National Cancer Institute

What's new and what is coming – other diseases
Circulatory disease

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Outline of talk

- Introduction
- Studies of moderate- and low-dose exposed groups (cardiac dose generally < 5 Gy)
  - Meta-analysis of circulatory disease in occupationally-exposed groups
- Studies of radiotherapeutically-exposed groups (cardiac dose generally > 5 Gy)
- Conclusions

Studies of moderate- and low-dose exposed groups (cardiac dose generally < 5 Gy)

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

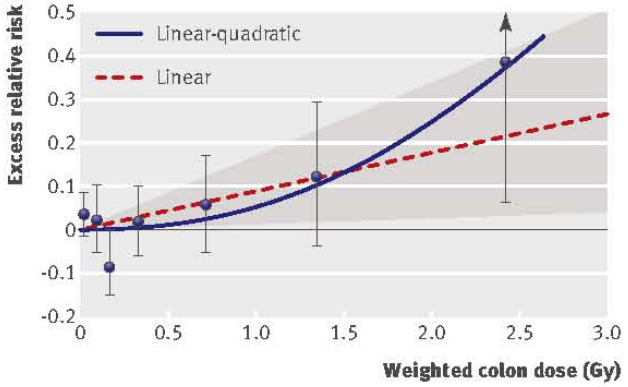


Fig 1 | Radiation dose-response relation (excess relative risk per Gy) for death from stroke, showing linear and linear-quadratic functions. Shaded area is 95% confidence region for fitted linear line. Vertical lines are 95% confidence intervals for specific dose category risks. Point estimates of risk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

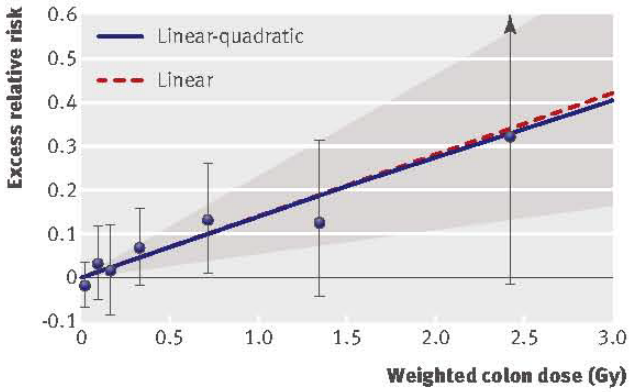


Fig 2 | Radiation dose-response relation (excess relative risk) for death from heart disease, showing linear and linear-quadratic functions. Shaded area is 95% confidence region for fitted linear line. Vertical lines are 95% confidence intervals for specific dose category risks. Point estimates of risk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

- **Highly significant dose response, but excess risk only clear above ~0.5 Gy**
- **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)

Ischemic heart	Cerebrovascular

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)**

Highly significant excess risk, only significant at > 0.5 Gy

Cardiovascular radiation effects at moderate/low doses (< 5 Gy)

- >0.5 Gy: up-regulation of number of cytokines involved in inflammation (Hallahan *et al Cancer Res* **56**:5150-5;1996; Hallahan *et al Biochem. Biophys Res Commun* **217**:784-95;1995; Hallahan *et al Cancer Res* **56**:5150-5;1996; Quarmby *et al AntiCancer Res* **20**:3375-81;2000), leading to leukocyte "rolling"
- <0.5 Gy: indications of down-regulation of inflammation (Kern *et al Radiother Oncol* **54**: 273-282;2000; Roedel *et al IJRB* **78**:711-719;2002; Hosoi *et al Int. J. Cancer* **96**:270-276;2001; Mitchel *et al Radiat. Res.* **175**: 665-76;2011)
- Important to consider low dose range (<0.5 Gy) separately

Meta analysis of circulatory disease (Little *et al. Env. Health Perspect.* 2012 **120** 1503-11)`

- PubMed+ISI Thompson search using terms “radiation” +“heart”+“disease” or “radiation”+“stroke” or “radiation” +“circulatory”+“disease”, published ≥1/1/1990
- Restricted to human data exposed to moderate/low uniform whole body doses (acute mean dose <0.5 Sv (suggested by radiobiology), chronic exposures allowed higher), with good quality dosimetry
- 10 studies identified (2 of them A-bomb)
- Fixed effect + random effects analysis (random effects needed when significant heterogeneity)
- Tests for selection/publication bias (but none suggested)

Why uniform whole body?

- We don’t know mechanism
- Uniform whole body dose removes the problem of identifying target tissue/organ – all organs get same dose (more or less)
- Two studies are arguably borderline in this respect – Mayak workers, German uranium miners, with some non-uniformity in liver, lung and bone dose, but circulatory system pretty uniformly exposed

Problem of overlapping of cohorts

- Where any cohort had follow-up ≤ 1 year longer than larger cohort within which subsumed, then removed it from meta-analysis
  - Howe *et al* 2004, Zablotska *et al* 2004 removed because of overlap with IARC 15-Country study (Vrijheid *et al* 2007)
  - Atkinson *et al* 2004 removed because of overlap with NRRW study (Muirhead *et al* 2009)
- Some problematic studies remained: McGeoghegan *et al.* 2008 and Richardson and Wing 1999 – dealt with by sensitivity analysis

Meta-analysis of circulatory disease: excess relative risk coefficients (Little *et al. Env. Health Perspect.* 2012 **120** 1503-11)

Circulatory disease subtype	Studies Included	Fixed-effect ERR / Sv (+95% CI)	Random-effect ERR / Sv (+95% CI)	Heterogeneity *p*
Ischemic heart disease	Ivanov *et al.*, Vrijheid *et al.* Muirhead *et al.* Azizova *et al.*, Laurent *et al.*, Lane *et al.*, Shimizu *et al.*, Yamada *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	Ivanov *et al.*, Kreuzer *et al.*, Vrijheid *et al.*, Azizova *et al.*, Muirhead *et al.*, Laurent *et al.* , Lane *et al.*, Shimizu *et al.* , Yamada *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	Ivanov *et al.*, Shimizu *et al.* , Yamada *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 ischemic heart disease and stroke (borderline significant for other circulatory)**
- **Significant heterogeneity in risk for stroke and other circulatory (so must use random effects model for these two)**

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)		
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

Circulatory excess relative risk Sv^{-1} (+95% CI) in moderate/low dose groups not considered in meta-analysis (Little *et al EHP* **120**:1503-11;2012)`

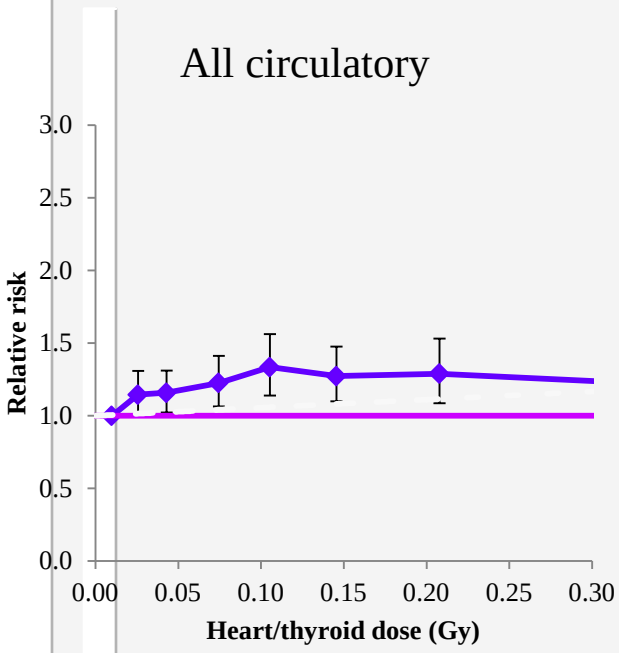
Circulatory disease subtype	Semipalatinsk study (Grosche *et al. Radiat Res* 2011 **176** 660-9)	Techa river study (Krestinina *et al Radiat Env Biophys* 2013 **52** 47-57)	German uranium miner study (Kreuzer *et al Radiat Env Biophys* 2013 **52** 37-46)	**Meta-analysis random-effect ERR / Sv**
Ischemic heart disease	0.06 (-0.39 to 0.52)	0.40 (-0.11, 0.99)	-0.03 (-0.38, 0.32)	0.10 (0.04 to 0.15)
Cerebrovascular disease	-0.06 (-0.65 to 0.54)	NA	0.44 (-0.16, 1.04)	0.21 (0.02 to 0.39)
All circulatory disease	0.02 (-0.32, 0.37)	0.24 (-0.08, 0.59)	-0.13 (-0.37, 0.13)	NA

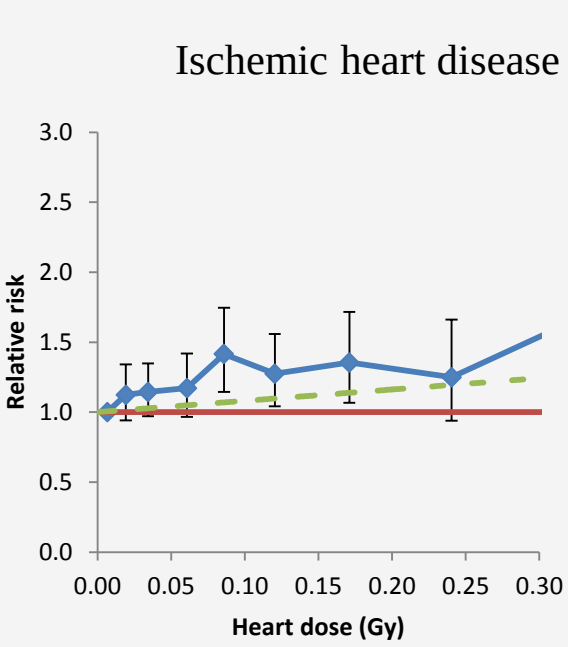
Studies consistent with findings of meta-analysis (Little *et al EHP* 2012 **120** 1503-11)

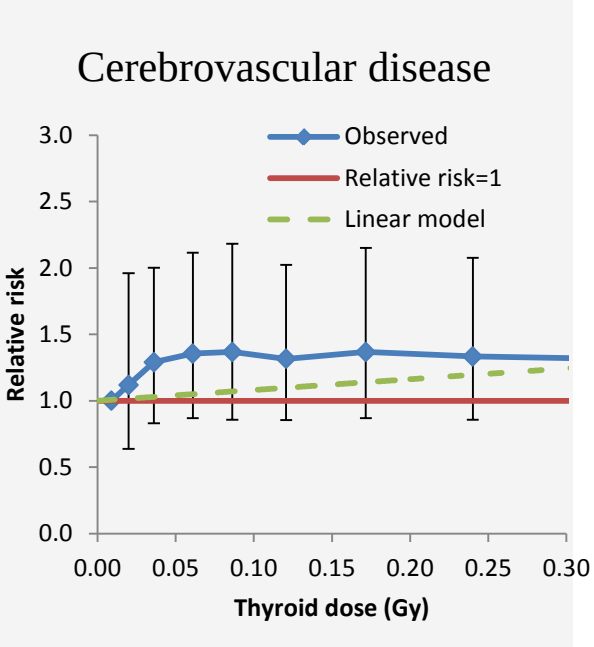
Interactions and risk modifiers

- Some information in LSS (Shimizu *et al BMJ* 2010 **340** b5349), Mayak data (Azizova *et al Radiat Res* 2010 **174** 155-68, 851-64) and in Techa River cohort (Krestinina *et al REB* 2013 **52** 47-57), and US radiologic technologists (Little *et al* 2014 submitted) particularly rich for technologists
- Dose response same in LSS (Shimizu *et al BMJ* 2010 **340** b5349) if adjusted for smoking, alcohol, education, obesity, diabetes mellitus
- Dose response same in Mayak workers (Azizova *et al Radiat Res* 2010 **174** 155-68, 851-64) if adjusted for smoking, alcohol
- Significantly higher (p=0.023) risk for smokers than non-smokers for all circulatory disease in US technologists (Little *et al* 2014 submitted)
- Significant interaction with ethnic group (p<0.05) for all circulatory disease, and borderline significant (p=0.07-0.08) higher risk for males for all circulatory disease and ischemic heart disease, in Techa River cohort (Krestinina *et al REB* 2013 **52** 47-57)
- Significant reduction in risk with increasing age at exposure in LSS (Shimizu *et al BMJ* 2010 **340** b5349), in Techa River cohort (Krestinina *et al REB* 2013 **52** 47-57) and in US radiologic technologists (Little *et al* 2014 submitted)

Shape of circulatory dose response at low dose in US radiologic technologists (Little *et al* 2014 submitted)`







- **Evidence of increased slope in low dose region for all three circulatory disease endpoints – and risks significantly elevated below 0.1 Gy (at least for all circulatory disease and ischemic heart disease)**
- **Similar increased low dose slope (relative to slope over full dose range) seen also in Canadian TB fluoroscopy** (Zablotska *et al Am J Epidemiol* 2014 **179** 120-31) **and in Massachusetts TB fluoroscopy** (Little *et al Eur J Epidemiol* 2014) **cohorts**

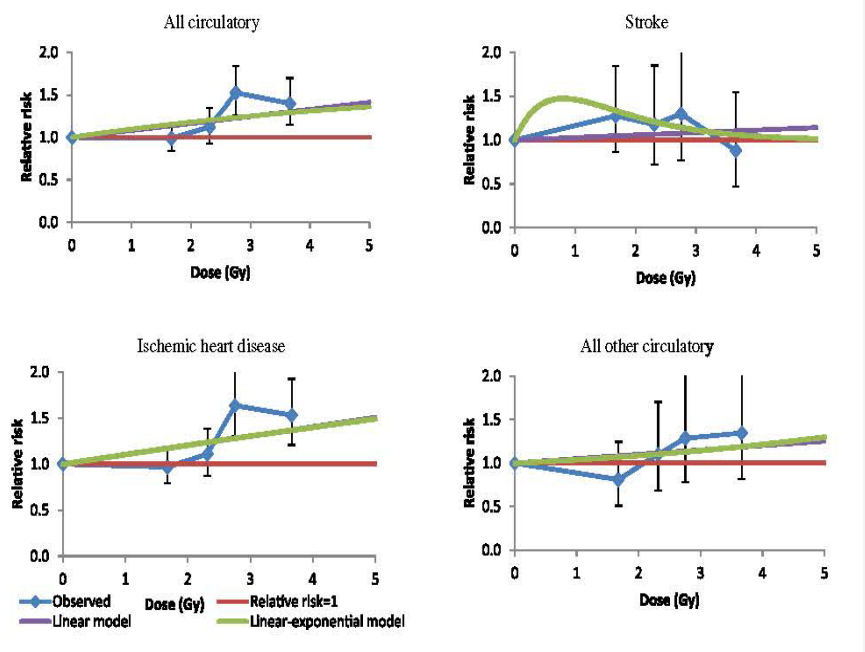
Studies of radiotherapeutically exposed groups (cardiac dose generally > 5 Gy)

Risks in high dose RT cohorts (adapted from Little *et al.* *Environ. Health Perspectives* 2012 **120** 1503-11)

Reference	Average heart/brain dose (range) (Sv)	Endpoint (mortality unless otherwise indicated)	Excess relative risk Sv^{-1} (and 95% CI)
Mulrooney *et al.* (*BMJ* 2009 **339** b4606)	n.a. (<5 – > 35)	Congestive heart disease morbidity	0.05 (0.02, 0.09)
		Myocardial infarction morbidity	0.04 (-0.02, 0.10)
		Pericardial disease morbidity	0.05 (-0.01, 0.11)
		Valvular disease morbidity	0.07 (-0.02, 0.16)
Tukenova *et al.* (*J Clin Oncol* 2010 **28** 1308-15)	11.1 (<1 – >15)	All cardiovascular disease	0.6 (0.2, 2.5)
Little *et al.* (*IJROBP* 2012 **84** 1101-9)	0.85 (0.0 – >6.20)	Ischemic heart disease (ICD8 410-414)	0.102 (0.039, 0.174)
		Stroke (ICD8 430-438)	0.028 (-0.085, 0.186)
		All other circulatory disease	0.050 (-0.053, 0.194)
		All circulatory disease (ICD8 390-459)	0.082 (0.031, 0.140
Darby *et al.* (*NEJM* 2013 **368** 987-98)	4.9 (0.03-27.72)	Ischemic heart disease (ICD10 I20-25), morbidity from myocardial infarction (ICD10 I21-24), coronary revascularization	0.074 (0.029, 0.145)
Low dose meta-analysis (Little *et al. EHP* 2012 **120** 1503-11)	Generally mean < 0.5	Ischemic heart disease (ICD10 I20-I25)	0.10 (0.04, 0.15)
		Stroke (ICD10 I60-I69)	0.21 (0.02, 0.39)

Excess risks / Gy in RT cohorts are not way out of line with (although tending to be lower than) moderate/low dose ones

Circulatory disease mortality after peptic ulcer (Little *et al. IJROBP* **84**:1101-9;2012)



Endpoint	Excess relative risk/Gy (+95% CI)
IHD	0.102 (0.039, 0.174)
Stroke	0.028 (-0.085, 0.186)
Other circulatory	0.050 (-0.053, 0.194)
All circulatory	0.082 (0.031, 0.140)

- **Mortality-based cohort study – using a variety of dose metrics**
- **Dose much lower than other RT cohorts – mean heart dose 0.85 Gy**
- **Significant dose response, significant excess above 2.5 Gy**

Interactions and risk modifiers

- Some information in French-UK childhood cancer study (Tukenova *et al JCO* 2010 **29**1308-15), Nordic breast cancer case-control study (Darby *et al NEJM* 2013 **368** 987-98) and in peptic ulcer study (Little *et al IJROBP* 2012 **84** 1101-9), particularly rich for Nordic study
- No interactions with concomitant chemotherapies in French-UK childhood cancer study (Tukenova *et al JCO* 2010 **29**1308-15) or with cardiac risk factors, medications, concomitant chemotherapies in Nordic study (Darby *et al NEJM* 2013 **368** 987-98)
- Borderline significant (p=0.045) interactions with alcohol for ischemic heart disease, none for smoking for any other endpoint in US peptic ulcer cohort (Little *et al IJROBP* 2012 **84** 1101-9)
- Significant (p<0.01) reduction in risk with increasing time after exposure for all circulatory disease, ischemic heart disease and stroke in US peptic ulcer cohort (Little *et al IJROBP* 2012 **84** 1101-9)

Conclusions

- Risk suggested both in high dose (RT) and moderate/low dose data
- Risk factors from moderate/low dose cohorts suggest radiation-associated population risks of circulatory disease are similar to radiation-induced cancer
- Suggestion of increased low dose slope at low dose (<0.5 Gy) in three groups (US radiologic technologists, Massachusetts+Canadian TB fluoroscopy)
- Weak evidence for interactions and risk modifiers – most consistently suggestion that relative risks reduce with increasing age at exposure