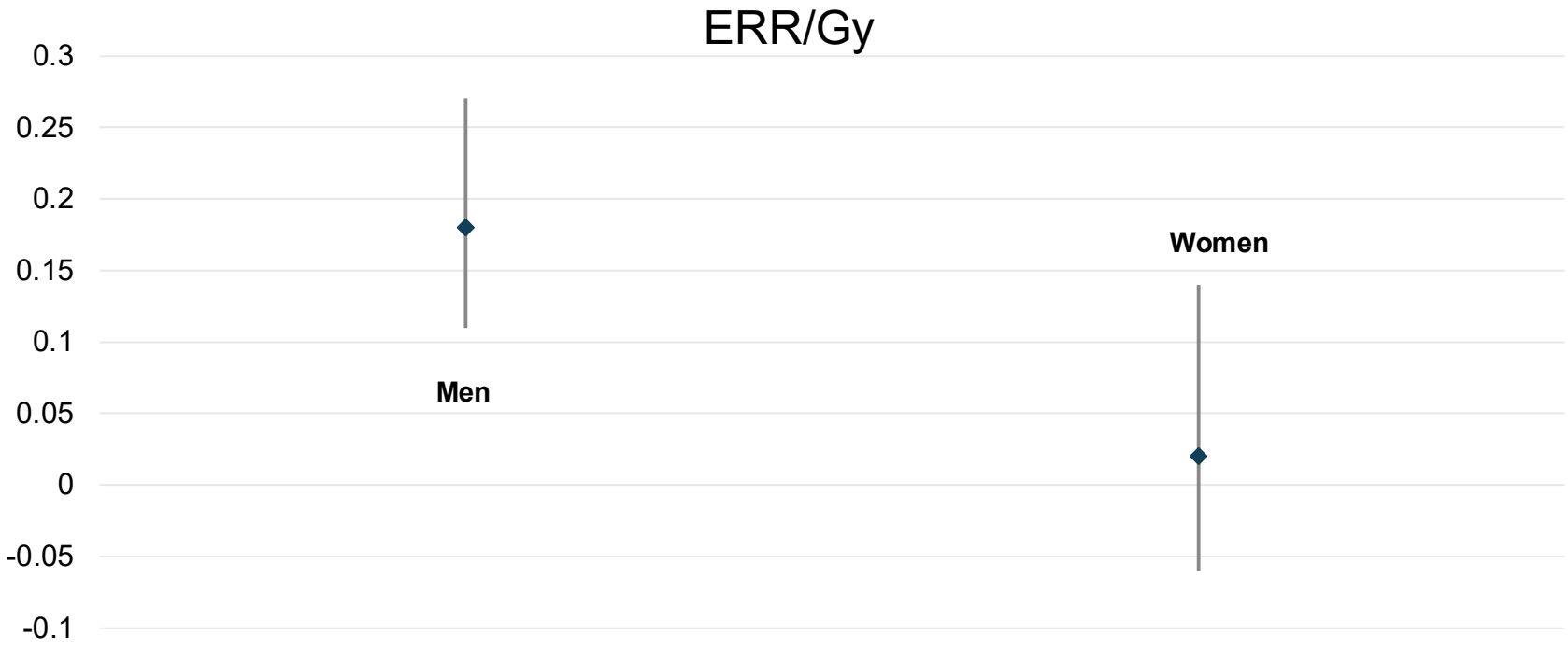
Azizova et al. 2015

Lag-time



Azizova et al. 2015

Effect size by sex

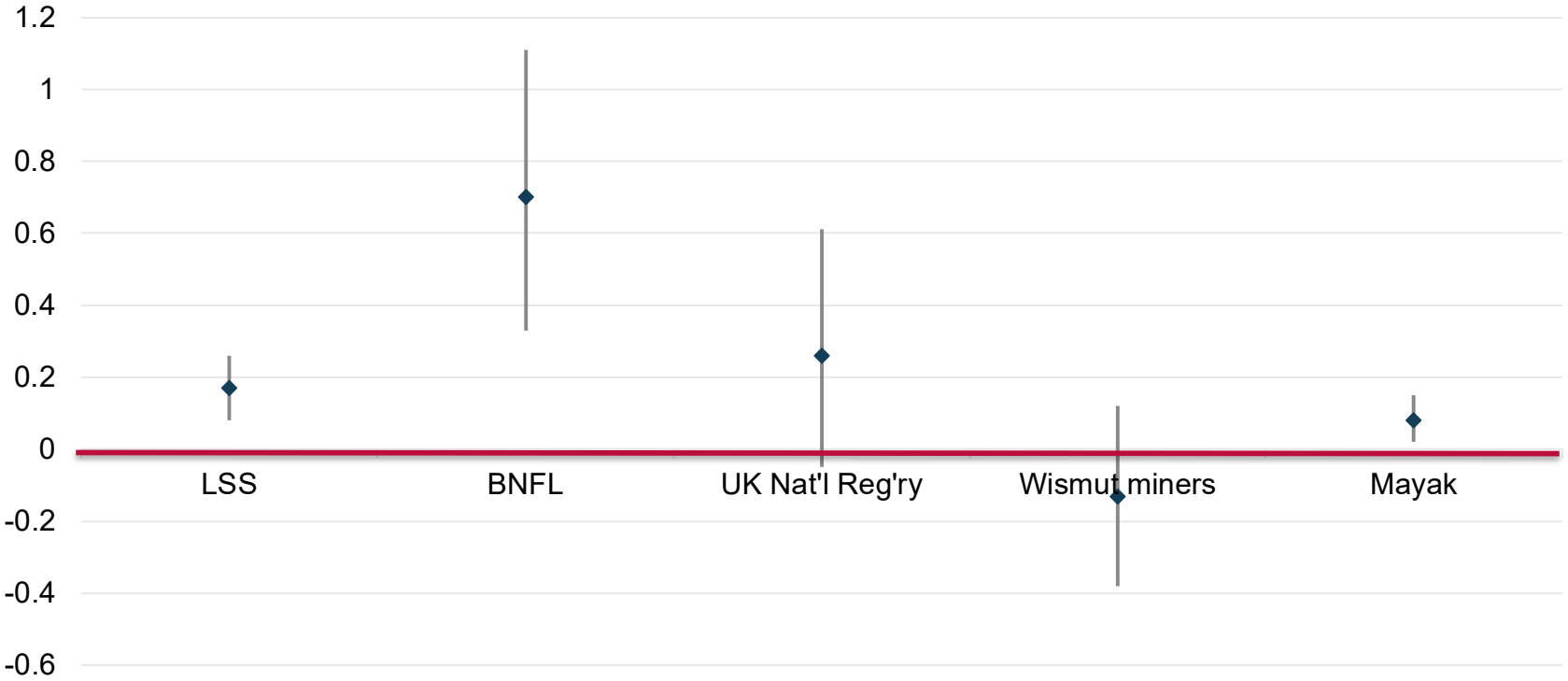


Azizova et al. 2015

Summary of occupational cohort studies

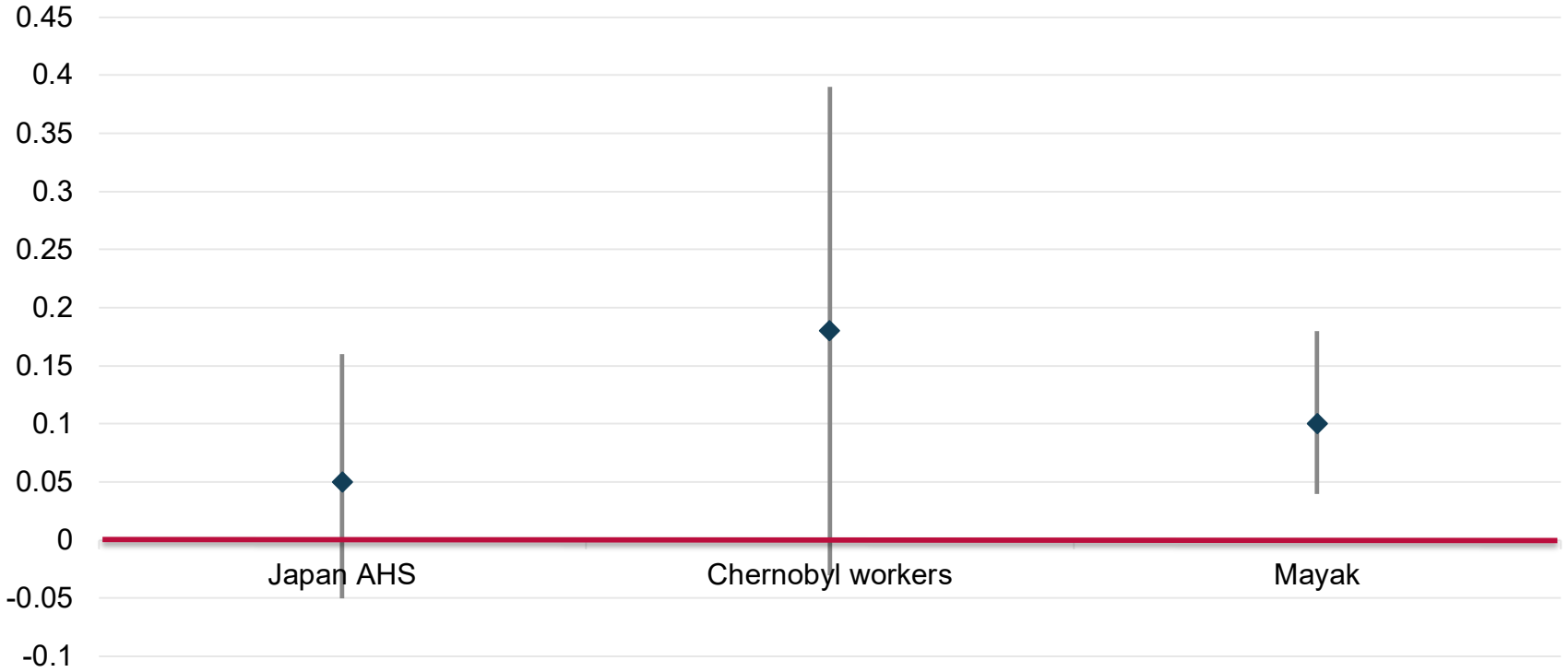
Study population	Reference	Cohort size (mean dose)	Circulatory disease	Ischemic heart disease
Nuclear workers	Vrijheid 2007	275,312 (0.02)	0.09 (-0.4, +0.7)	-0.01 (-0.6, +0.7)
Chernobyl emergency workers	Ivanov 2006	53,772 (0.16)	0.18 (-0.03, +0.39)	0.41 (0.05-0.78)
Uranium miners	Kreuzer 2013	58,982 (0.05)	-0.13 (-0.38, +0.12)	-0.03 (-0.38, +0.32)

Mortality from circulatory disease, worker studies



Little *Mutat Res* 2016

Circulatory disease incidence, worker studies

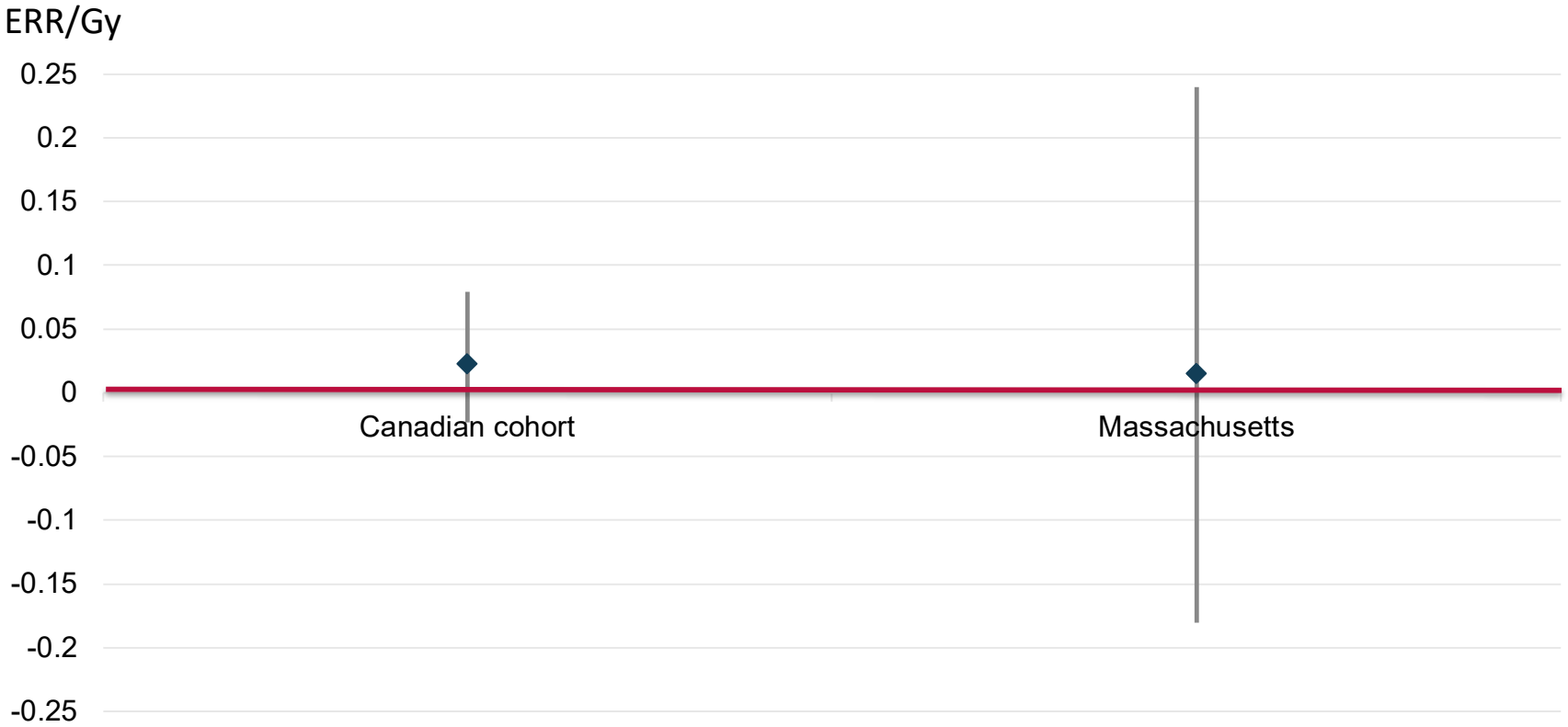


Medical exposures

Studies of diagnostic radiation exposure

- Canadian TB fluoroscopy cohort
  - Zablotska et al. *Am J Epid* 2014
  - 63,707 patient, 30-year follow-up for mortality
  - Mean heart dose 0.79
- Massachusetts TB fluoroscopy cohort
  - Little et al. *Eur J Epide* 2016
  - 13,568 patients, 25-year mortality follow-up
  - Mean lung dose 0.36 Gy

Circulatory disease mortality, diagnostic x-ray studies



Radiotherapy

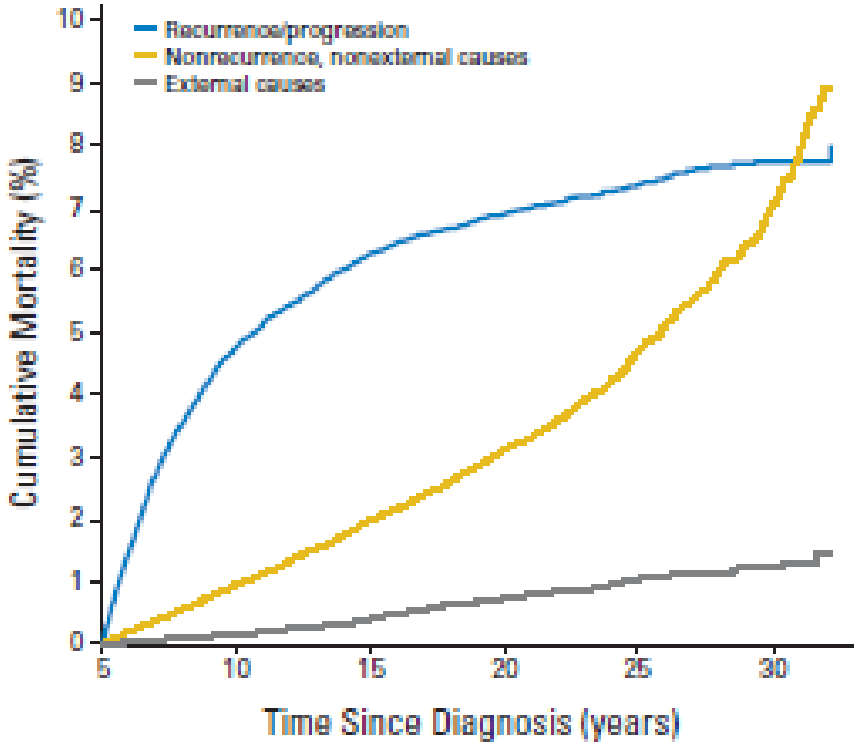
Radiotherapy studies

- Often predominantly very high doses >2 Gy
- Frequently in combination with cardiotoxic chemotherapy
- Childhood cancers, breast cancer, Hodgkin lymphoma

Accelerated aging?

- Physiological changes affecting several organs and processes
  - Hypertension, dyslipidemia, obesity, diabetes
- Increased morbidity and disease burden from several diseases
  - Endocrine
  - Neurological
  - Cardiovascular
- Onset at earlier age
- Increased premature mortality
- Signs, symptoms and markers of ageing (frailty)
- Induced by both radiotherapy and chemotherapy (and possibly other cancer treatments)

Cumulative mortality after childhood cancer

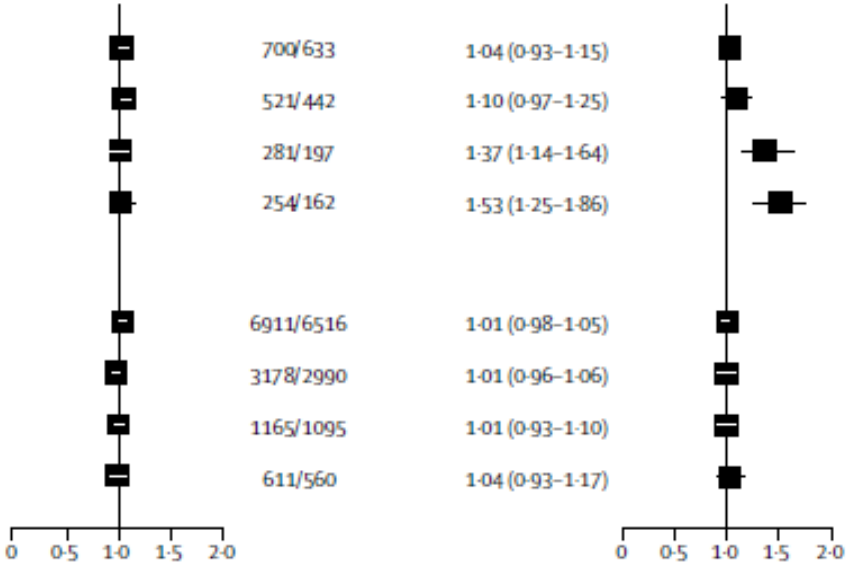


Second malignancy SMR=15 (14-17) (19% of deaths)
Cardiac disease SMR=7.0 (5.9-8.2) (7%)
Pulmonary disease SMR=8.8 (6.8-11) (3%)

Armstrong et al. *J Clin Oncol* 2009

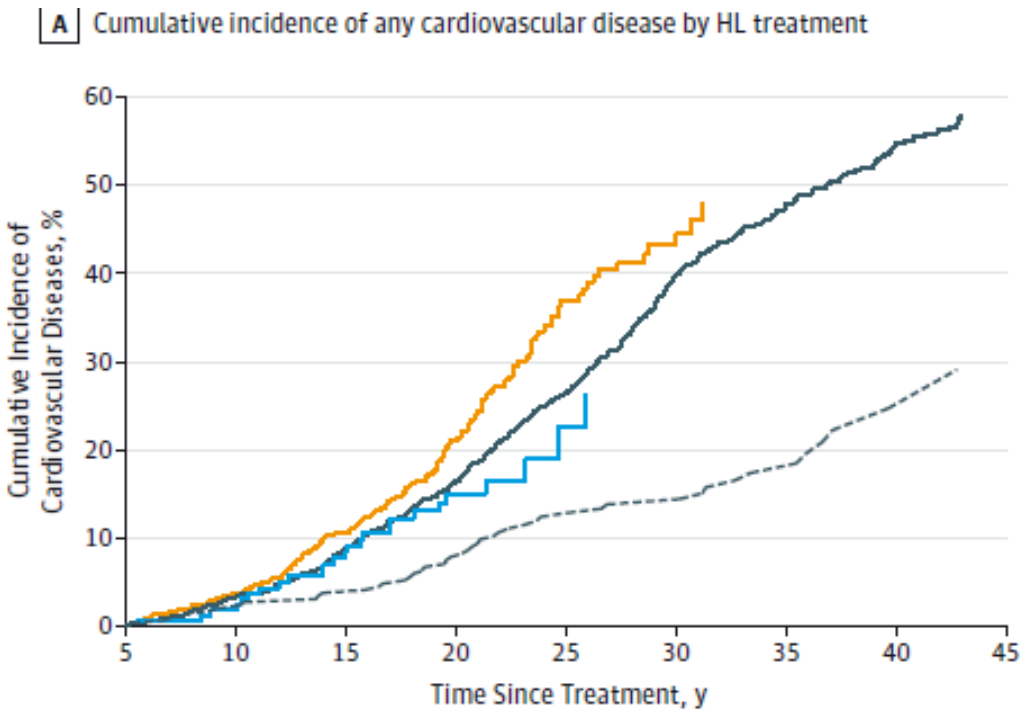
Heart disease mortality after left or right-sided breast cancer

Years since breast cancer diagnosis	No radiotherapy: Number of deaths left/right	No radiotherapy: Mortality ratio, left-sided vs right-sided (95% CI)	Radiotherapy: Number of deaths left/right	Radiotherapy: Mortality ratio, left-sided vs right-sided (95% CI)
Death from heart disease				
<5 years	2164/1972	1·03 (0·97–1·09)	700/633	1·04 (0·93–1·15)
5–9	1632/1479	1·05 (0·98–1·13)	521/442	1·10 (0·97–1·25)
10–14	806/758	1·01 (0·91–1·11)	281/197	1·37 (1·14–1·64)
≥15	568/524	1·02 (0·91–1·15)	254/162	1·53 (1·25–1·86)
Death from all other known causes				
<5 years	14775/13522	1·04 (1·01–1·06)	6911/6516	1·01 (0·98–1·05)
5–9	8009/7863	0·97 (0·94–1·00)	3178/2990	1·01 (0·96–1·06)
10–14	3472/3343	0·99 (0·94–1·04)	1165/1095	1·01 (0·93–1·10)
≥15	2106/2040	0·98 (0·92–1·04)	611/560	1·04 (0·93–1·17)



Darby et al. *Lancet Oncol* 2005

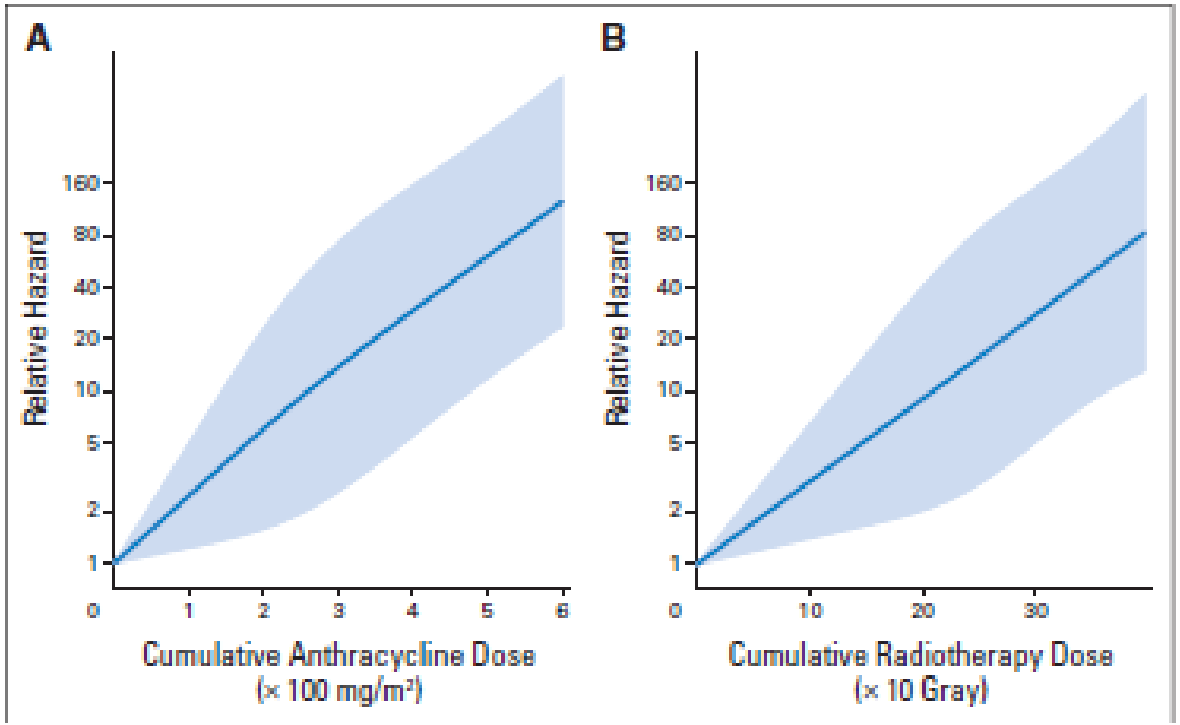
Heart disease after treatment for Hodgkin lymphoma



Coronary heart disease SIR=4.5 (3.6-5.6)
Heart failure SIR=16.9 (12.8-21.8)

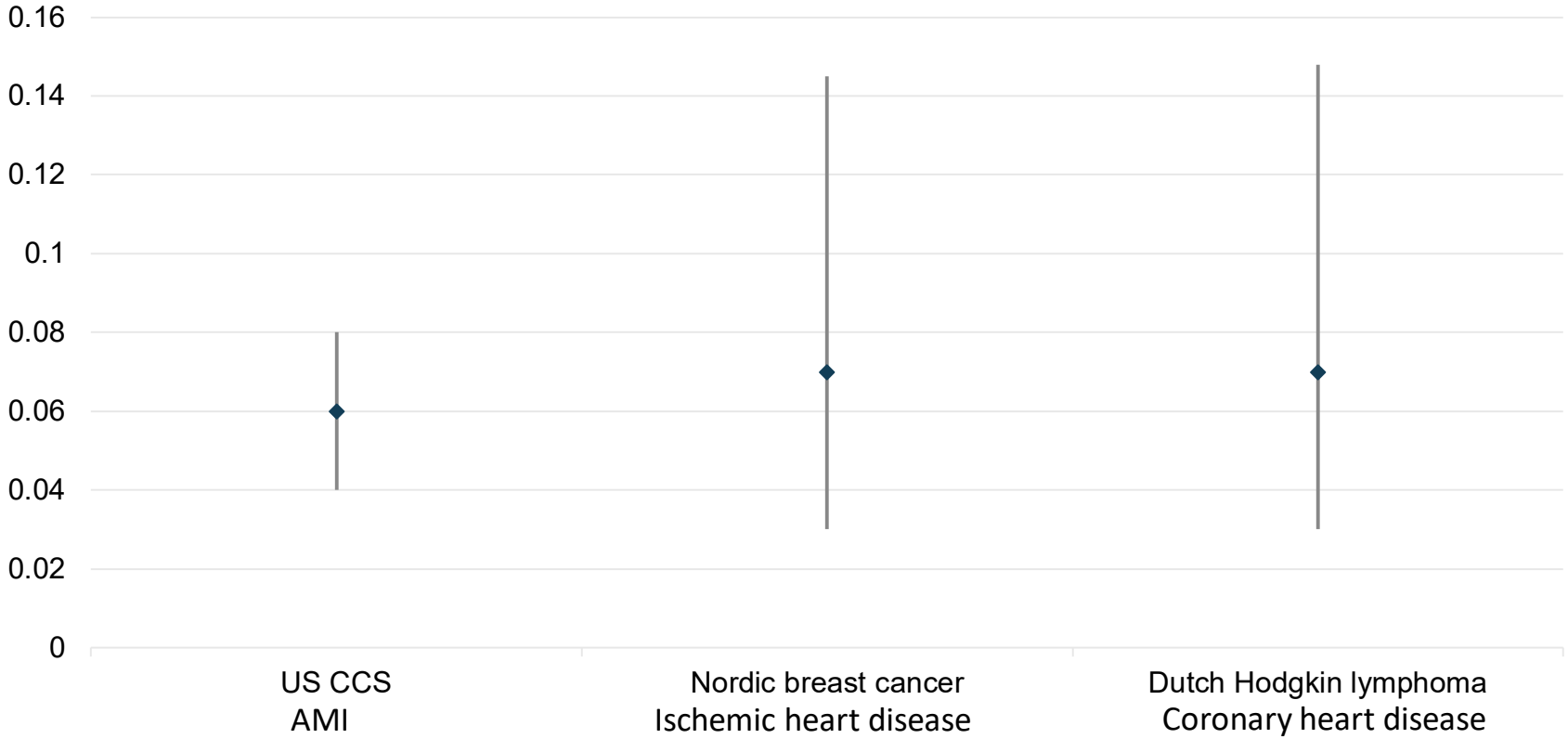
Van Nimwegen et al. *JAMA Intern Med* 2015

Cardiac events after treatment of childhood cancer



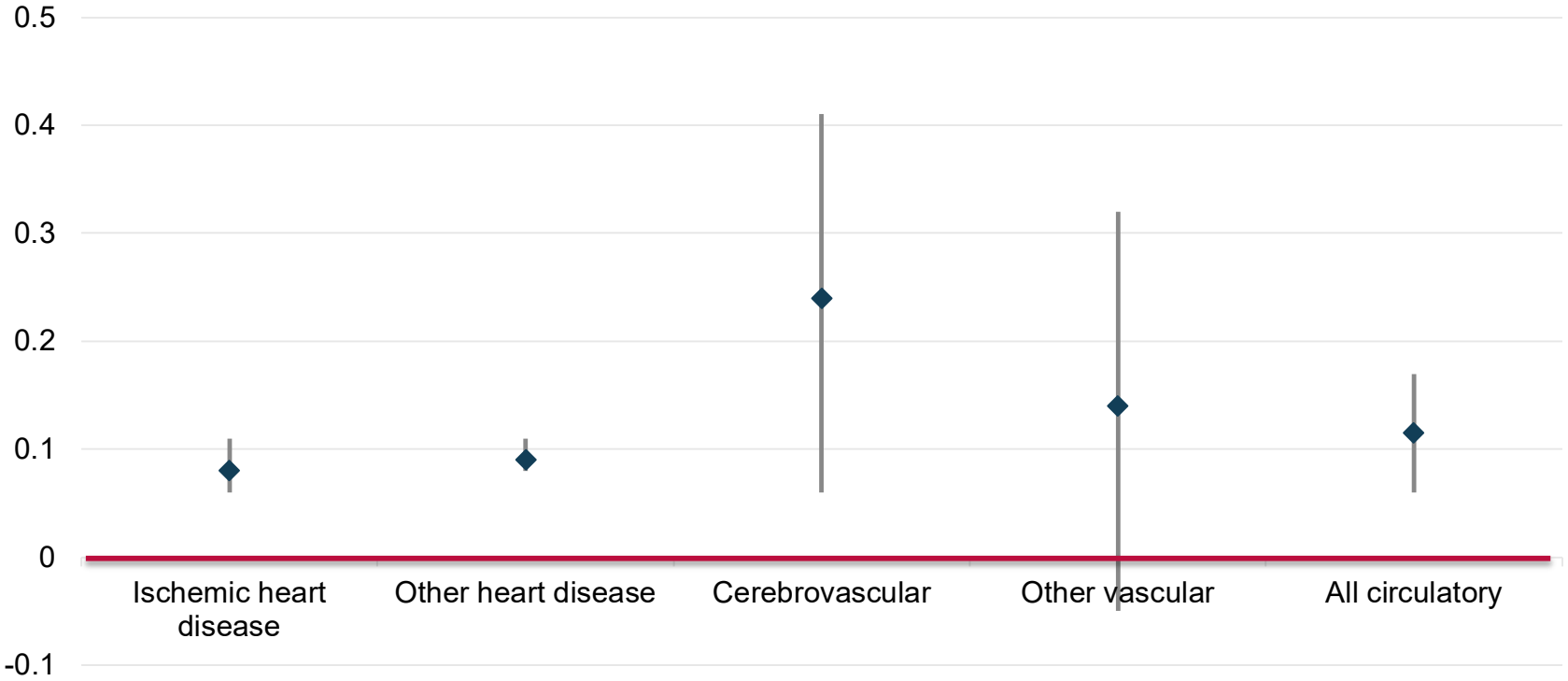
Van der Pal et al. *J Clin Oncol* 2012

Cardiac disease incidence ERR/Gy, radiotherapy studies



Summary for circulatory disease

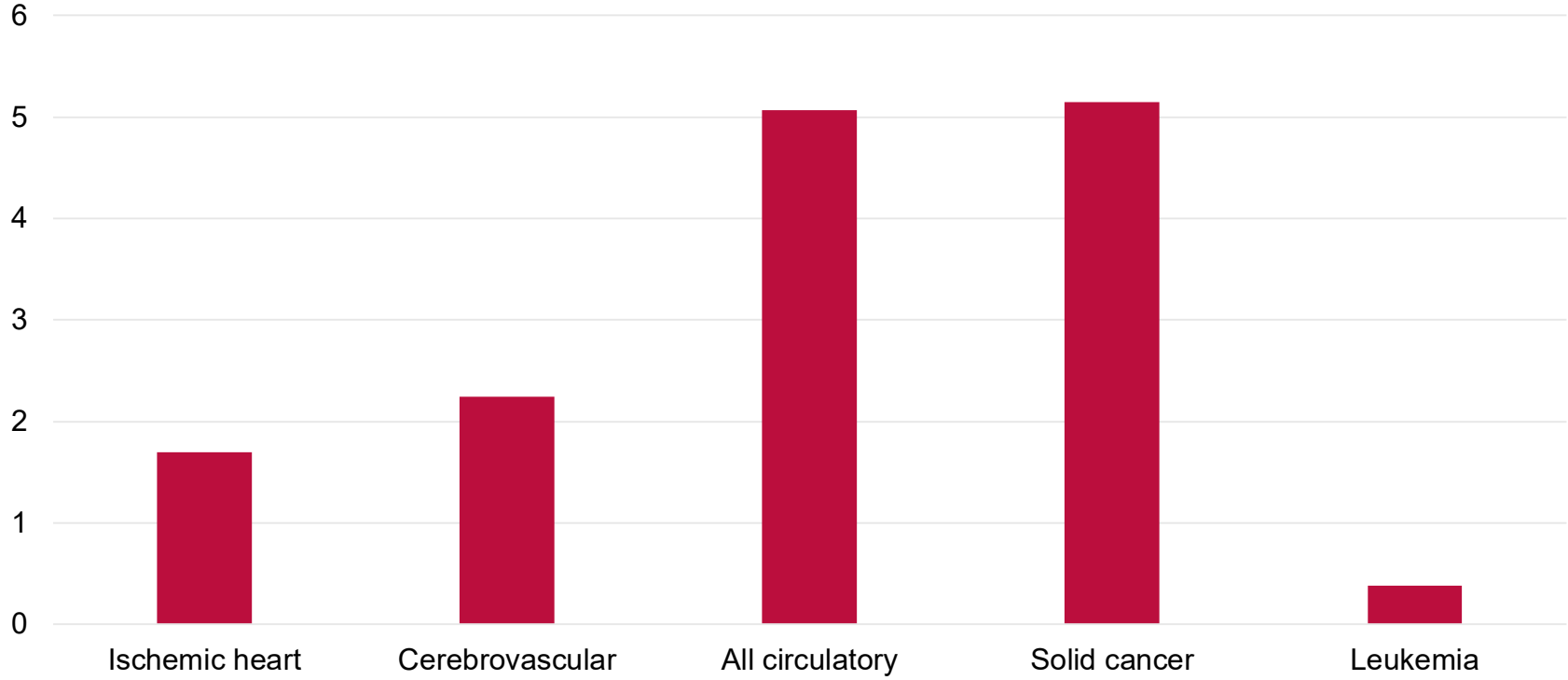
Risk by disease end-point, all 20 studies



Little 2016

Absolute risk as REID for vascular disease and cancer

From Little et al. 2012, risk if exposure-induced death (REID) for UK, expressed as 10^{-2}/Sv



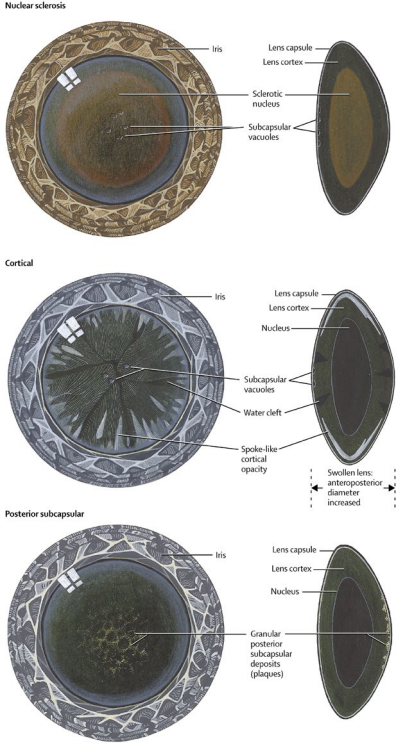
Open questions

- Consistency of results
  - Risk estimates
  - Lag/latency
- Dose-response at low exposure levels
- Mechanism(s)?
  - Direct tissue damage unlikely at low doses
  - Inflammation?
- Modifiers?

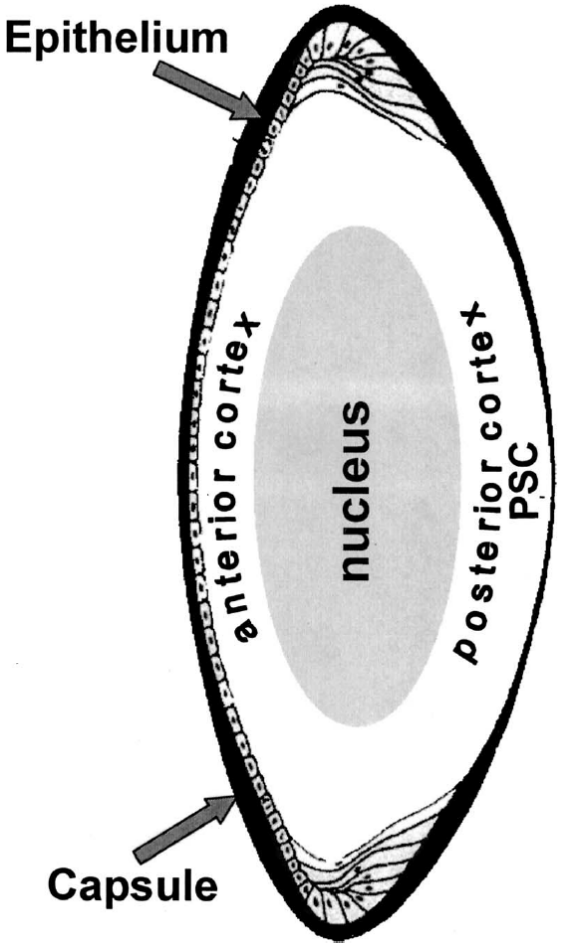
Radiation and eye lens opacities

Cataract

- Clouding of crystalline lens
  - Minimal turnover of cells
  - Progression, regression?
- Three types defined by location
  - Nuclear, cortical, posterior subcapsular
- Affects vision → cataract
- Cataracts are the leading cause of blindness worldwide



Cataract types



Radiation and the lens

- Lens among the most radiosensitive tissues in the body
- Radiation → genomic damage → abnormal proliferation and differentiation of lens epithelial cells → morphological changes
- Originally reported in A-bomb survivors in 1949
- Threshold for vision-impairing cataract 0.5 Gy (ICRP 2012)
- Eye lens dose threshold for workers 20 mSv/year over 5 yrs (>50 any single year), public 15 mSv/year revised in 2012

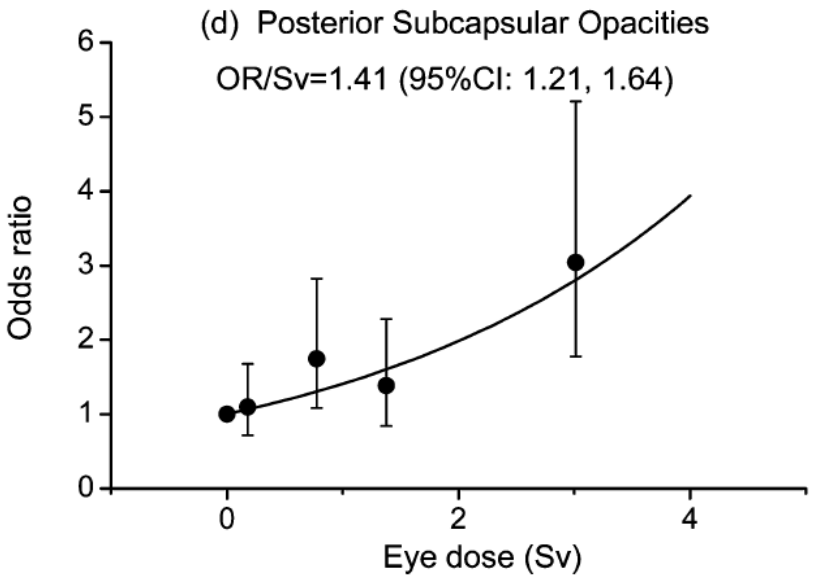
Major studies

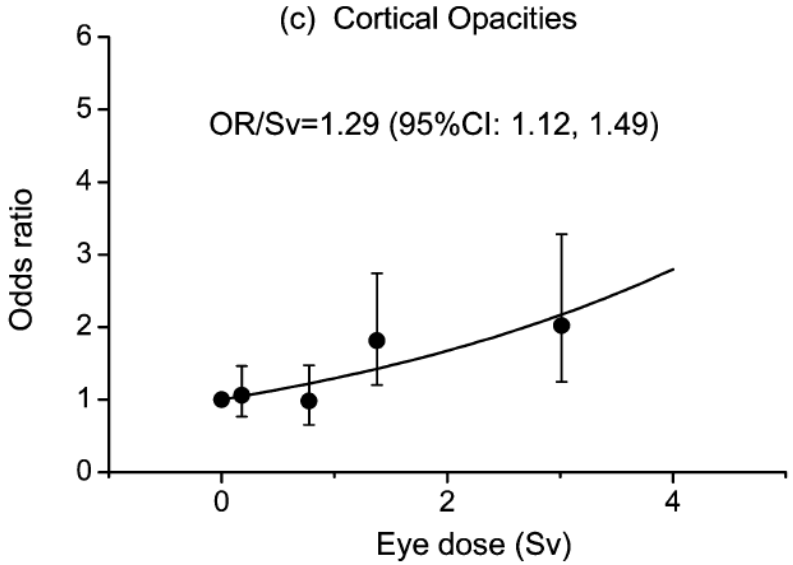
- Atomic bomb survivors
- Chernobyl clean-up workers
- Mayak workers
- U.S. x-ray technologists
- (Taiwanese cohort of CT patients)
- Radiotherapy studies

Hiroshima and Nagasaki A-bomb survivors

- Ophthalmologcal examinations (Nakashima et al. *Health Phys* 2006)
- 730 participants, mean eye dose 0.52 Sv (DS02)
- Opacities graded using LOCS II
- OR for posterior sucbcapsular cataract 1.44 (95% CI 1.19-1.73)/Sv, for cortical cataract 1.30 (95% CI 1.10-1.53)/Sv
  - Decreasing risk with age at exposure
- Cataract surgery (Neriishi et al. 2007, 2012)
- 3761 AHS participants
- OR=1.39 (95% CI 1.24-1.55)/Sv, consistent with a threshold at 0.5 Gy

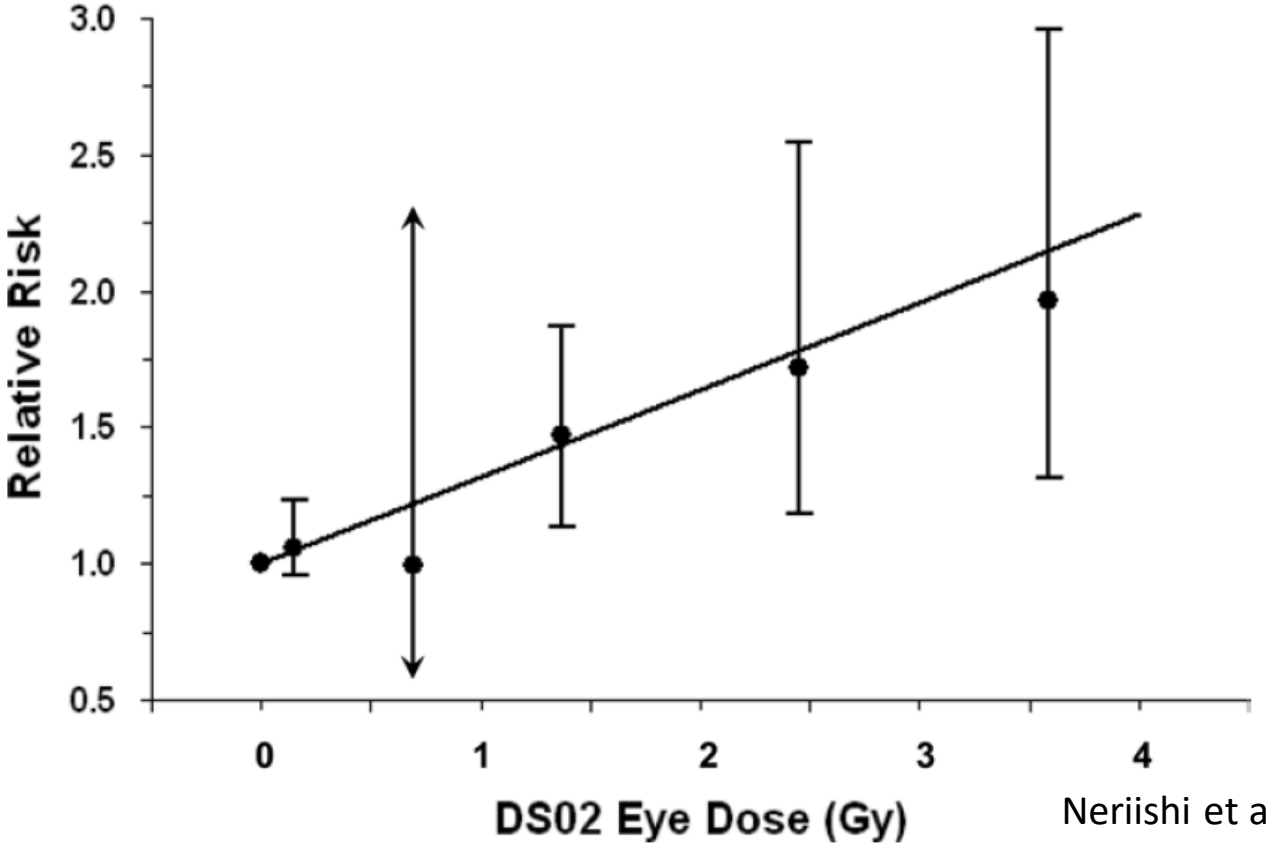
Dose-response for PSC and cortical opacities





Minamoto et al. 2004

Dose-response for cataract surgery



Neriishi et al. Radiology 2012

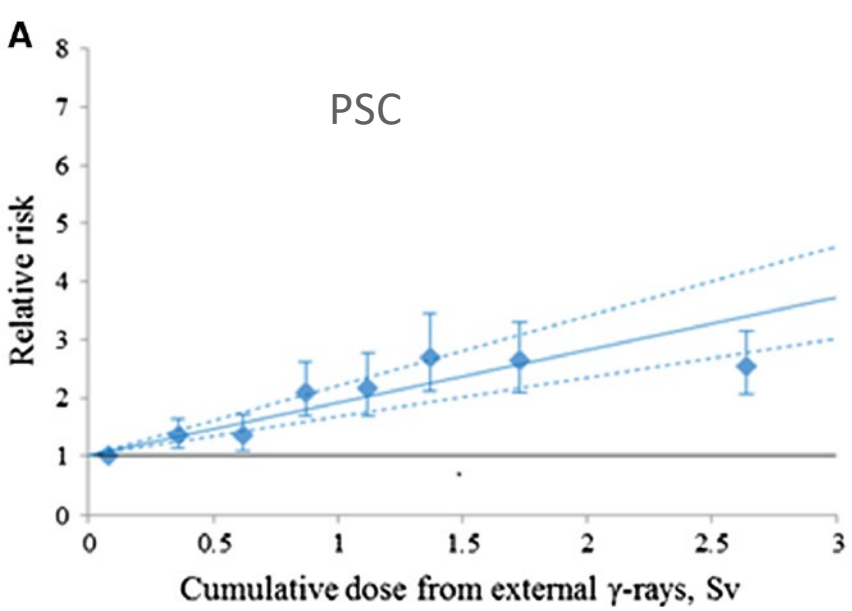
Chernobyl recovery workers

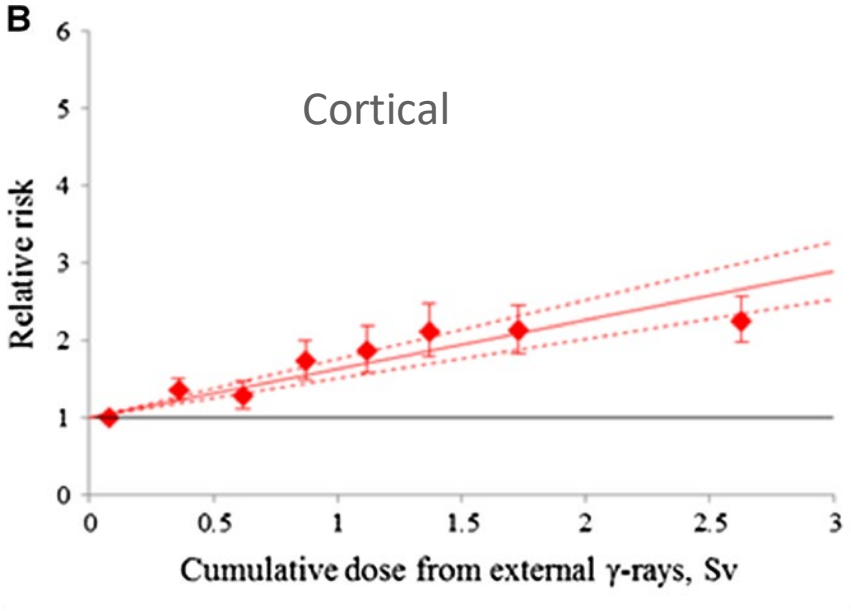
- 8607 workers (Worgul et al. 2007)
- Examined 12-14 years after exposure
- Information collected also on smoking, diabetes, medications
- Merriam-Focht grading of opacities
- Prevalence of PCS or cortical cataract 25%
- For PSC, OR=1.52 (1.02-2.00) @1 Sv
- Dose threshold for PSC estimated as 0.35 (0.19-0.66) Sv

Mayak workers

- Azizova et al. *Eur J Epidemiol* 2018
- Worker cohort 22,377, 22-year follow-up
  - Information on smoking (ever/never), diabetes, myopia available
- Cataract data from annual health check-ups including a standard ophthalmological examination
  - Slit lamp examination by an ophthalmologist
- Mean external gamma dose (Hp10) 0.54 Sv men, 0.44 Sv women
  - Some neutrons (0.03 Sv)
- Cataract cases 3132 cortical (cum. incidence 14%), 1239 PSC (11%)
  - 19% extracted, separate analysis (Azizova et al. 2019)

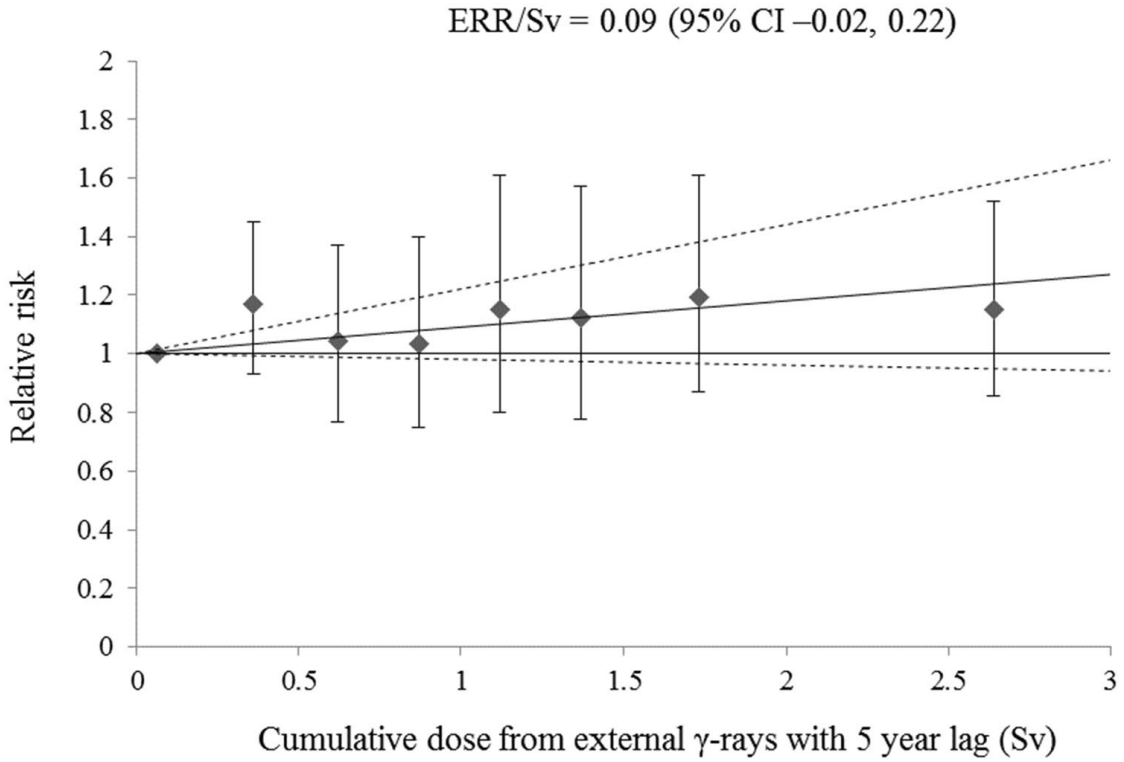
Dose-response for PSC and cortical cataract





ERR/Gy PSC 0.91 (0.67-1.20), cortical 0.63 (0.51-0.76)
nuclear 0.47 (0.35-0.60)

Dose-response for cataract removal

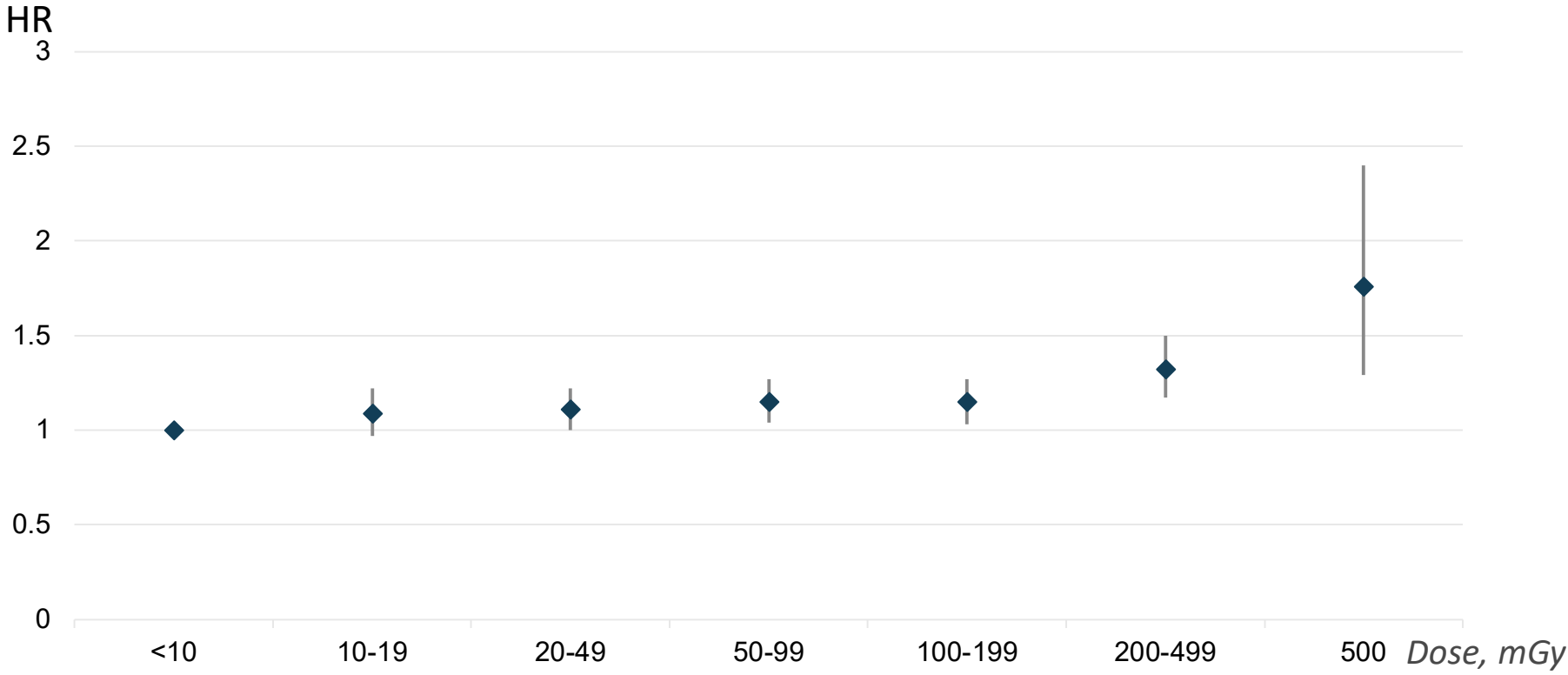


Azizova et al. 2019

U.S. radiologic technologists

- 67,246 participants (Little et al. 2018)
- Median eye dose 56 mGy
- Mean follow-up 13 years
- Self-reported cataract cases and surgeries
- For cataract incidence, EHR=0.69 (95% CI 0.27-1.16)/Gy
- For cataract surgery, EHR=0.34 (95% CI -0.19, +0.97)/Gy

Dose-response for cataract incidence, radiotechs

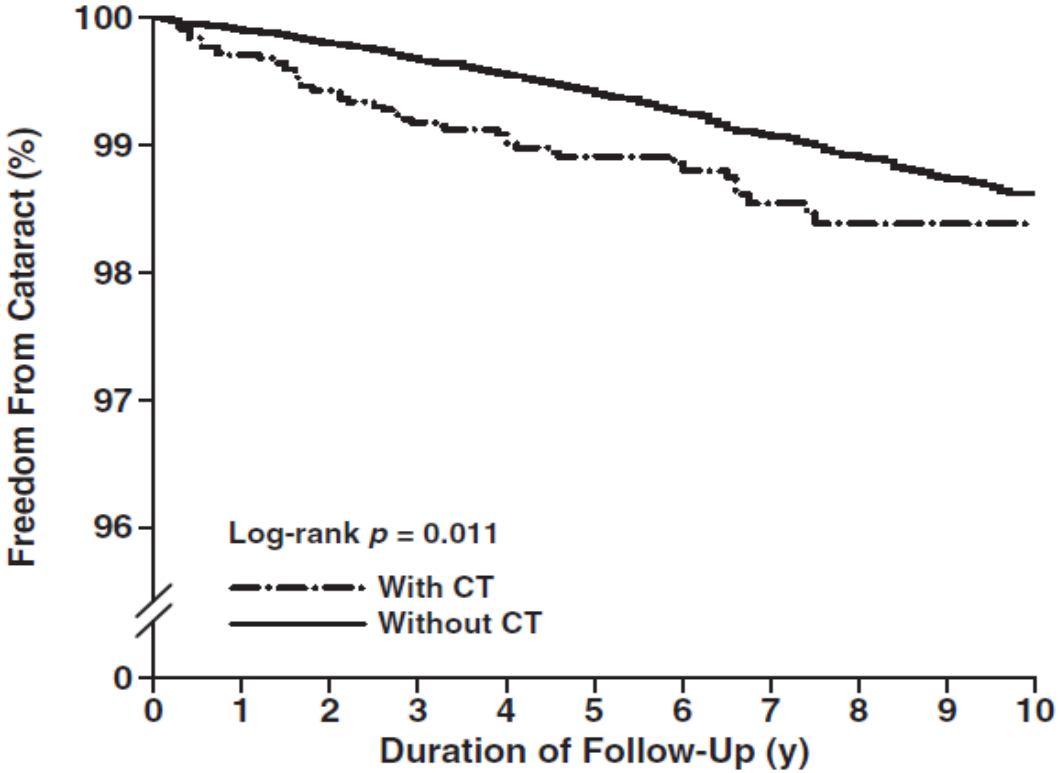


Little et al. 2018

CT examination and cataract

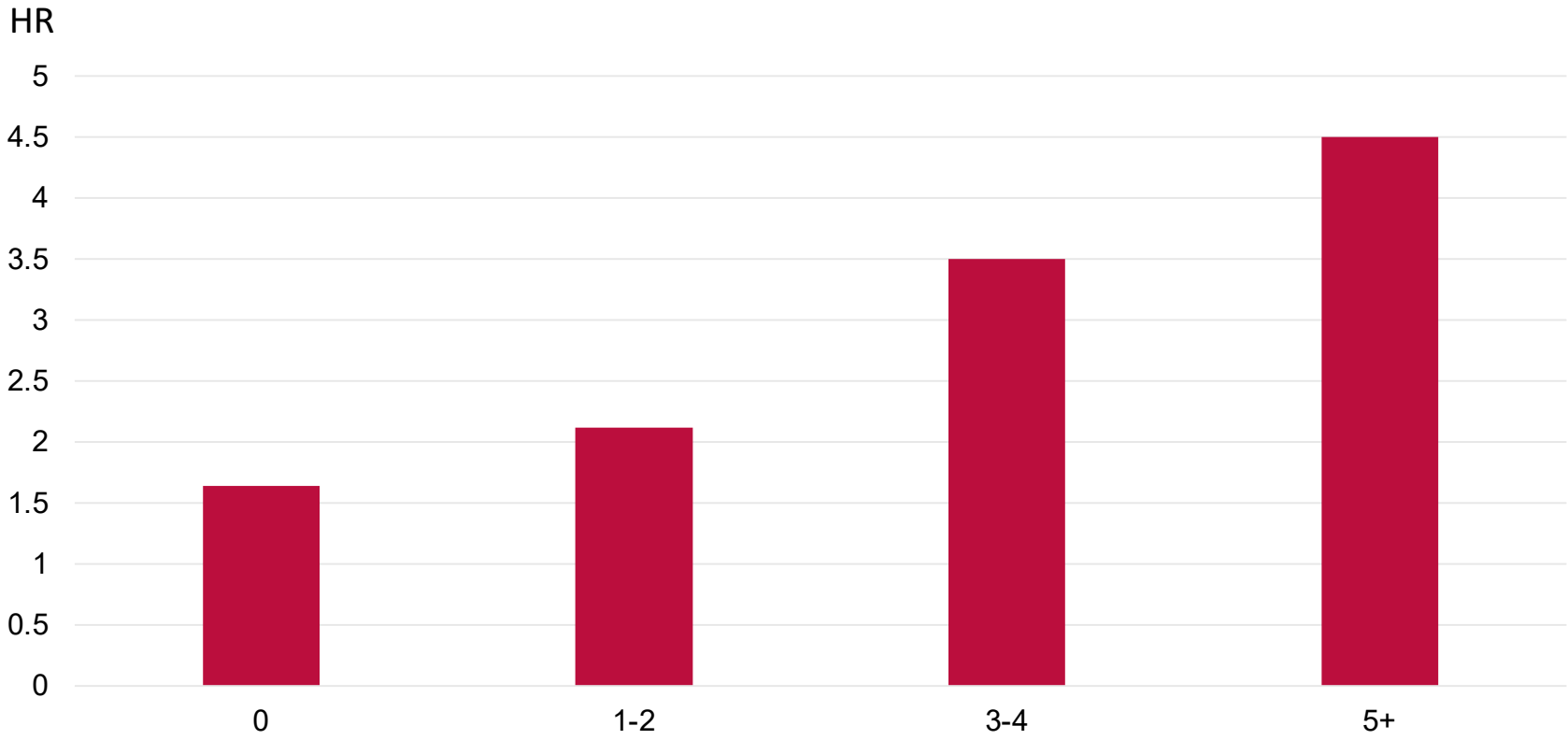
- Taiwanese cohort study (Yuan et al. 2013)
- 2776 exposed people aged 10-50 years
- 27,761 non-exposed control group
- Follow-up 10 years
- Cataract extraction or 2+ health care contact with cataract dg
- Cataract incidence 0.97% vs 0.72%
- HR 1.76 (95% CI 1.18-2.63) for head/neck CT

CT and cataract incidence



Yuan et al. 2013

Number of CT examinations and cataract risk

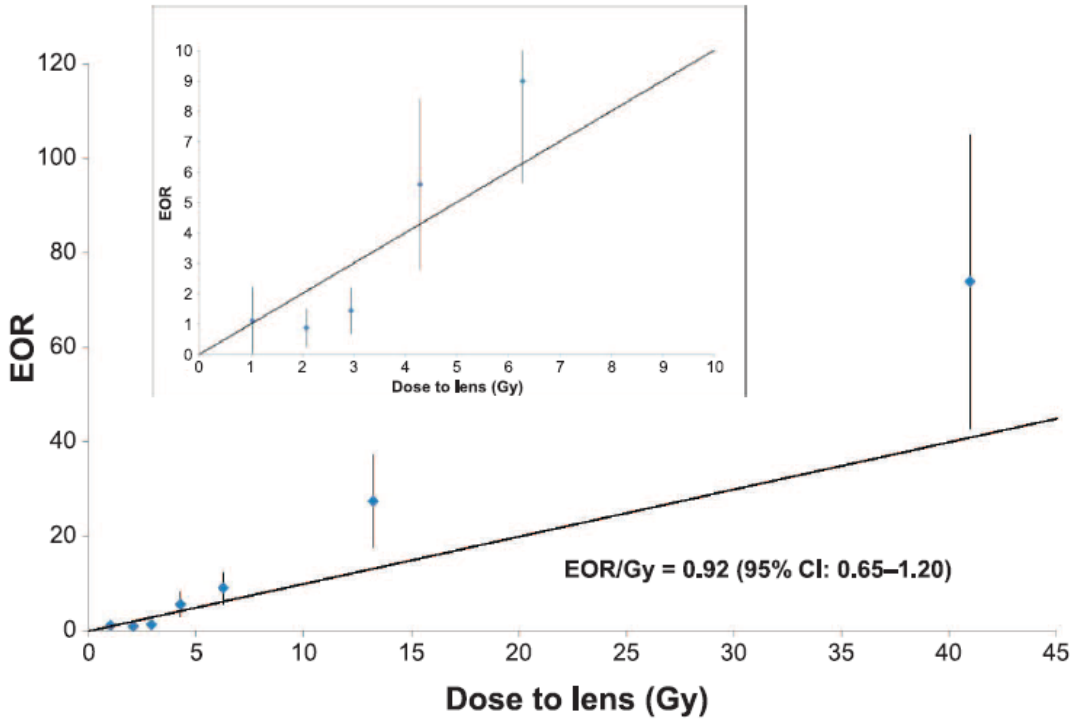


Yuan et al. 2013

Cataract after radiotherapy for childhood cancer (1)

- 13,902 five-year survivors of childhood cancer followed up for 21 years (leukemia 34%, lymphoma 14%, CNS 12%)
- Mean lens dose 2,2 Gy (Chodick et al. *Radiat Res* 2016)
- Cumulative risk 3.5% (483 cases)
  - Self-reported, no information on type of cataract
- Linear dose-response eOR 0.92/Gy (95% CI 0.65-1.20), significantly elevated risk from 0.5-1.5 Gy

Dose-response for cataract after radiotherapy



Chodick et al. 2016

Cataract after radiotherapy for childhood cancer (2)

- A cohort of 1833 childhood cancer survivors (Allodji et al. *JAMA Ophthalmol* 2016)
- Mean dose to the eye 2.6 Gy
- Cumulative risk 2.3% during 32-year follow-up (47 cataracts in 33 patients)
- Any radiotherapy HR=4.4 (95% CI 1.5-13)
- Chemotherapy with melphalan associated with very high risks (HR=26, 95% CI 7-97)

Summary for lens opacities

- Radiation can induce lens opacities at dose levels below tissue reactions (deterministic effects)
- Mainly posterior subcapsular but also cortical cataract
- Children more susceptible
- Is there a threshold at or below 0.5 Gy?
- Do the minor opacities progress into cataract?
- Modifiers?
  - A-bomb survivors M>F, Mayak M<F

Quiz (1)

Effect of radiation on vascular disease is comparable to cancer risk in terms of

A. Relative risk per dose unit

B. Absolute risk per dose unit

C. Lag-time (latency from exposure to manifestation of risk)

D. Weight of evidence base

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Quiz (2)

Effect of radiation on the lens of the eye

A. Affects all types of cataracts in a similar fashion
B. Has led to a change in exposure limit to the eye
C. Is of unknown clinical relevance
D. Remains to be demonstrated in humans

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And our musical cat, Elle

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