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Low-dose and low-dose-rate epidemiology of cancer and non-cancer effects

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Outline of talk

- Studies of cancer after low-dose radiation exposure in early life
  - Studies of childhood cancer risk in relation to obstetric exposure
  - Studies of childhood cancer risk in relation to natural background radiation
    - UK Childhood Cancer Study - case-control study
    - Danish study – case-control study
    - UK National Registry of Childhood Tumours (NRCT) study
  - UK-NCI study of cancer in relation to use of computerized tomography (CT)
- Studies of circulatory disease
  - Studies of moderate- and low-dose exposed groups (cardiac dose generally < 5 Gy)
    - Meta-analysis of circulatory disease in occupationally-exposed groups
  - Studies of high dose-exposed groups (cardiac dose generally > 5 Gy)
- Conclusions

Studies of childhood cancer in relation to obstetric (*in utero*) radiation exposure

Childhood leukemia and other cancers in relation to obstetric radiation exposure

(Stewart *et al Lancet* 1956 **268** 447, Bithell & Stewart *Br J Cancer* 1975 **31** 271-87)

Oxford Survey of Childhood Cancers (OSCC)

Obstetric X-rays and risk of childhood cancer

Type of cancer	Odds ratio (+95% CI)
Lymphatic leukemia	1.54 (1.34, 1.78)
Myeloid leukemia	1.47 (1.20, 1.81)
All solid cancers	1.45 (1.30, 1.62)
All cancers	1.47 (1.34, 1.62)

Significant excess risks for most types of childhood cancer in relation to obstetric radiation exposure

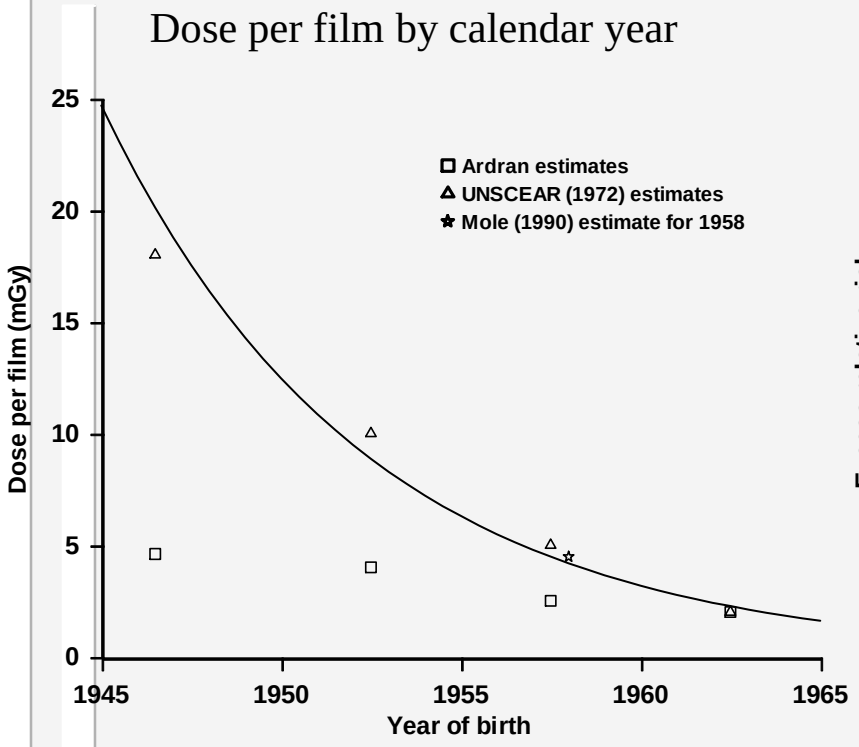
Childhood leukemia case-control studies in relation to obstetric radiation exposure

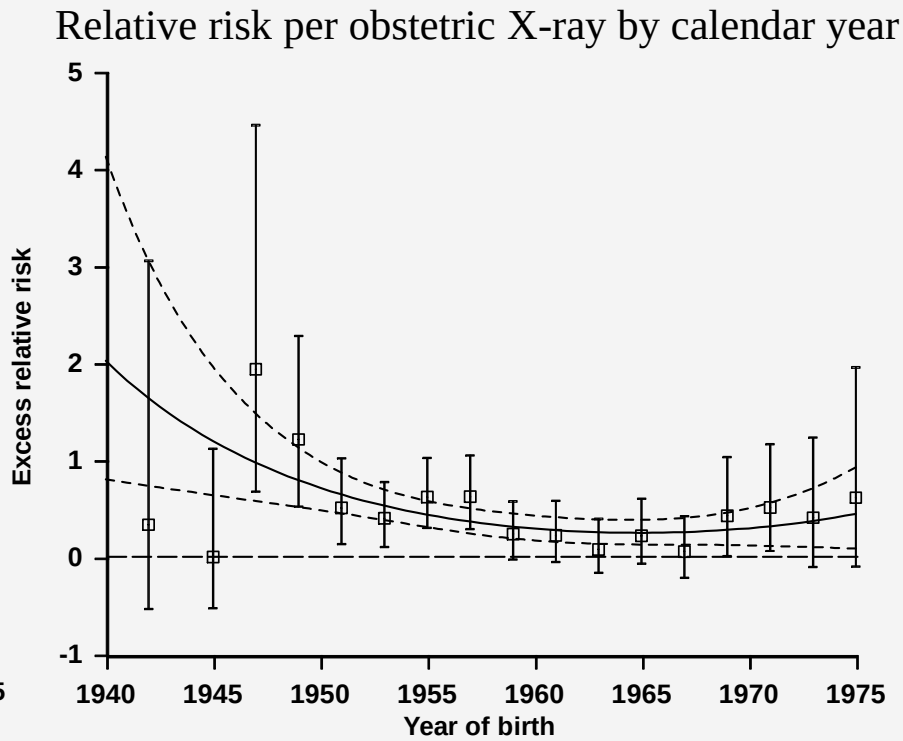
(Wakeford *Radiat Prot Dosim* 2008 **132** 166-74)

Period	Study	Relative risk (95% CI)
1947-1960	Monson & MacMahon (1984)	1.48 (1.18, 1.85)
1950-1957	Polhemus & Koch (1959)	1.23 (0.82, 1.85)
1953-1967	Bithell & Stewart (1975) [OSCC]	1.49 (1.33, 1.67)
1955-1956	Kaplan (1958)	1.60 (1.00, 2.57)
1960-1969	Robinette & Jablon (1976)	1.08 (0.80, 1.46)
1969-1977	Hirayama (1979)	1.60 (1.42, 1.79)
1973-1979	Van Steensel-Moll et al (1985)	2.22 (1.27, 3.88)
1980-1983	Hopton et al (1985)	1.35 (0.86, 2.11)
1980-1998	Infante-Rivard (2003)	0.85 (0.56, 1.30)
1989-1993	Shu et al (2002)	1.16 (0.79, 1.71)
1992-1996	Roman et al (2005)	1.05 (0.73, 1.52)

Risks in later studies tend to be lower, probably because of lower obstetric radiation doses used

Oxford Survey of Childhood Cancer (OSCC) childhood cancer obstetric radiation risk and dose by birth year (Wakeford & Little *IJRB* 2003 **79** 293-309)





General reduction in childhood cancer risk per film in Oxford Survey of Childhood Cancer (OSCC) over time, paralleling reduction in dose per film over this period

Possible problems in causal interpretation of obstetric case-control studies

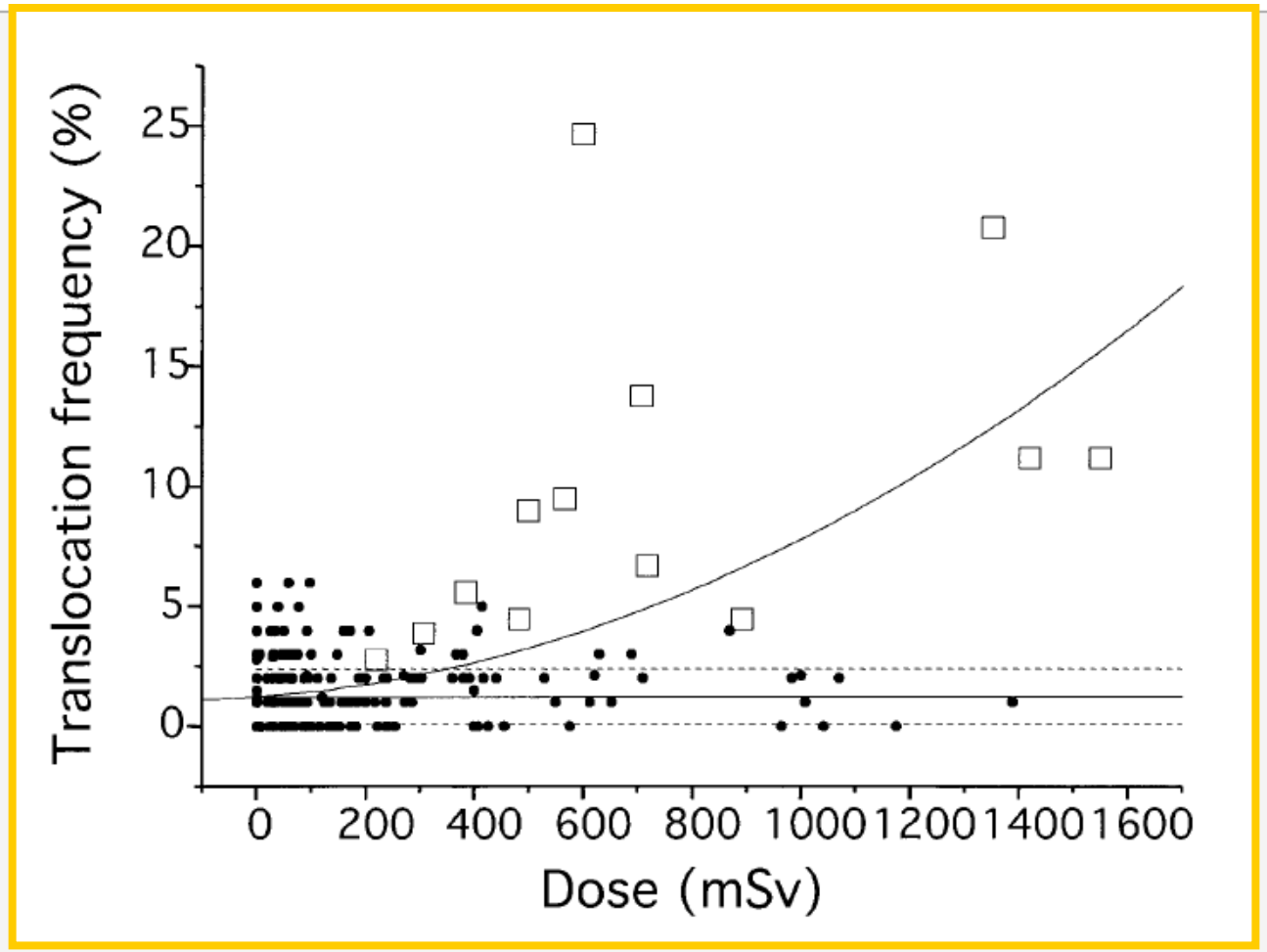
- Similar risk in all endpoints [lack of specificity]
  - OSCC leukemia RR=1.51 *vs* non-leukemia RR=1.46
  - non-OSCC leukemia RR=1.27 *vs* non leukemia RR=1.26
- Discrepancy between risks in:
  - OSCC+other case-control *in utero* irradiation, in which all cancers at equal risk
  - Exposure risks after birth in Japanese A-bomb Life Span Study data, when only leukemias are elevated in childhood (although later solid cancer excess at older ages)
- Lack of risk in *in utero* cohort studies
- Lack of risk in Japanese A-bomb *in utero* study

Resolution of possible problems in causal interpretation of obstetric case-control studies

- Known biological differences between *in utero* irradiation and period shortly after birth (animal studies)(UNSCEAR 1986)
- Many cohort studies have insufficient cases/deaths (lack statistical power), and in some cases may be subject to bias (e.g. selection bias in Court Brown *et al* (*BMJ* 1960 **2** 1539-45) study)
- Excess relative risk (ERR) per Sv in Japanese *in utero* study is compatible with OSCC (Wakeford & Little *IJRB* 2003 **79** 293-309)
  - Japanese leukemia ERR/Sv <0 (95% CI <0, 50)
  - Japanese solid cancer ERR/Sv 22 (95% CI 0, 78)
  - OSCC all cancer ERR/Sv 51 (95% CI 28, 76)

  So risk in OSCC compatible with Japanese *in utero*
- Doll & Wakeford (*Br J Radiol* 1997 **70** 130-9) concluded "on the balance of evidence … irradiation of the fetus *in utero* [by doses of the order of 10 mGy] increases the risk of childhood cancer"

Chromosome translocation frequencies in peripheral blood lymphocytes from A-bomb survivors exposed *in utero* (●) and some of their mothers (□) (Ohtaki *et al Radiat Res* 2004 **161** 373-9)



Indications of low dose hypersensitivity among *in utero* exposed, but not their mothers – possible explanation of lack of *in utero* leukemias

Studies of childhood leukemia and other cancers in relation to natural background radiation

Feasibility of studies of childhood leukemia in relation to natural background radiation

- Advantage of studying childhood leukemia
  - Highly radiogenic (arguably most radiogenic tumor)
  - Apart from radiation, relatively few things associated with it – so confounding unlikely
- Linear extrapolation of risks derived from Japanese A-bomb data imply ~15-20% of childhood leukemia in UK attributable to natural background radiation (mostly γ) (Wakeford *et al Leukemia* 2009 **23** 770-6, Little *et al J Radiol Prot* 2009 **29** 467-82)
- However, numbers required for study to have adequate statistical power (and so good chance of detecting statistically significant expected effect) are daunting

Power of studies of childhood leukemia in relation to natural background radiation (Little et al *Radiat Res* 2010 **178** 387-402)

- Assuming UK natural background radiation distribution, numbers years of follow-up in UK required for 80% power for 1-sided test with α=0.05 [standard for adequate power] are:
  - Cohort study — 14 years (6400 cases)
  - Case-control study (5 controls/case) — 17 years (7800 cases)
  - Case-control study (1 control/case) — 28 years (12,800 cases)
  - Ecological correlation study — 19 years (8700 cases)
- Assumes combined (red bone marrow) doses from radon and gamma – slightly larger numbers required if dose purely from gamma

Case-control study of childhood leukemia in relation to natural background radiation (UKCCS *Br J Cancer* 2002 **86** 1721-6, UKCCS *Br J Cancer* 2002 **86** 1727-31)

- UK Childhood Cancer Study (UKCCS) natural radiation study had 2226 cases of all childhood cancer, 951 leukemia, 2 controls/case
- Underpowered (needs 10 x leukemia cases for adequate power) (Little et al *Radiat Res* 2010 **178** 387-402)
- Highly significant (p=0.002) inverse association of childhood cancer with radon, but no relation of childhood cancer with gamma (p>0.1)
  - Reflect participation bias – 50% of eligible cases had radon measurements [and thus included in study] *vs* 31% of eligible controls, leaving considerable scope for bias

Register-based studies of childhood leukemia in relation to radon daughter exposure

- Register-based studies not subject to participation bias
- Register-based case-control study of Rn exposure and cancer, Denmark 1968-94 (Raaschou –Nielsen *et al Epidemiology* 2008 **19** 536-43)
  - 1153 childhood leukemia cases, 2306 controls
  - Underpowered (33% power) (Little et al *Radiat Res* 2010 **178** 387-402) but significant excess risk for leukemia
- Ecological register-based (National Registry of Childhood Tumours) cohort study of γ+Rn exposure and leukemia, UK 1969-83 (Richardson *et al Stat Med* 1995 **14** 2487-2501)
  - 6691 leukemia cases – so just about adequate power (>60%)
  - No relation of leukemia rate with background radiation
  - Use of dose rate rather than cumulative dose likely incorrect

UK NRCT case-control study of childhood cancer in relation to natural background radiation

Kendall *et al Leukemia* 2013 **27** 3-9

- Case-control study of childhood cancer in Great Britain in period 1980-2006
- Cases matched to either 1/2 controls (2 per case in later period) by sex, date of birth (< 6 months) and birth registration district within National Registry of Childhood Tumours (NRCT)
- 27,447 childhood cancer cases
- 9058 leukemia cases
- 36,793 controls

UK NRCT case-control study of childhood cancer in relation to natural background radiation

Kendall *et al Leukemia* 2013 **27** 3-9

- Address at birth of cases and controls used to assess γ dose rates based on National Survey data
- Rn exposure rates at birth derived from 400,000 measurements, grouped by geological boundaries
- γ dose rates averaged over County Districts
- Cumulative γ dose
  = γ dose rate x attained age of case/control
- Cumulative Rn exposures
  = Rn exposure rate x attained age of case/control

UK NRCT case-control study of childhood cancer in relation to natural background (air γ) radiation

Kendall *et al Leukemia* 2013 **27** 3-9

Excess relative risk per cumulative gamma air dose (Gy)

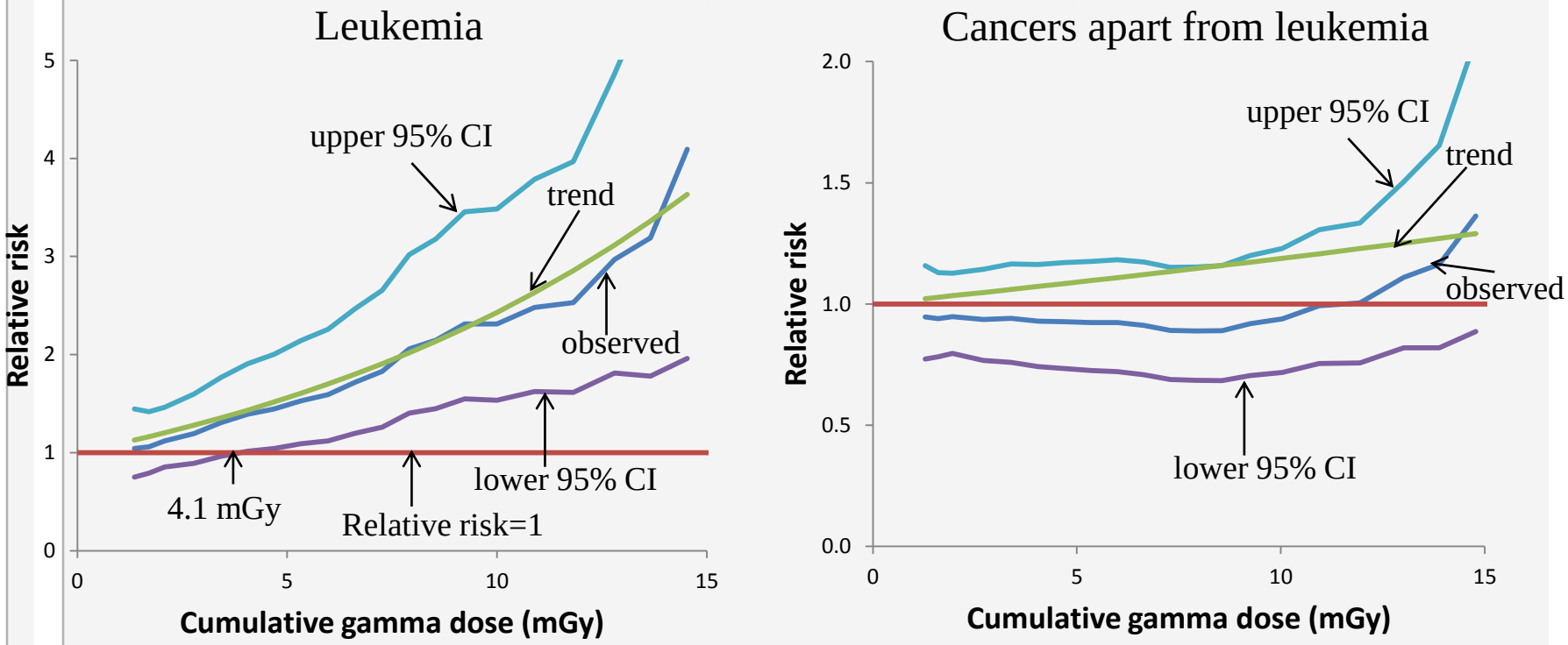
Endpoint	Excess relative risk per Gy (γ) (95% CI)	p-value
Lymphoid leukemia	100 (20,190)	0.01
All leukemia	90 (20, 170)	<0.01
Lymphoid leukemia + non-Hodgkin lymphoma	90 (20, 160)	0.02
Total leukemia + non-Hodgkin lymphoma	80 (20, 150)	0.01
All lymphoma	10 (-70, 90)	0.86
Brain/CNS	20 (-40, 90)	0.49
All cancer	30 (0, 70)	0.04

Highly significant ($p<0.01$) excess risk for all leukemia
No excess risk for other cancers

UK NRCT case-control study of childhood cancer in relation to natural background radiation

Kendall *et al Leukemia* 2013 **27** 3-9

Trend risk estimates by cumulative gamma dose



Lower 95% CI for observed leukemia crosses relative risk = 1 at 4.1 mGy

So threshold of > 4.1 mGy for leukemia inconsistent with data

Nothing much going on for solid cancers, but relative risk>1 at ≈12 mGy

Risks compatible with those in Japanese A-bomb survivors

UK NRCT case-control study of childhood cancer in relation to natural background radiation

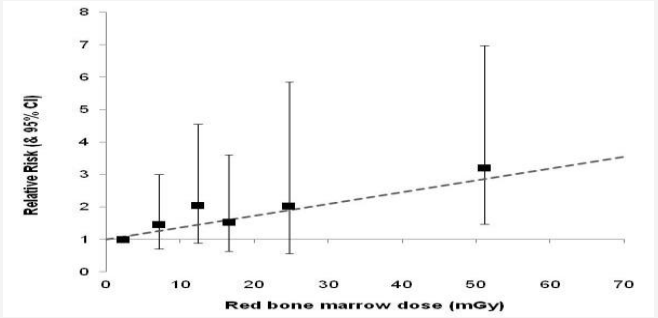
Kendall *et al Leukemia* 2013 **27** 3-9

- Strengths
  - Register-based study, so free from participation + other biases that case-control studies (e.g., UK Childhood Cancer Study) prone to
  - Adequate power (~50%)
- Weaknesses
  - County-district averaged γ dose estimates
    - Matching by birth register mean that about 50% of case/control sets largely uninformative in relation to γ, so loss of power, but no bias
  - Full residential history not available for cases and controls
    - Results in Berkson error, so no bias, although confidence intervals will be inflated

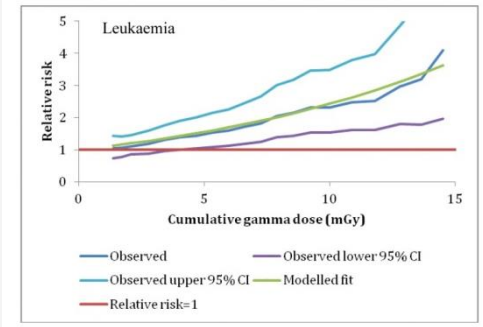
UK-NCI CT *vs* childhood-exposed LSS leukemia+brain *vs* UK NRCT risks (ERR / Sv + 95% CI)

	Leukemia ERR /Gy	Brain/CNS ERR/Gy
UK-NCI CT cohort (Pearce *et al. Lancet* 2012 **380** 499-505)	36 (5, 120)	23 (10, 49)
LSS age at exposure < 20, follow-up < 20 years after exposure	37.08 (14.22, 127.2)	6.14 (0.12, 63.93)
UK NRCT study (Kendall *et al. Leukemia* 2013 **27** 3-9)	90 (20, 170)	20 (-40, 90)

UK-NCI CT leukemia



UK-NRCT leukemia



Both for solid cancer and brain cancer risks in UK-NCI CT and UK-NRCT studies are compatible with those in Japanese A-bomb survivors

Circulatory disease in relation to moderate- and low-dose exposure (cardiac dose generally < 5 Gy)

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

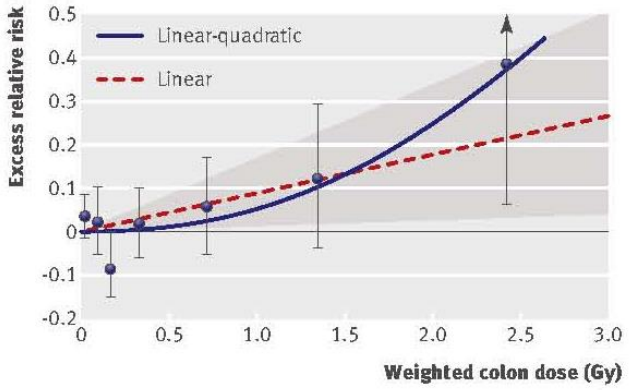


Fig 1| Radiation dose-response relation (excess relative risk per Gy) for death from stroke, showing linear and linear-quadratic functions. Shaded area is 95% confidence region for fitted linear line. Vertical lines are 95% confidence intervals for specific dose category risks. Point estimates of risk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

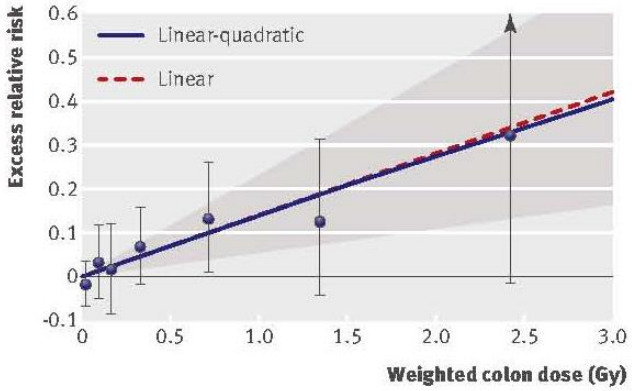


Fig 2| Radiation dose-response relation (excess relative risk) for death from heart disease, showing linear and linear-quadratic functions. Shaded area is 95% confidence region for fitted linear line. Vertical lines are 95% confidence intervals for specific dose category risks. Point estimates of risk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

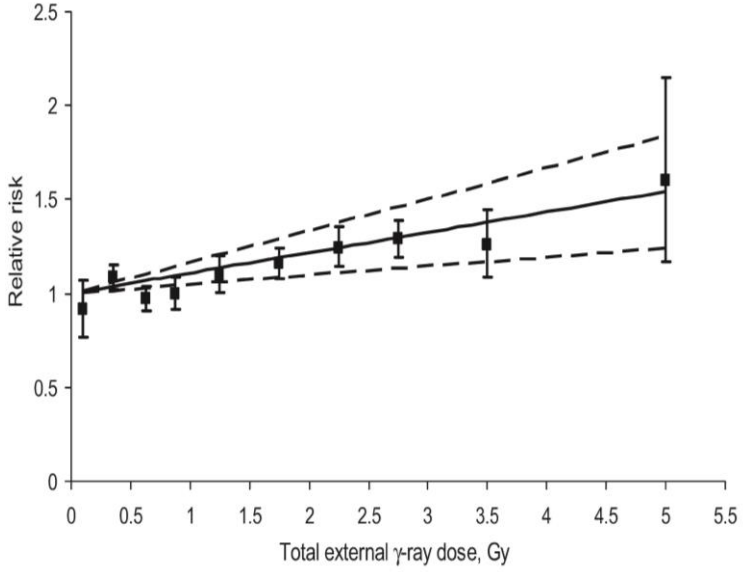
ERR/Sv stroke (ICD9 430-438) 0.12 (95% CI 0.05, 0.19)

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

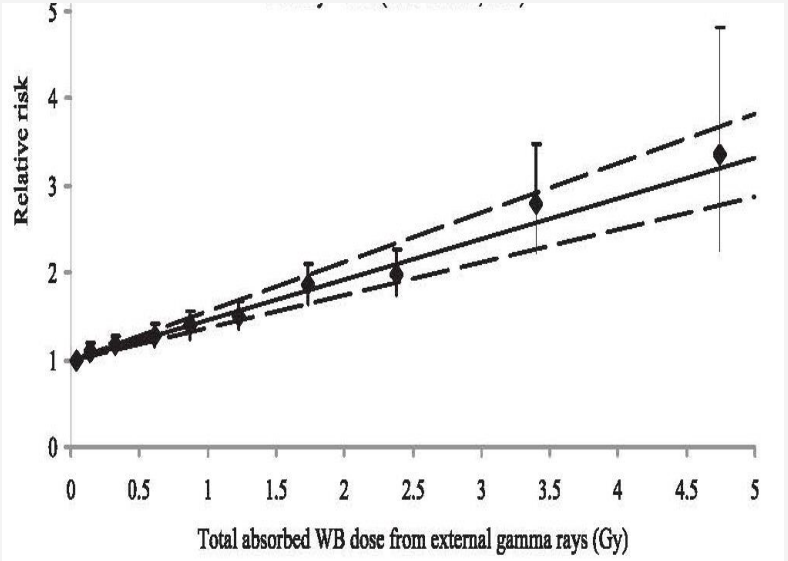
- **Highly significant dose response, but excess risk only clear above ~0.5 Gy**
- **Shape of dose-response uncertain: no significant curvature for stroke or heart disease ($p>0.1$)**

Dose response for ischemic heart disease +stroke morbidity in Mayak nuclear workers (Azizova *et al. Radiat. Res.* **174**:155-68; 2010, *Radiat. Res.* **182**:529-44; 2014)

Ischemic heart



Cerebrovascular



ERR/Gy ischemic heart (ICD9 410-414) **0.12 (95% CI 0.05, 0.19)**

ERR/Gy cerebrovascular (ICD9 430-438) **0.46 (95% CI 0.37, 0.57)**

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

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

Circulatory disease subtype	Number of datapoints	Random-effect ERR / Sv (+95% CI)	Heterogeneity *p*-value
Ischemic heart disease	7	0.10 (0.04 to 0.15)	0.408
Non-ischemic heart disease	4	0.08 (-0.12 to 0.28)	0.199
Stroke	8	0.21 (0.02 to 0.39)	<0.001
Circulatory disease excluding heart disease & stroke	8	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) – and limits causal interpretation**

Lifetime radiation risk of circulatory disease vs cancer (Little *et al. Environ. Health Perspectives* 2012 **120** 1503-11)

Radiation-exposure-induced death, x 10^{-2} Sv using random effects models (summed over four circulatory endpoints)

Country	All circulatory disease (+95% CI)	UNSCEAR cancer risks (range using relative /additive risk model)
China	6.76 (2.63, 10.89)	4.16 - 4.37
Japan	4.01 (1.13, 6.89)	4.97 - 5.33
UK	5.07 (2.55, 7.58)	4.78 – 5.58
USA	4.48 (2.22, 6.74)	4.83 – 5.21

⇒ **Lifetime circulatory disease risk comparable with cancer risk**

Circulatory disease in relation to high-dose exposure (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

Conclusions for moderate/low dose cancer risk

- Many case-control studies show risk associated with obstetric radiation exposure, although no risk in obstetric cohort studies (but problems of power and bias in latter)
- Extrapolation from LSS suggests 15-20% childhood leukemia caused by natural background γ + Rn
- Various studies of childhood leukemia and background radiation
  - Most underpowered
  - Some prone to participation bias, e.g., UK Childhood Cancer Study
- UK NRCT case-control study has adequate power & demonstrates excess leukemia risk of natural background radiation, and at ~4 mSv this is significant
- Elevated risks of leukemia and brain cancer in UK-NCI CT study, compatible with UK NRCT case-control study and with LSS

Conclusions for moderate/low dose circulatory disease risk

- Risk suggested both in high dose (RT) and moderate/low dose data – but heterogeneity for some endpoints (stroke, other circulatory disease) limits causal interpretation
- Risks per unit dose at low/moderate dose are same as at higher (RT) doses – similar mechanism?
- Risk factors from moderate/low dose cohorts suggest lifetime radiation-associated population risks of circulatory disease are similar to those of radiation-induced cancer