Cardiovascular Effects at Low Doses of Radiation: Perspectives from Epidemiology

Mark P Little
Radiation Epidemiology Branch, National Cancer Institute, Bethesda, USA

5th Gilbert W Beebe webinar "After BEIR VI and BEIR VII"

19-20 October 2021

Outline of talk

- Introduction
- Some preliminaries – meaning of low dose etc
- Recent systematic reviews/meta-analyses of circulatory disease in moderate & low-dose epidemiological data
- Some of the larger and more informative circulatory disease studies since 2016
- Other considerations – interactions with other risk factors, risk <0.5 Gy, absolute risks, epidemiological challenges
- Conclusions

Some preliminaries – meaning of low dose etc

Inflammation and circulatory disease

- Subtypes of circulatory disease associated with atherosclerosis largely inflammatory etiology (Ross *N Engl J Med* 1999 340 115-26)
- In LSS long-lasting dose-related increases in pro-inflammatory (Hayashi *et al Am J Med* 2005 **118** 83-86; Hayashi *et al FASEB J* 2012 **26** 4765-73)
  - C-reactive protein
  - erythrocyte sedimentation rate
  - reactive oxygen species
  - IL-6, TNF-α, IFN-γ
- In LSS long-lasting dose-related reductions in anti-inflammatory
  - IL-4

Inflammation and senescence

- Endothelial cell activation results in differential up/down-regulation of inflammatory ICAM-1, PCAM-1 etc (Little *et al Radiat Res* 2008 **169** 99-109; Baselet *et al Cell Molec Life Sci* 2019 **76** 699-728)
  - upregulation at doses >0.5 Gy
  - downregulation at doses <0.5 Gy
- Senescent cells are potent source of many inflammatory cytokines (Stojanovic *et al Eur Heart J* 2020 **41** 2983-96)
- Senescence can be induced at low doses and dose rates (4.1 mGy/h) (Rombouts *et al Int J Radiat Biol* 2014 **90** 560-74)

What do we mean by low dose? Or moderate dose?

- For cancer there has been a lot of emphasis by ICRP, UNSCEAR, EU in recent years on ascertaining risk at low dose – that is < 0.1 Gy
- As per previous slide for circulatory disease consideration of < 0.5 Gy [=low-moderate dose (Little *et al Int J Radiat Biol* 2021 97 782-803)], may make more sense than < 0.1 Gy
- In any case, as we shall see, little information on circulatory disease risk at < 0.1 Gy, although there is starting to be for < 0.5 Gy

Recent systematic reviews/meta-analyses of circulatory disease in moderate & low-dose epidemiological data

Second systematic review and meta-analysis of circulatory disease

(Little *et al. Env. Health Perspect.* 2012 **120** 1503-11)`

- Restricted to human data exposed to:
  - acute mean dose <0.5 Gy or chronic exposures
  - good quality dosimetry
- Published ≥1/1/1990
- 10 studies identified (2 of them A-bomb) out of 1480 articles (ISI Thompson) and 6497 (PubMed)
- Fixed effect + random effects analysis (random effects needed when significant heterogeneity)

Third meta-analysis (Little *Mut Res Revw* 2016 **770B** 299-318)

- Non-systematic review – but recently initiated systematic review suggests captured most studies to mid 2016
- No restriction on dose, publication date
- 25 studies identified (19 of them moderate/low dose)
- Meta regression analysis – to explore effects of dose, dose rate

Random effects excess relative risk coefficients for circulatory diseases from exposure to <0.5 Gy mean dose or chronic exposure in 2nd and 3rd meta-analyses

(Little *et al. Env. Health Perspect.* 2012 **120** 1503-11, Little *Mut Res Revw* 2016 **770B** 299-318)

Circulatory disease subtype	**Little *et al* 2012 ERR / Sv (+95% CI)**	**Little 2016 ERR / Sv (+95% CI)**
Ischemic heart disease	0.10 (0.04 to 0.15)	0.11 (0.04 to 0.17)
Non-ischemic heart disease	0.08 (-0.12 to 0.28)	0.06 (-0.08 to 0.19)
Cerebrovascular disease	0.21 (0.02 to 0.39)	0.23 (0.06 to 0.41)
Circulatory disease apart from heart disease and stroke	0.19 (-0.00 to 0.38)	0.14 (-0.05 to 0.32)

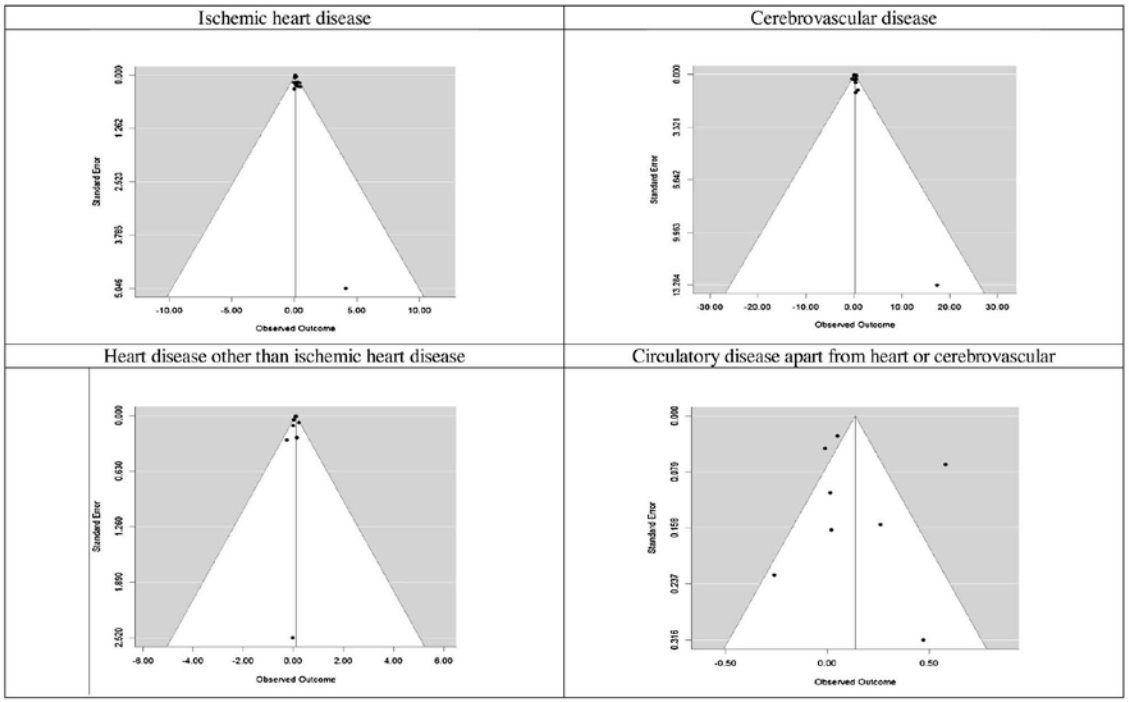
Evidence strongest for ischemic heart disease and stroke

Not much changes between two meta-analyses [but some overlap in studies assessed e.g. IARC 15-country, LSS]

Problems with meta-analysis: publication/selection bias?

(Little *Mut Res Revw* 2016 **770B** 299-318)

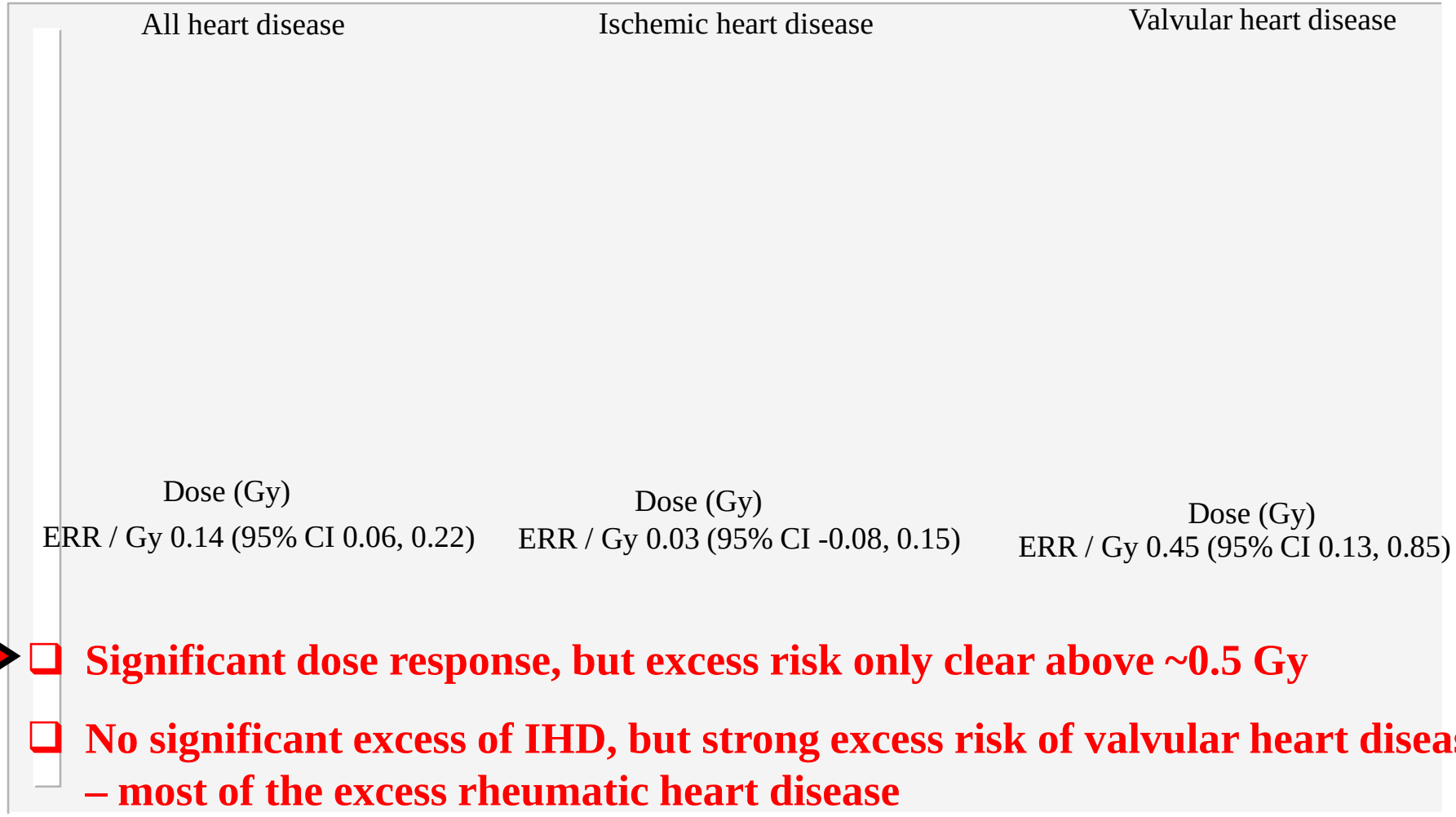
- Generally expect bias towards publications with significant results
- Funnel plot (mean *vs* SE) is reasonably symmetric, implying little or no bias, as does more formal Egger test
- However, small number of datapoints limits power of Egger test



Some of the larger and more informative circulatory disease studies since 2016

Dose response for heart disease in A-bomb survivors

(Takahashi *et al Radiat Res* 2017 **187** 319-32)



- **Significant dose response, but excess risk only clear above ~0.5 Gy**
- **No significant excess of IHD, but strong excess risk of valvular heart disease – most of the excess rheumatic heart disease**
- **No indication of curvature in dose-response (p>0.5)**

Dose response <0.5 Gy for circulatory disease other than heart, stroke in A-bomb survivors

(Shimizu *et al BMJ* 2010 **340** b5349)

Dose range	ERR / Gy (95% CI)
Unrestricted	0.58 (0.45, 0.72)
< 1 Gy	0.45 (0.26, 0.66)
< 0.5 Gy	0.67 (0.35, 1.01)
< 0.2 Gy	1.01 (0.31, 1.78)

- **Significant dose response under 0.2 Gy**
- **No significant excess of heart disease or stroke under 0.5 Gy**

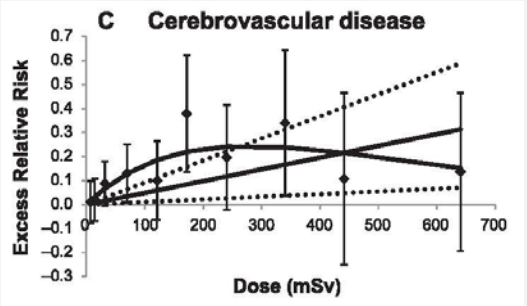
Circulatory disease mortality in INWORKS study

(Gillies *et al Radiat Res* 2017 **188** 276-90)

ERR /Gy = 0.22 (90% CI 0.08, 0.37)

ERR /Gy = 0.18 (90% CI 0.004, 0.36)

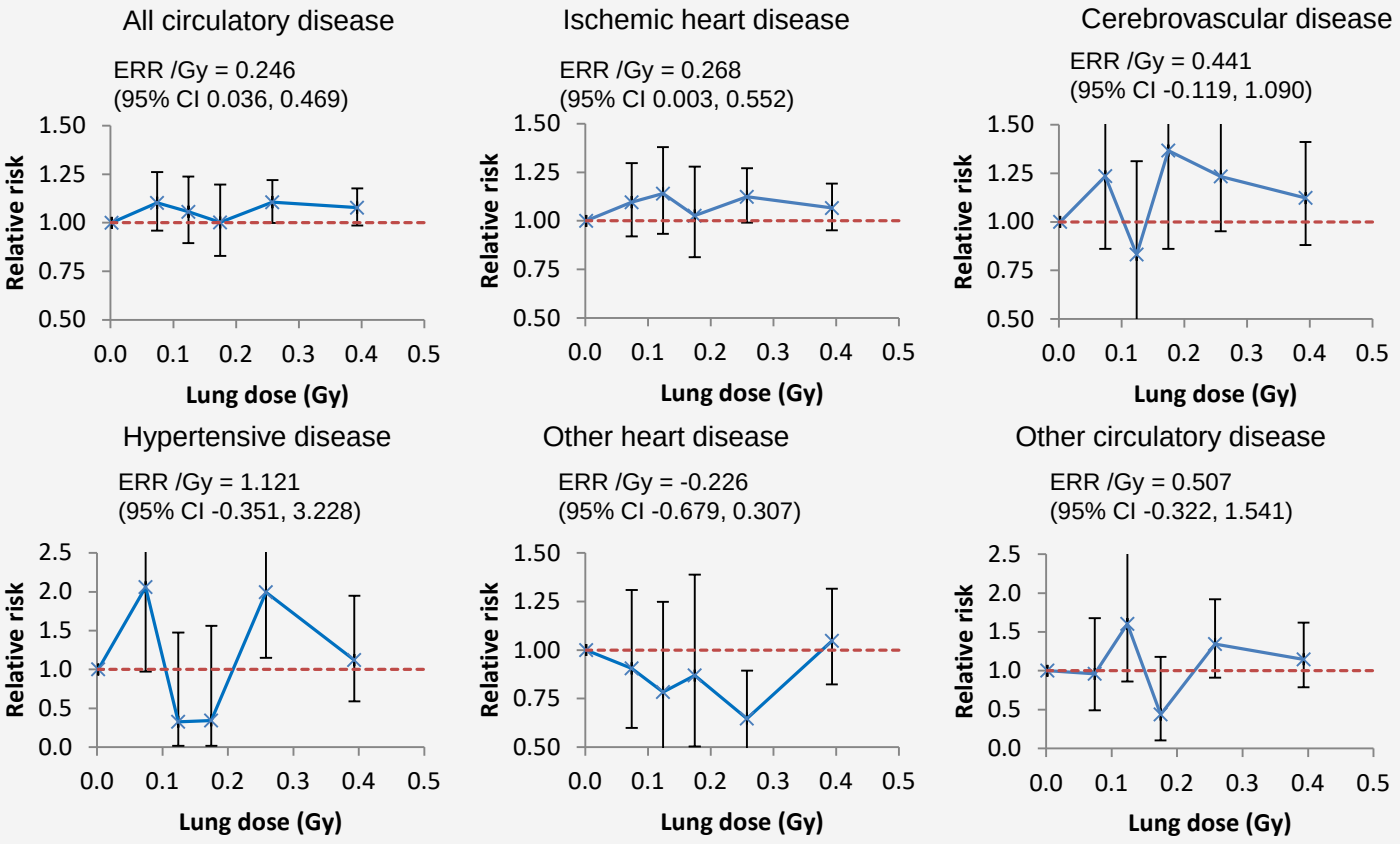
ERR /Gy = 0.50 (90% CI 0.12, 0.94)



- **Significant excess risk for all circulatory disease, ischemic heart, acute MI, cerebrovascular disease**
- **Significant downward curvature (p=0.017) in cerebrovascular disease**
- **For all circulatory disease dose trend significant over 0-0.3 Gy**
- **For ischemic heart disease dose trend significant over 0-0.5 Gy**
- **Null risk for COPD (ERR/ Gy =-0.07) suggests smoking does not confound radiation dose response**

Circulatory disease risks in Canadian and Massachusetts tuberculosis fluoroscopy cohorts

(Tran *et al Sci Rep* 2017 **7** 44147)



- **Significant risks for all circulatory disease and ischemic heart disease – but risks only significant <0.5 Gy**

Cardiovascular disease morbidity in Russian liquidators

(Kashcheev *et al Health Phys* 2017 **113** 23-29)

ERR /Gy = 0.47 (95% CI 0.31, 0.63)

- **Precise definition of "cardiovascular disease" used here unclear – but includes all major subtypes of circulatory disease**
- **Although authors do not say so, apparently significant risk for all circulatory disease and circulatory disease excluding IHD for < 0.35 Gy (and possibly lower than that)**

Heart disease mortality in UK NRRW (1)

(Zhang *et al J Radiol Prot* 2019 **39** 327-53)

All heart disease	ERR /Gy = 0.37 (95% CI 0.11, 0.65)
Ischemic heart disease	ERR /Gy = 0.32 (95% CI 0.04, 0.61)
Myocardial infarction	ERR /Gy = 0.54 (95% CI 0.16, 0.95)

- **Significant excess risk for heart disease (HD), IHD and myocardial infarction <0.4 Gy**
- **No evidence of curvature in HD dose response overall, although borderline significant (p=0.048) downward curvature for IHD over full dose range (but not <0.4 Gy)**
- **Some evidence of biphasic dose response – curving upwards at low doses, downwards at high doses**

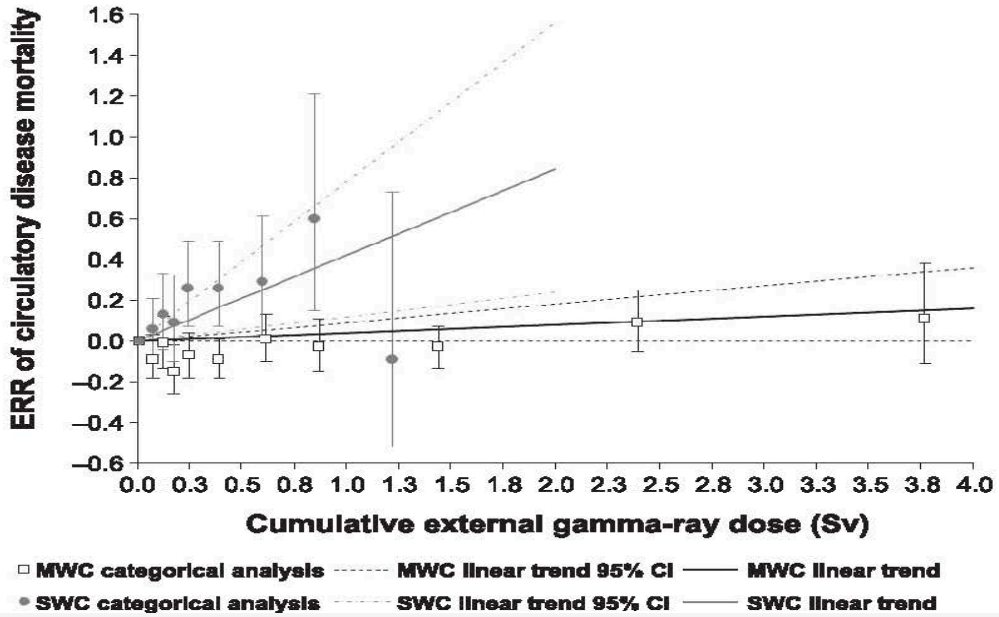
Heart disease mortality in UK NRRW (2)

(Zhang *et al J Radiol Prot* 2019 **39** 327-53)

- **Evidence that restricting to doses <0.4 Gy causes slight increase in risk**
- **Further restricting causes ERR/Gy to decrease**
- **Suggests biphasic dose response, turning over at high doses, upward curving at lower doses**

Circulatory disease mortality in combined Sellafield and Mayak workers study

(Azizova *et al Radiat Res* 2018 **189** 371-88)



Sellafield ERR /Gy = 0.42 (95% CI 0.12, 0.78)
Mayak ERR /Gy = 0.04 (95% CI -0.00, 0.09)

- **Significant excess risk for all circulatory disease in both groups, but startling discrepancy in magnitude: Sellafield ~10 x Mayak**
- **Significant excess risk for Sellafield workers for all circulatory and IHD <0.3 Gy**
- **Some evidence of downward curvature in Sellafield cohort, but not in Mayak – curvature largely driven by IHD**

External doses to Sellafield and Mayak workers

(Azizova *et al Radiat Res* 2018 **189** 371-88)

Sellafield and Mayak cumulative external doses (Sv)

Sellafield and Mayak mean external doses (Sv)

	Sellafield	Mayak
Males	0.08	0.55
Females	0.01	0.44

- **Mean doses much higher in Mayak worker cohort than in Sellafield**
- **Might this, in conjunction with curvature in dose response for IHD and CeVD, explain some of discrepancy in risk?**

Circulatory disease mortality in US uranium enrichment workers

(Anderson *et al Occup Environ Med* 2021 78 105-11)

Ischemic heart disease

Cerebrovascular disease

- **No significant trend overall, either for ischemic heart disease or stroke**
- **Suggestion of increasing trend per unit dose as dose range restricted, implying downwardly curving dose response**
- **Non-significant excess trend with internal uranium dose**

Other considerations – interactions with other risk factors, risk <0.5 Gy, absolute risks, epidemiological challenges

Interactions with other lifestyle and medical risk factors

- Some studies (greater % of therapeutic vs moderate/low dose) collected information on major independent lifestyle/medical risk factors
  - (a) diabetes (b) hypertension (c) obesity (d) high cholesterol (e) smoking

Study	Risk factors
LSS	Smoking, alcohol intake, obesity, education, occupation, diabetes
Mayak	Smoking. alcohol intake, obesity, blood pressure
INWORKS+NRRW	Industrial/non-industrial classification
British Nuclear Fuels fuel cycle workers	Obesity, blood pressure, smoking, shift work, noise, SES
Mass+Canadian TB fluoroscopy	Smoking, tuberculosis stage (and for part diabetes, antibiotic use, alcohol consumption)
US peptic ulcer	Smoking, alcohol consumption
Nordic breast cancer	Concomitant CT, smoking, diabetes, obesity
Netherlands Hodgkin lymphoma	Concomitant CT, smoking, obesity, diabetes, hypertension, hypercholesterolemia

Moderate/low dose | Therapeutic dose

- Little evidence that these risk factors confound radiation dose response in these studies – but might in others

Summary moderate dose risk (<0.5 Gy)

(Little *et al Int J Radiat Biol* 2021 97 782-803)

Population	Dose range (Gy)	Reference	All circulatory ERR (95% CI)	Heart/IHD ERR (95% CI)	Stroke ERR (95% CI)
Canadian + Mass TB fluoroscopy	<0.5	Tran *et al* (2017)	0.246 (0.036, 0.469)	0.268 (0.003, 0.552)	0.441 (-0.119, 1.090)
LSS	<0.5	Shimizu *et al* (2010)	0.11 (-0.03, 0.25)	0.15 (-0.04, 0.35)	-0.06 (-0.25, 0.14)
INWORKS	<0.5	Gillies *et al* (2017)	0.28 (0.10, 0.47)	0.23 (0.01, 0.47)	0.86 (0.35, 1.43)
Mayak workers	<0.5	Azizova *et al* (2018)	-0.24 (-0.47, 0.01)	-0.26 (-0.56, 0.09)	-0.33 (-0.71, 0.12)
Sellafield workers	<0.5	Azizova *et al* (2018)	0.73 (0.24, 1.31)	1.07 (0.43, 1.85)	-0.06 (-0.87, 1.09)
NRRW	<0.4	Zhang *et al* (2019)	NA	0.70 (0.27, 1.16)	NA
French nuclear fuel cycle	<0.027	Zhivin *et al* (2018)	10 (-20, 40)	0 (-50, 40)	-10 (-50, 30)
French U-miners	<0.4701	Drubay *et al* (2015)	0.4 (-1.6, 2.9)	-1.0 (-3.9, 3.3)	2.4 (-0.6, 11.4)
US U-enrichment	<0.5	Anderson *et al* (2021)	NA	0.26 (-0.48, 1.1)	0.53 (-0.91, 2.6)
Chernobyl emergency workers (morbidity)	<0.35	Kashcheev *et al* (2016, 2017)	0.27 (0.10, 0.44)	0.14 (-0.04, 0.33)	NA

- ERR for all circulatory endpoints tend to be ~0.1-1 / Gy
- For many of larger studies ERR are significant
- Even when NS trends tend to be positive
- Some overlap e.g. Sellafield ⊂ NRRW ⊂ INWORKS

Radiation-Exposure-Induced Death for Various Subtypes of Circulatory Disease, by Country (Little *et al. Environ. Health Perspectives* 2012 **120** 1503-11)

Country	Radiation-Exposure-Induced Death, x 10^{-2} Sv (+95% CI) using Random Effects Model						
				Other	All	UNSCEAR cancer risks	
	Ischaemic heart disease	Other heart disease	Stroke	circulatory disease	circulatory disease	All solid cancer	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)	-	-
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 absolute risks comparable with cancer risk**

Epidemiological challenges

- ERR slightly lower than for cancer – typically 0.1-1 /Gy vs 0.5-2.0 /Gy
  - Statistical power generally lower
- At least five major independent risk factors for circulatory disease (all varying risks by factor of ~2)
  - Not many datasets have information on all five
  - No evidence that they confound in studies where examined – but might in others
- Most studies are of mortality rather than incidence
  - Problem of misdiagnosis and ascertainment (e.g. Mayak mortality outside Ozyorsk)
- Many types of circulatory disease – are all equally radiogenic?
- What is target tissue? So what is correct dose?

Conclusions

- Meta-analysis of moderate+low-dose data suggests significant excess risk for two out of four CD endpoints (ischemic heart, stroke), and aggregate risk significant
- Emerging evidence of risk at <0.5 Gy
- Although ERR tend to be modest, because of high baseline prevalence the population risk is comparable to radiation-induced cancer
- A-bomb + Mayak and many medical cohorts have information on most major lifestyle factors for CD (smoking, drinking, obesity, HDL+LDL cholesterol, hypertension, diabetes), but little indication that these confound
- Importance of getting other major risk factor data in other cohorts