Epidemiological Evidence for Radiation-induced Circulatory Diseases – Non-occupational Exposure

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Objective of Presentation

We shall explore the evolving evidence for a radiation-associated excess risk of diseases of the blood circulatory system (heart disease, stroke, etc.) among the Japanese survivors of the atomic bombings of Hiroshima and Nagasaki in August 1945.

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Japanese Atomic Bomb Survivors

- The cohort study of the Japanese survivors of the atomic bombings of Hiroshima and Nagasaki represents the "Gold Standard" for radiation epidemiology.

- It is upon the experience of these Japanese survivors that the radiation risk estimates underlying radiological protection are primarily (but not solely) based.

Life Span Study (LSS)

- Follow-up of ~87 000 survivors, ~48 000 of whom were non-trivially exposed.

- Started in October 1950, still underway.

- Includes both sexes and all ages; "healthy" individuals in a general population.

- Mortality and cancer incidence investigated. Effectively complete cancer ascertainment.

- Wide range of doses received; detailed organ dose estimates.
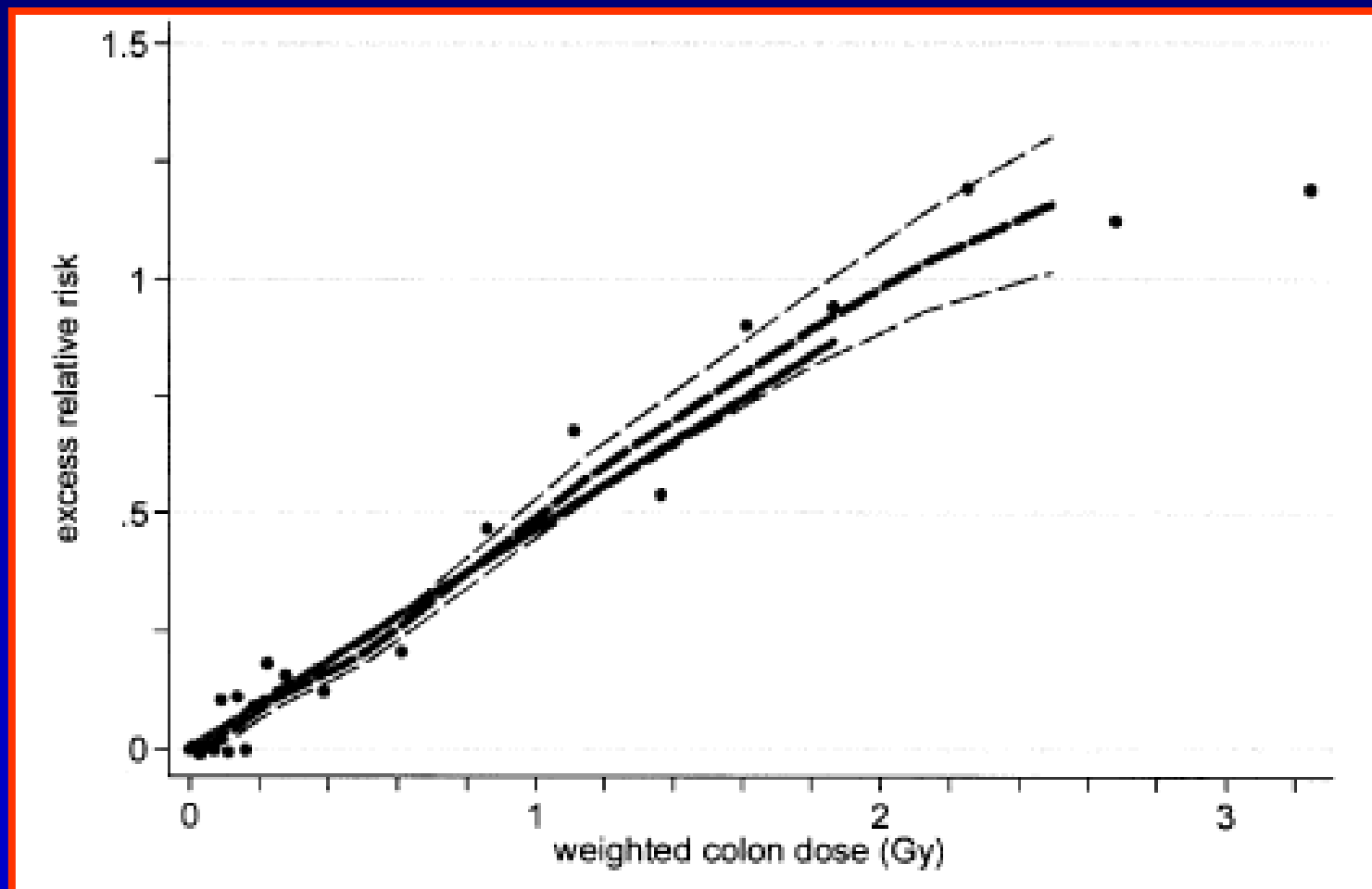
Life Span Study (LSS)

- Acute, high dose-rate exposure.

- Malnourished Japanese population; low proportion of men of military age.

- Some (retrospective) dose estimates uncertain; predominantly external γ doses.

- "Healthy survivor effect".

- Almost half of the survivors still alive.

- Data prior to October 1950 missing.

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Hiroshima and Nagasaki

The Japanese atomic bomb survivors do not provide evidence for a marked deviation from a linear no-threshold (LNT) dose-response relationship for the excess relative risk of solid cancer incidence.

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Solid Cancer Incidence among Japanese Atomic Bomb Survivors (1958-1998)

(Preston *et al., Radiat Res* 2007; **168**: 1-64)

Adult Health Study (AHS)

- Established in 1958.

- Subset of Life Span Study.

- ~20 000 study subjects.

- Biennial health examinations.

- 10 339 study subjects with DS86 doses.

- AHS allows disease morbidity to be investigated for a range of diseases.

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Initial Evidence (1950-1970)

(Jablon & Kato, *Radiat Res* 1972; **50**: 649-98)

Males showed no evidence of radiation effect on circulatory system disease mortality; but females did. Among females, the mortality ratios for the entire 20-year period were elevated in all dose groups from 10 rads up, and especially so above 50 rads. Two of the differences are significant.

Non-cancer Mortality (1950-1978)

(Kato *et al. Radiat Res* 1982; **91**: 243-64)

- Variation of mortality from diseases of the circulatory system with dose is unremarkable, and no mention is made of the risk in subgroups.

Observed Number of Deaths and Ratio of Observed to Expected Mortality by Dose, and Excess Deaths per Million PYR for Major Causes of Death, 1950–1978

| Cause of death | | Total | T65 kerma dose (rad) | | | | | | | | Test (P value)[a] | | Excess deaths per 10^6 PYR (90% confidence interval) |
			0	1–9	10–49	50–99	100–199	200–299	300–399	400+	Homo	Trend	
Diseases of circulatory system except CNS	Obsd	3,724	1518	1013	721	234	126	51	29	32	0.43	0.44	0.06 (−0.58, 0.69)
	O/E		1.01	0.96	0.99	1.14	0.95	0.94	1.19	0.96			

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Circulatory Disease Incidence

(Robertson *et al. RERF TR 12-79* 1979
Kodama *et al. RERF TR 22-84* 1984)

- During 1958-1978 the incidence of myocardial infarction increased with radiation dose for Hiroshima females.

- A similar effect was not found for Hiroshima males or Nagasaki survivors.

- Finding for Hiroshima female survivors considered tentative.

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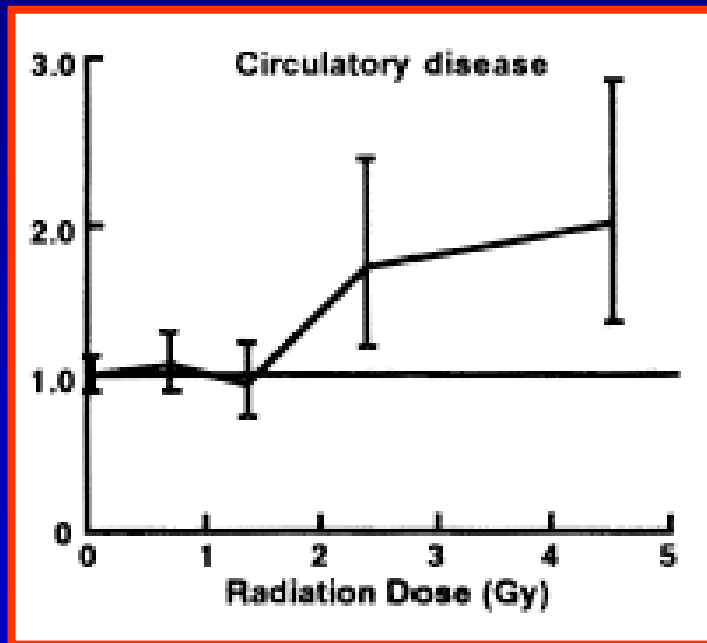# Non-cancer Mortality (1950-85)
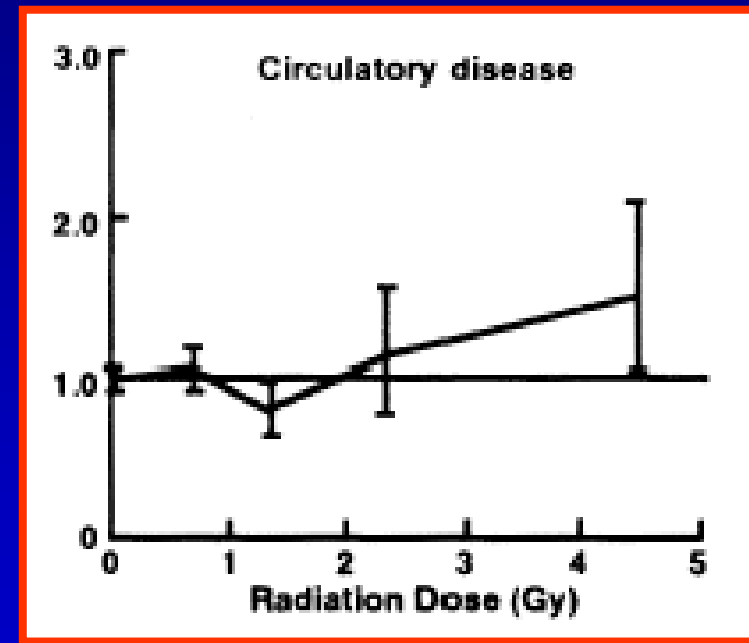
(Shimizu *et al. Radiat Res* 1992; **130**: 249-66)
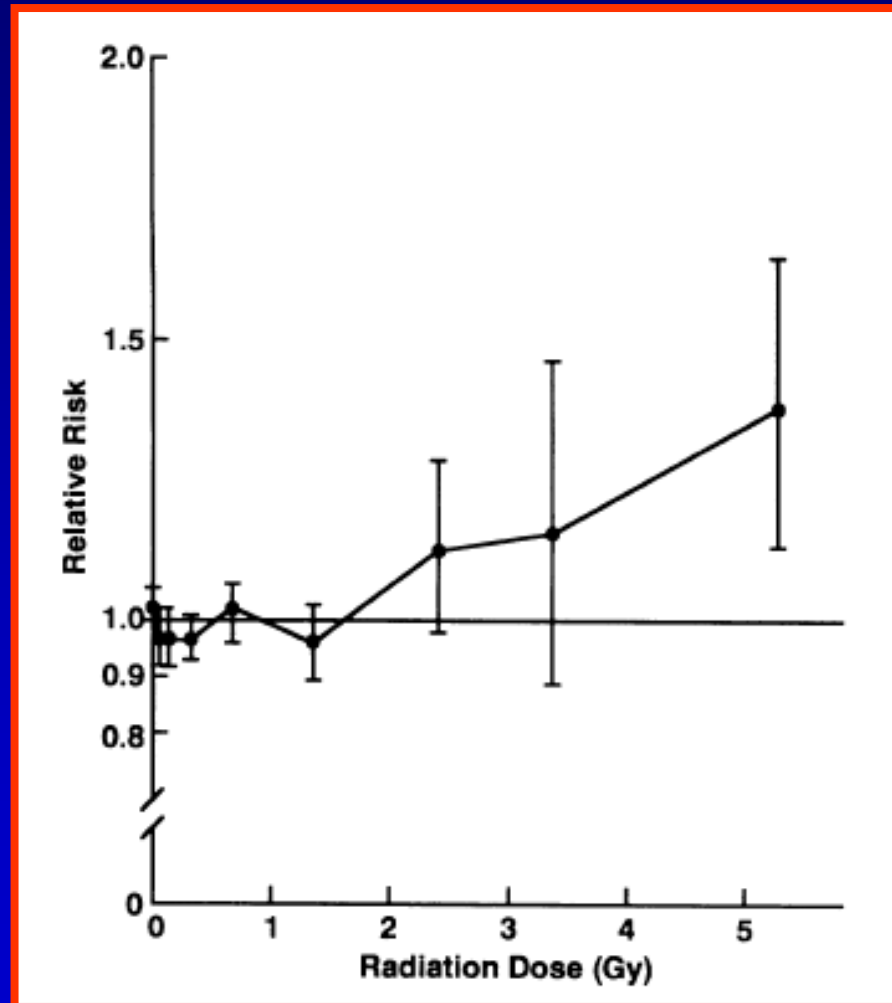
Circulatory Disease Mortality

(Shimizu *et al. Radiat Res* 1992; **130**: 249-66)

Age ATB <40, 1966-85

Age ATB 40+, 1950-65

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Cause of Death Misclassification

- 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 the risk coefficient remains statistically significant.

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Circulatory Disease Incidence

(Wong *et al. Radiat Res* 1993; **135**: 418-30)

Summary Measures of Dose Response for Noncancer Diseases Incident between 1958 and 1986 in Hiroshima and Nagaski, Males and Females

Disease	P	No. cases	Estimated RR at 1 Gy	Average excess risk × 10⁴ PY Gy[a]	Attributable risk (%)
Hypertension	0.31	4353	1.02 (0.98–1.06)[b]	6.30 (−5.62–18.86)	1.5 (−1.4–4.6)
Hypertensive heart disease	0.78	1697	0.99 (0.94–1.06)	−0.84 (−6.21–5.11)	−0.7 (−5.1–4.2)
Ischemic heart disease	0.37	1040	1.04 (0.96–1.13)	1.95 (−2.16–6.57)	2.6 (−2.9–8.8)
Myocardial infarction[d]	0.32	77	1.15 (0.83[c]–1.62)	0.53 (−0.65[c]–1.84)	10.8 (−13.4[c]–37.7)
Occlusion, stenosis	0.51	233	0.95 (0.83[c]–1.13)	−0.65 (−2.08[c]–1.46)	−4.3 (−13.8[c]–9.7)
Aortic aneurysm	0.80	117	0.97 (0.83[c]–1.33)	−0.18 (−1.23[c]–1.65)	−2.1 (−14.0[c]–18.8)
Stroke	0.65	280	0.97 (0.86–1.14)	−0.47 (−2.13–1.78)	−2.6 (−11.6–9.7)

[a] Total PY = 1.90×10^5; male = 6.36×10^4 PY; female = 1.26×10^5 PY (actual numbers depend on the disease).
[b] 95% confidence interval.
[c] Minimum feasible value.
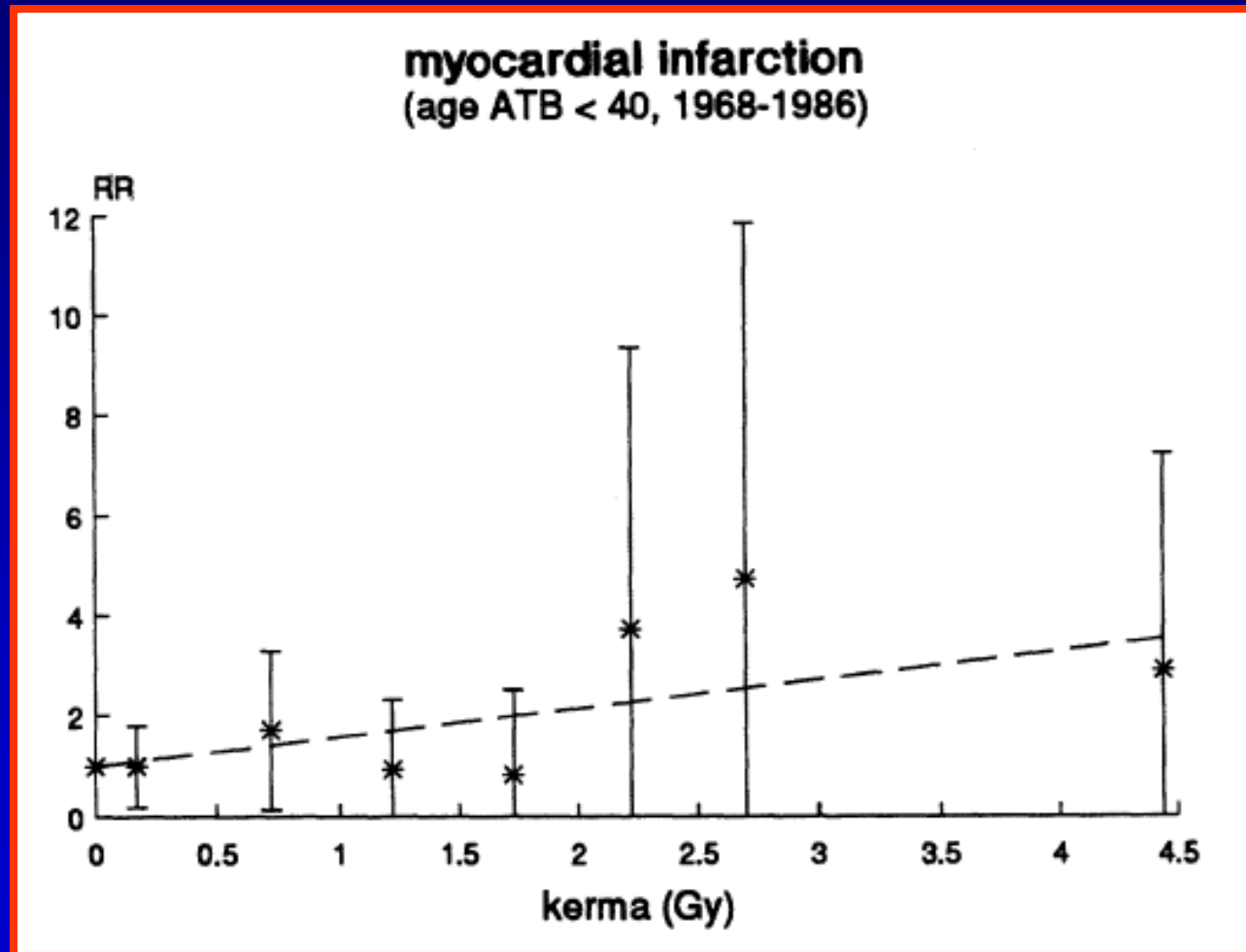[d] Incidence between 1964 and 1986.

Circulatory Disease Incidence

(Wong *et al. Radiat Res* 1993; **135**: 418-30)

- For those <40 years of age ATB, the relative risk of myocardial infarction was
  - deaths during 1964-1986

    1.40 (95% CI: 1.00, 2.30) Gy^{-1}
  - deaths during 1968-1986

    1.57 (95% CI: 1.26, 2.76) Gy^{-1}
- No effect in those 40+ years of age ATB

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Circulatory Disease Incidence
(Wong *et al. Radiat Res* 1993; **135**: 418-30)

myocardial infarction
(age ATB < 40, 1968-1986)

Circulatory Disease

"The two [LSS mortality and AHS incidence] results together indicate that both the fatal and the nonfatal forms of coronary heart disease are possible consequences of exposure to a *high level* of ionizing radiation." [*our emphasis*]

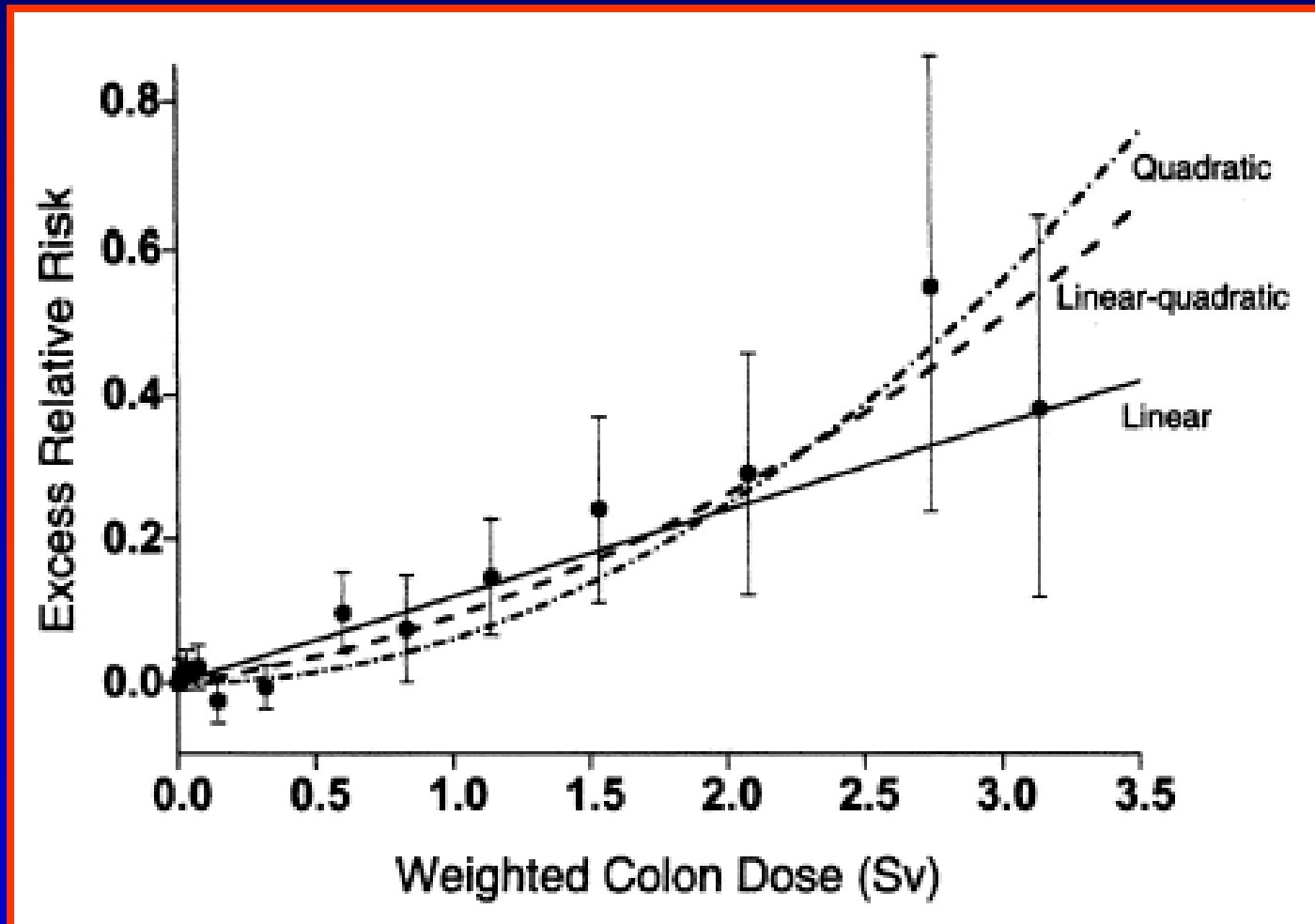Wong *et al. Radiat Res* 1993; **135**: 418-30

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Non-cancer Mortality (1950-1990)
(Shimizu *et al. Radiat Res* 1999; **152**: 374-89)
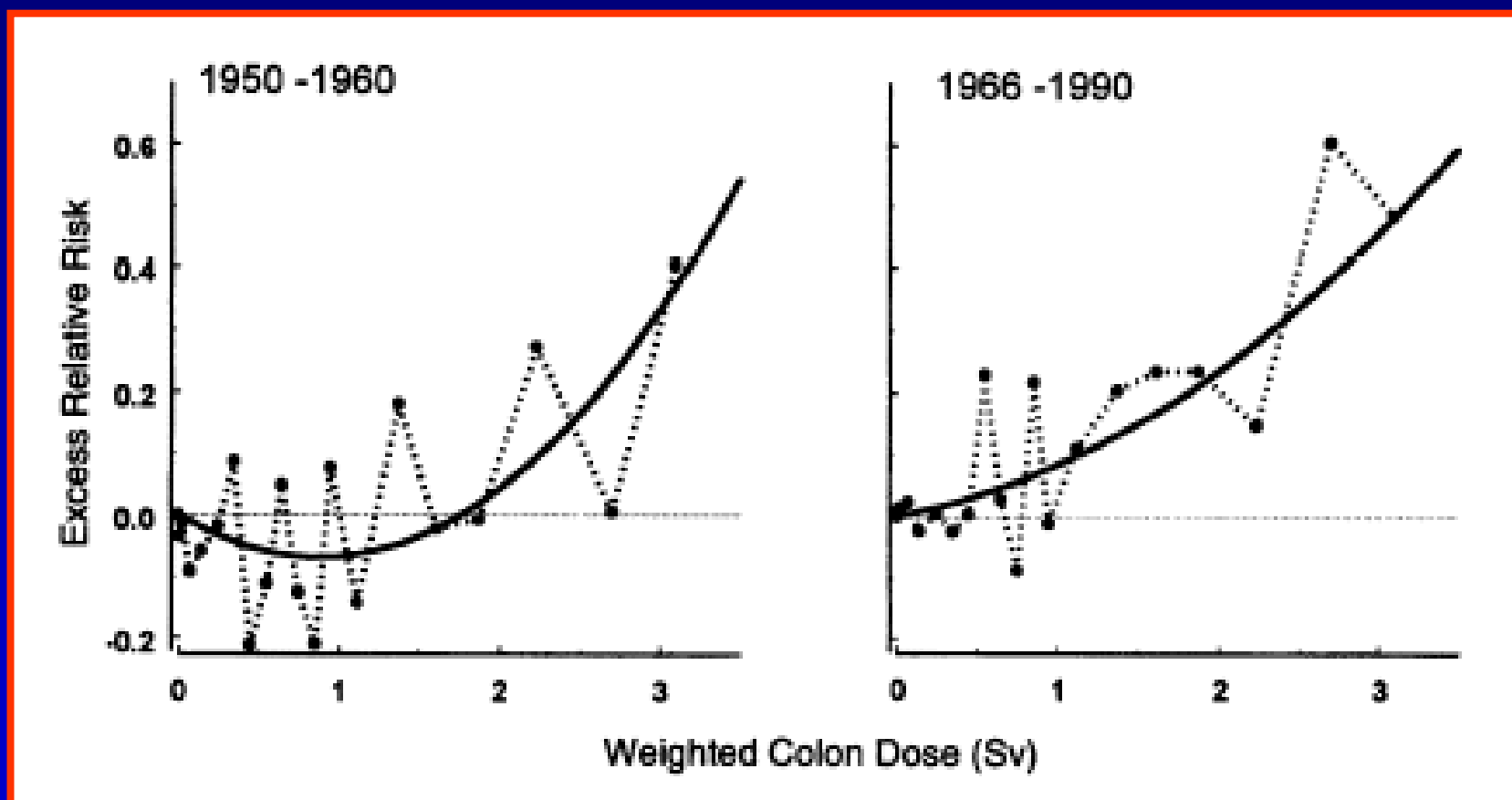
Non-cancer Mortality (1966-1990)

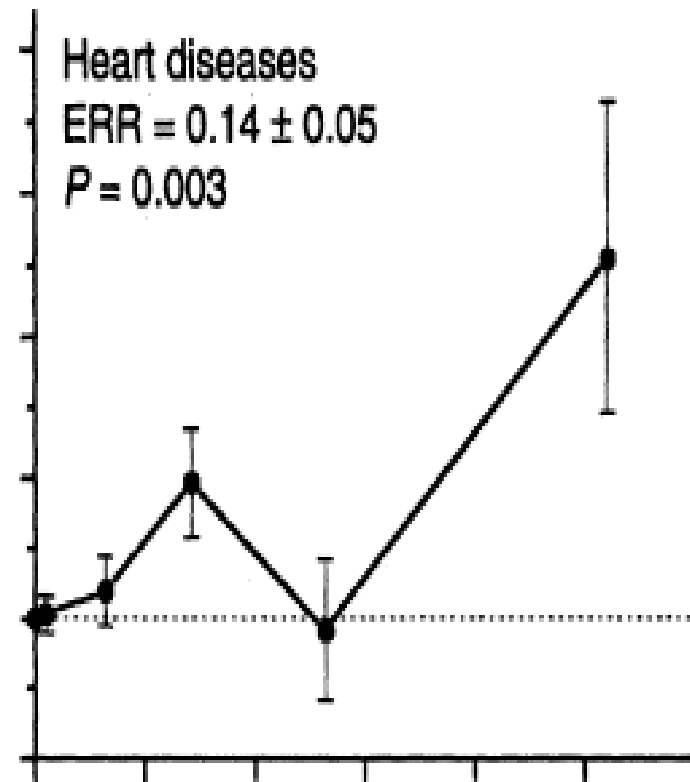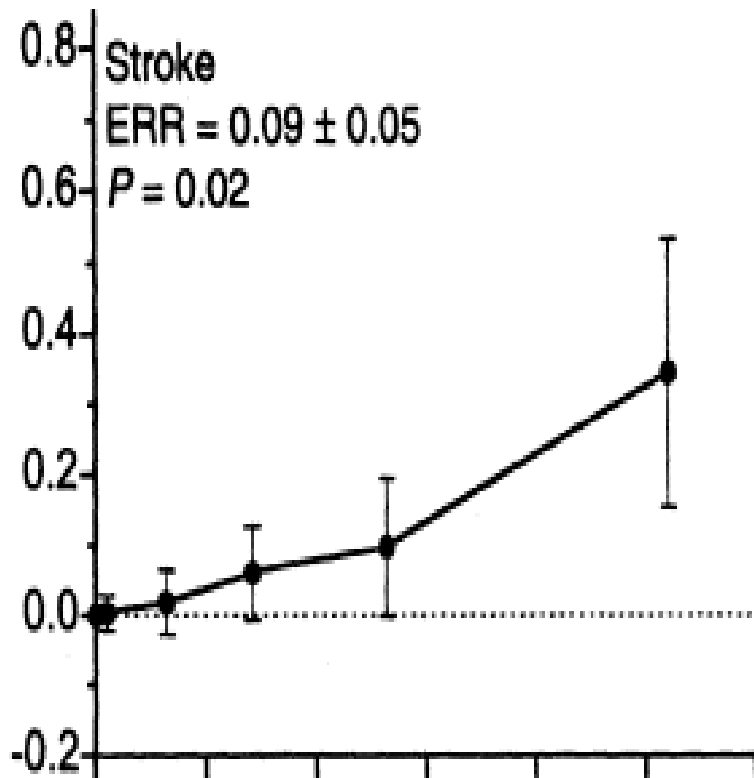(Shimizu *et al. Radiat Res* 1999; **152**: 374-89)

Possible Confounding

- Confounding is less likely to be an explanation for the statistical association when small areas are considered.

- Proximal survivors are those <3 km from the hypocentres (~60 000 survivors).

- Non-cancer mortality ERR/Sv is raised to a statistically significant extent for proximal survivors (and also for ~3000 survivors between 0.9 and 1.2 km from hypocentres).

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Circulatory Disease Mortality (1950-90)

(Shimizu *et al. Radiat Res* 1999; **152**: 374-89)

Variation of ERR in dose range 0-3 Sv

Potential Confounding Factors

(Shimizu *et al. Radiat Res* 1999; **152**: 374-89)

Noncancer Disease Radiation Risk Estimates with and without Adjustment for Potential Confounding Effects

Risk factor	Number with data available	Dose effect (ERR/Sv) Unadjusted	Dose effect (ERR/Sv) Adjusted
Highest education level	38,035	0.086	0.088
Occupation	36,766	0.098	0.097
Physical activity at work (1965 survey only)	7,364	0.088	0.097
House size per person (quartiles of tatami mats per person)	26,562	0.071	0.068
Current marital status	37,543	0.104	0.097
Current smoking status	38,975	0.083	0.079
Regular alcohol use (1978 survey only)	34,470	0.133	0.144
Percentage of Japanese food in diet (quartiles) (1965 survey only)	7,292	0.085	0.084

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Potential Confounding
(Shimizu *et al. Radiat Res* 1999; **152**: 374-89)

Taken together, the strong indications of a dose response even when analyses are limited to proximal survivors and the minimal impact of some potentially important confounding factors for which mail survey data are available suggest that the association between radiation and noncancer mortality in the LSS is unlikely to be an artifact of confounding.

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Non-cancer Mortality (1950-1997)

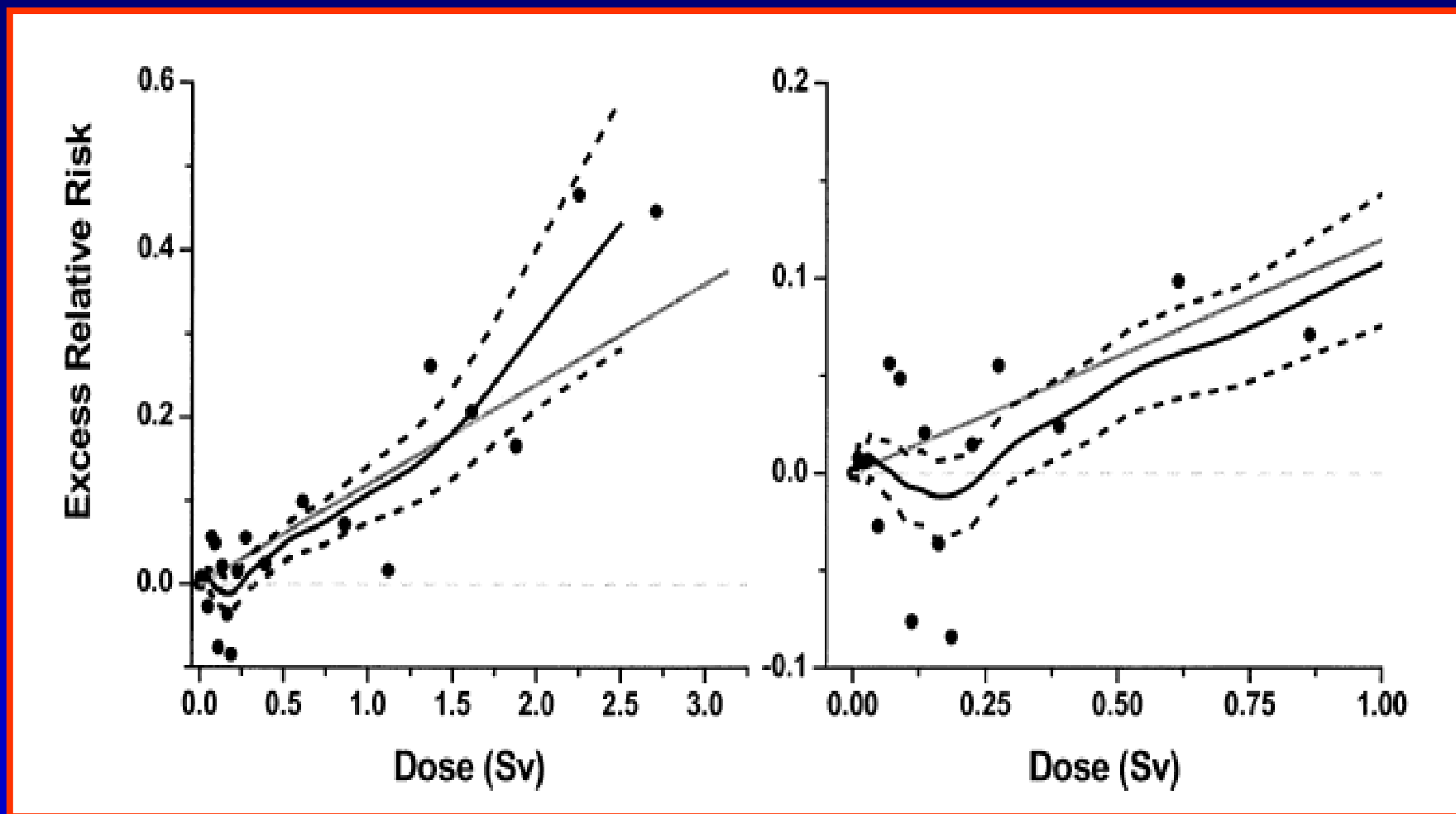(Preston *et al.*, *Radiat Res* 2003; **160**: 381-407)

Excess Relative Risk; proximal group and full cohort
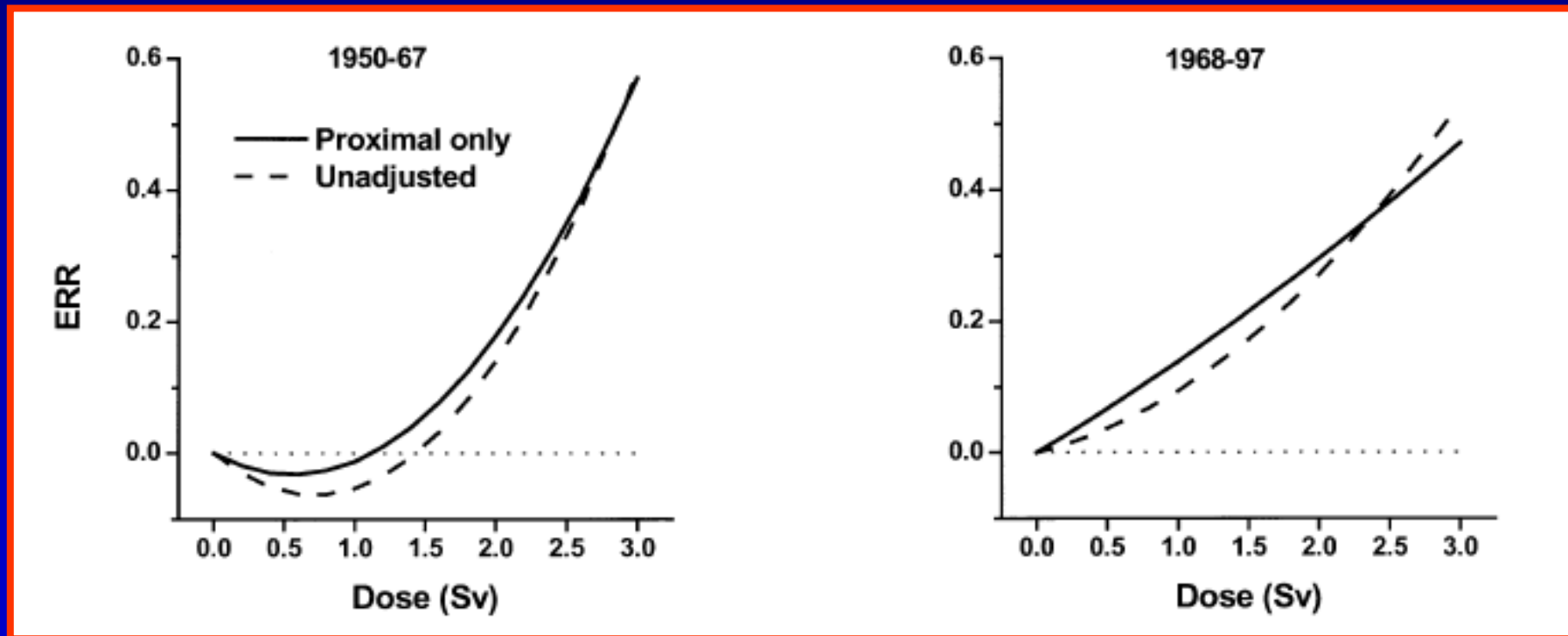
Non-cancer Mortality (1968-1997)

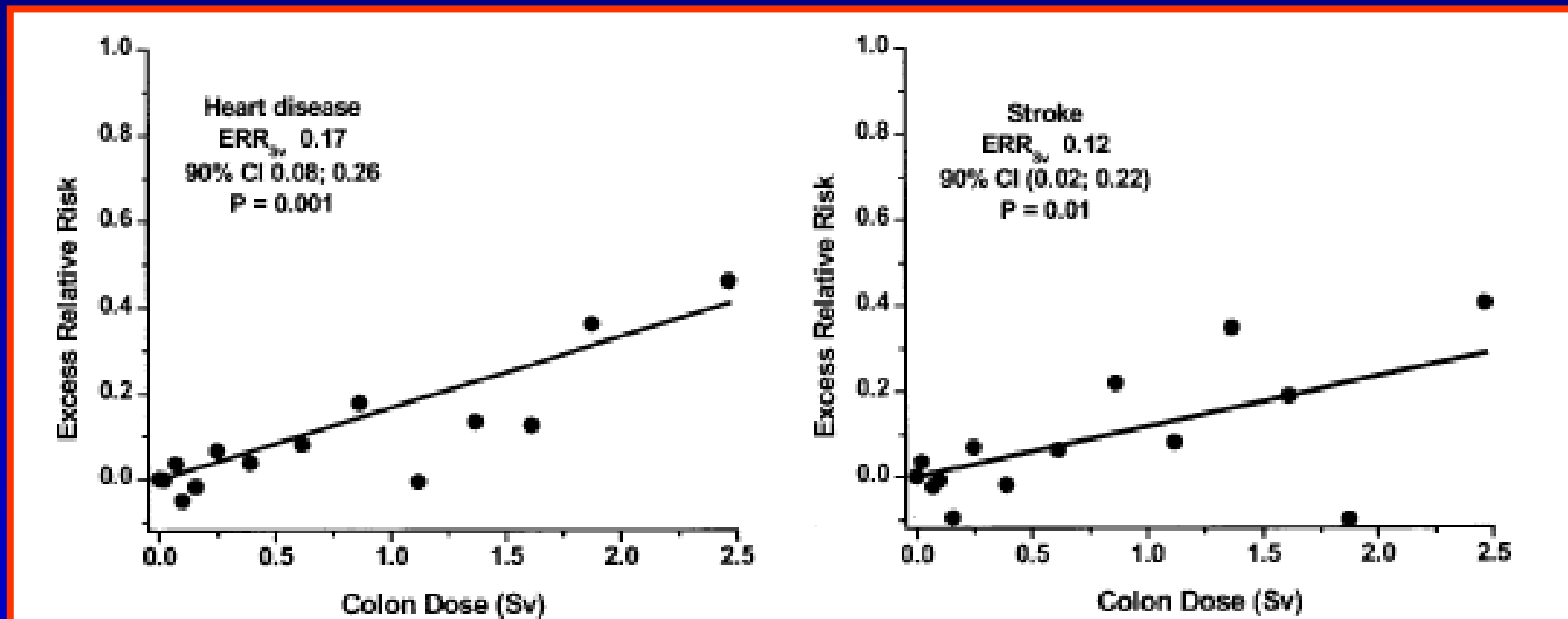(Preston *et al.*, *Radiat Res* 2003; **160**: 381-407)
linear fit and smoothed fit (±1SE)

Circulatory Disease Mortality (1968-97)

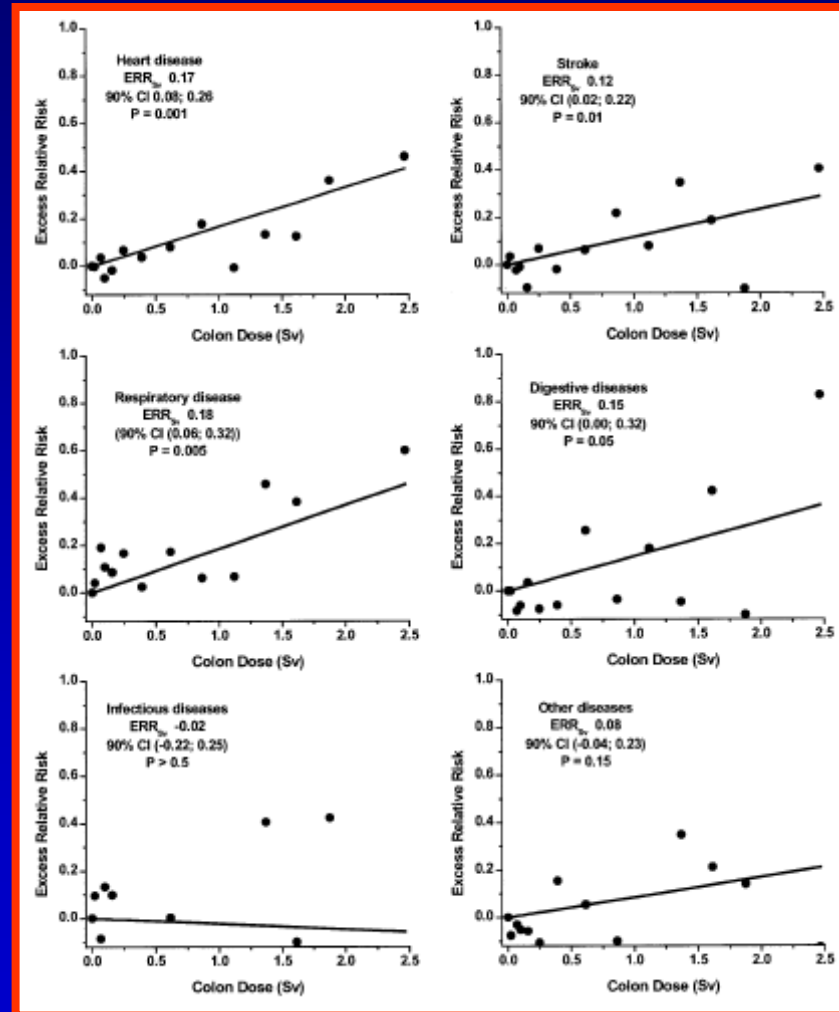(Preston *et al.*, *Radiat Res* 2003; **160**: 381-407)

Linear fits

Non-cancer Mortality (1968-1997)

(Preston *et al.*, *Radiat Res* 2003; **160**: 381-407)

Linear fits

Non-cancer Mortality (1968-1997)

(Preston *et al.*, *Radiat Res* 2003; **160**: 381-407)

Endpoint	ERR /Sv (90% CI)
Heart disease	0.17 (0.08, 0.26)
Stroke	0.12 (0.02, 0.22)
Respiratory disease	0.18 (0.06, 0.32
-Pneumonia	0.16 (0.00, 0.32)
Digestive disease	0.15 (0.00, 0.32)
-Cirrhosis	0.19 (-0.05, 0.50)
Infectious disease	-0.02 (<-0.2, 0.25)
-Tuberculosis	-0.01 (<-0.2, 0.4)
Other diseases	0.08 (-0.04, 0.23)
-Urinary diseases	0.25 (-0.01, 0.60)
All non-cancer	**0.14 (0.08, 0.20)**

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Non-cancer Mortality (1968-1997)

(Preston *et al. Radiat Res* 2003; **160**: 381-407)

Life-Span Study Cause-Specific Noncancer Disease ERR Estimates 1968–1997

Cause	ERR per Sv	Deaths[a]	Estimated number of radiation-associated deaths	
All noncancer diseases (0–139, 240–279, 290–799)	0.14 (0.08; 0.2)[b]	14,459	273	(176; 375)[b]
Heart disease (390–429)	0.17 (0.08; 0.26)	4,477	101	(47; 161)
Stroke (430–438)	0.12 (0.02; 0.22)	3,954	64	(14; 118)

[a] Deaths among proximal survivors between 1968 and 1997.
[b] 90% confidence interval.
[c] Excluding diseases of the blood and blood-forming organs.

- The 273 radiation-associated non-cancer disease deaths (of which 165 are due to heart disease and stroke) compare with 421 cancer deaths attributable to radiation exposure.

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Circulatory Disease Incidence (1958-98)

(Yamada *et al. Radiat Res* 2004; **161**: 622-32)

Statistically significant <u>quadratic</u> dose-responses

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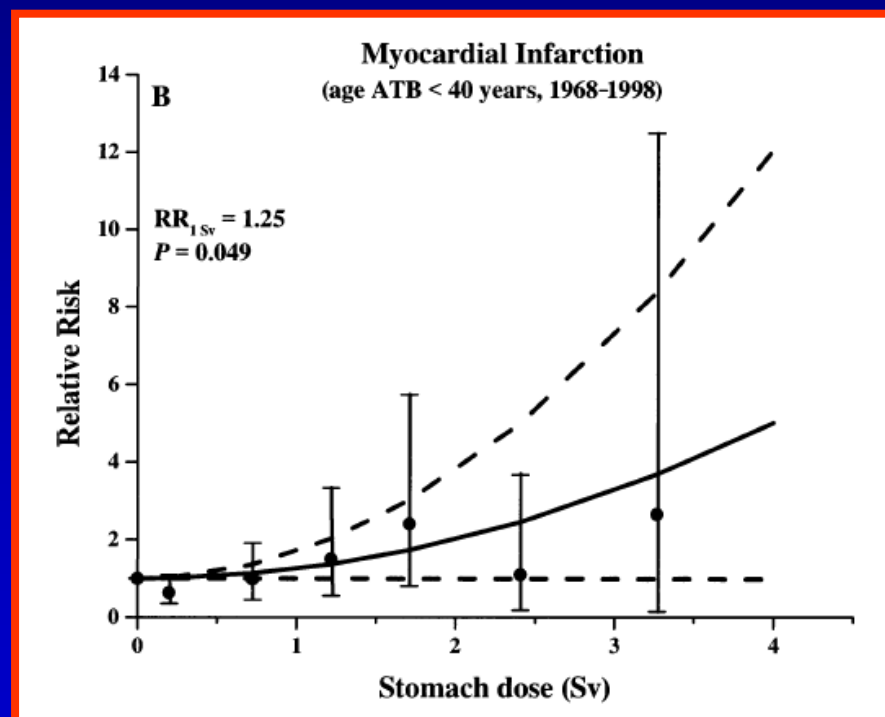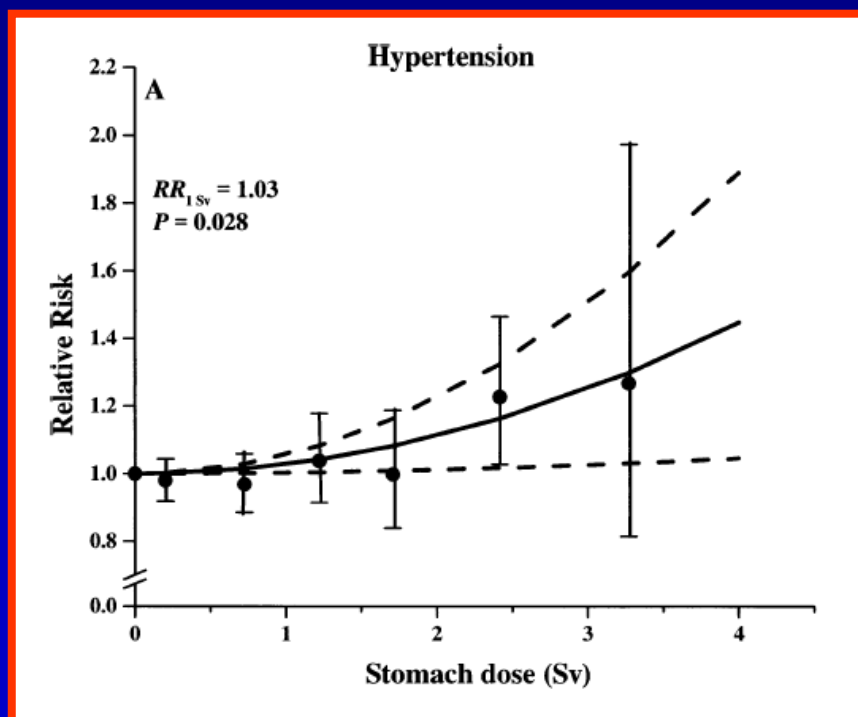
Potential Confounding

(Yamada *et al. Radiat Res* 2004; **161**: 622-32)

Disease (quadratic dose-response)	RR at 1 Sv (95% CI) No adjustment for smoking and drinking	RR at 1 Sv (95% CI) Adjusted for smoking and drinking
Hypertension (incidence, 1958-98)	1.03 (1.00, 1.06)	1.03 (1.01, 1.06)
Myocardial infarction (<40 year of age ATB) (incidence, 1968-98)	1.25 (1.00, 1.69)	1.17 (0.97, 1. 56)

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Circulatory Disease Risk Factors

- Adult Health Study clinical studies show radiation-associated effects on some circulatory disease risk factors (such as blood pressure and cholesterol levels) that could be indicative of underlying biological mechanisms relating to the statistical association between circulatory disease and radiation dose.

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Circulatory Disease

(Preston *et al. Radiat Res* 2003; **160**: 381-407
Yamada *et al. Radiat Res* 2004; **161**: 622-32)

Endpoint (LSS: mortality; AHS: morbidity)	ERR/Sv (LSS: 90% CI; AHS: 95% CI)
LSS heart disease	0.17 (0.08, 0.26)
LSS stroke	0.12 (0.02, 0.22)
AHS hypertension	0.05 (-0.01, 0.10)
AHS hypertensive heart disease	0.01 (-0.09, 0.09)
AHS ischemic heart disease	0.05 (-0.05, 0.16)
AHS myocardial infarction	0.12 (-0.16, 0.60)
AHS stroke	0.07 (-0.08, 0.24)

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Circulatory Disease Dose-response

(Little *Radiat Environ Biophys* 2004; **43**: 67-75)

Linear threshold: ERR = $\alpha \, (D - D_t)_+$
Linear-quadratic threshold: ERR = $\alpha \, (D - D_t)_+ + \beta \, (D - D_t)_+^2$
Power of dose: ERR = $\alpha \, D^k$

Mortality Endpoint; dose-response model	Dose threshold (Sv) (95% CI)	Power of dose (95% CI)
Heart disease; linear threshold	0.14 (<0, 1.08)	–
Heart disease; linear-quadratic threshold	0.15 (<0, 1.22)	–
Heart disease; power of dose	–	1.12 (0.17, 3.34)
Stroke; linear threshold	0.30 (<0, 3.11)	–
Stroke; linear-quadratic threshold	0.45 (<0, >5.00)	–
Stroke; power of dose	–	1.54 (0.02, >10.00)

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Exposure *In Utero*

(Tatsukawa *et al. Radiat Res* 2008; **170**: 269-74)

- AHS used to investigate circulatory disease incidence during 1978- 2003 among ~500 survivors exposed *in utero* in comparison with incidence among ~1000 survivors exposed as children.

- No significant effects among *in utero* exposed, but significant effects for hypertension and cardiovascular disease among childhood exposed.

- *In utero* exposed still aged <60 years.

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Circulatory Disease Mortality
(Work in progress − D L Preston)

- LSS follow-up extended to 1950-2003.

- ~19 000 circulatory disease deaths.

- Significant dose-response for cardiovascular and cerebrovascular mortality.

- ERR/Sv estimates similar to previous analyses.

- Suggestion of heterogeneity within cardiovascular diseases

  – risk of ischemic heart disease could be lower.

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A-bomb Survivors − Summary

- Increased risks of circulatory diseases are apparent below doses of 2 Gy.

- Represents a significant proportion of radiation-associated mortality.

- Data consistent with a linear no-threshold dose-response relationship, *but*

- Data also consistent with a threshold dose of around 0.5 Gy.

- Cannot yet reliably eliminate bias and confounding as possible explanations.