Radiation Effects on Circulatory Diseases
Scientific Understandings and Uncertainties

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Topics

- Epidemiological evidence
  - Radiotherapy patients (High dose 5+ Gy)
  - Atomic bomb survivors
  - Other low dose populations
- Mechanisms
- Implications for radiation protection

Circulatory disease

- Cardiovascular disease (heart disease)
  - Ischaemic (coronary) heart disease (mainly MI)
  - Hypertensive heart disease
  - Valvular heart disease
- Cerebrovascular disease (stroke)
- Peripheral vascular disease

High-Dose Cancer Radiotherapy Patients

- Radiation-induced heart disease (primarily MI)
  - Hodgkin's lymphoma patients
  - Childhood cancer survivors
  - Breast cancer patients
  - Testicular cancer patients
- Thought to be high dose tissue reaction (deterministic) effect

A-Bomb Survivor Studies

- Mounting evidence of increased risks for non-cancer diseases at lower doses (< 2 Gy)
- Prompting increased interest in possibility of effects at doses relevant for radiation protection
  - UNSCEAR 2006
  - McGale & Darby 2005
  - Little et al 2008

A-Bomb Survivor Studies History

- Suggestions of elevated circulatory disease risks
  - Life Span Study (LSS) mortality 1950-70 (Jablon et al, 1971)
    - Only in women
  - Adult Health Study (AHS) morbidity 1958-78 (Robertson et al, 1974, Kodama et al 1984)
    - Stroke and heart disease Hiroshima females only
  - LSS Report 11 1950-85 mortality (Shimizu et al, 1992)
    - Heart disease in men and women

A-Bomb Survivor Studies
Initial Concerns

- Effects initially limited to specific subgroups
  - Over time effect has become apparent in men and women in both cities
- Death certificate misclassification
- Confounding by non-radiation factors
  - Are radiation risk estimates affected by smoking, economic status, or other factors
- Selection effects
  - Does the fact of survival affect inference about dose response

A-bomb Survivors
Death Certificate Misclassification

- 22% cancer-to-noncancer misclassification in autopsy data
- Statistical adjustment
  - Reduced non-cancer disease excess relative risk (ERR) by 20% (ERR per Gy 0.06 → 0.05)
  - Increased solid cancer ERR estimate by 13% (ERR per Gy 0.85 → 0.96)
  - Non-cancer risk remains highly significant (P = 0.006)

Sposto et al 1992

Atomic Bomb Survivors
Effect of Confounding

People		Deaths	Non-cancer ERR/Gy	
			Undajusted	Adjusted
Men	10,308	1,163	0.07	0.09
Women	13,154	1,121	0.14	0.14

Adjustment based on mail survey responses did not appreciably change non-cancer risk estimates

Potential Confounders

- Smoking
- Education
- Occupation
- Marital status
- House size
- Japanese diet
- Physical activity

LSS Report 12 Shimizu et al 1999

LSS Noncancer Mortality 1950-90 Unmeasurable Confounders

- Confounding less likely when analyses limited to survivors in smaller areas
- Significant dose response seen for
  - 60,000 survivors within 3 km of hypocenter
  - 2,900 survivors between 0.9 and 1.2 km from hypocenter

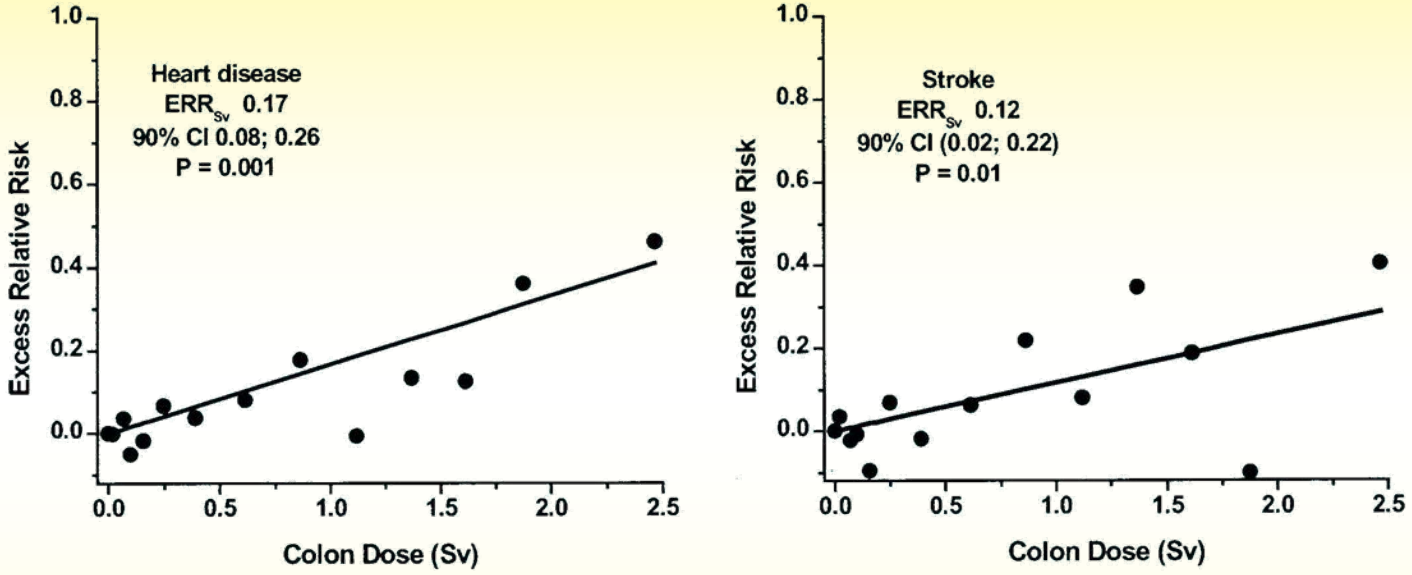
A-Bomb Survivors
Noncancer Mortality 1968-1997

Dose (Gy)	Noncancer disease deaths		Excess
	Observed	Expected	
<0.005	13,832	13,954	0
0.005-0.1	11,633	11,442	17
0.1-0.2	2,163	2,235	17
0.2-0.5	2,423	2,347	47
0.5-1	1,161	1,075	61
1-2	506	467	68
2+	163	111	40
Total	31,881	31,631	250

- > 50% of the noncancer disease deaths are circulatory disease deaths
- Solid cancer 7,578 deaths 334 excess
- Leukemia: 249 deaths 87 excess

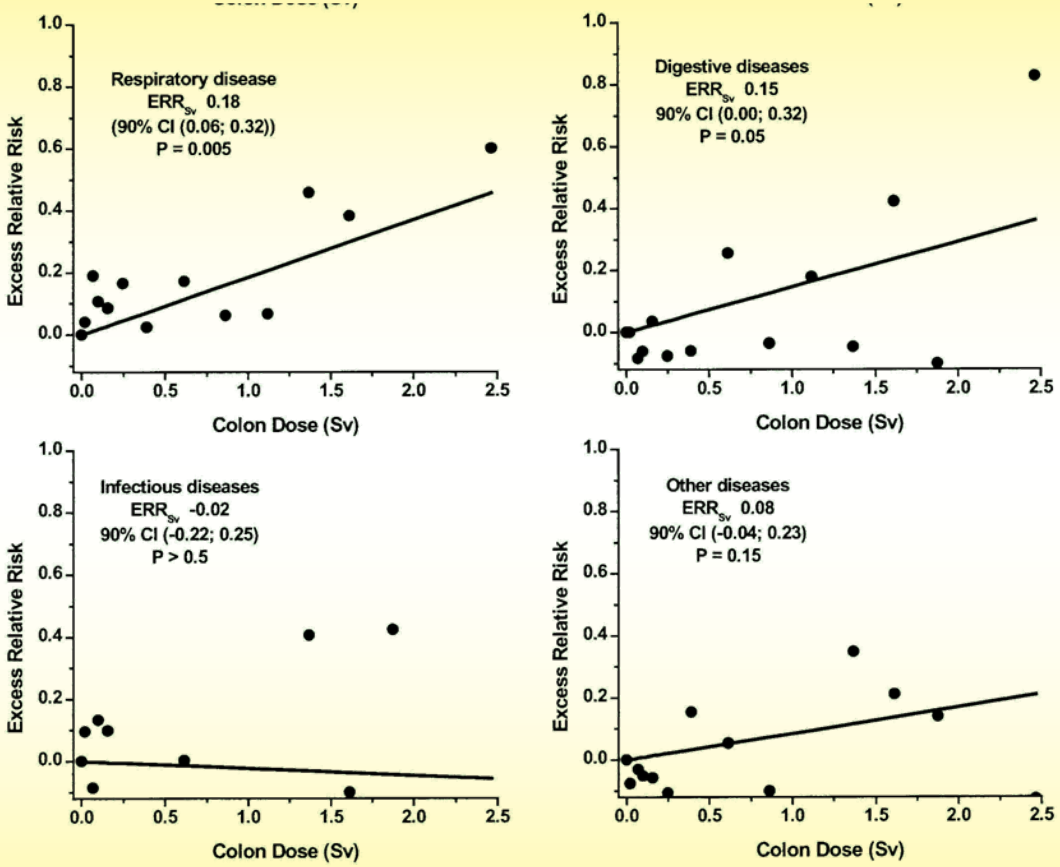
Preston et al 2003

A-Bomb Survivors
Circulatory Disease Mortality 1968-1997



- Significant effect for both heart disease and stroke
- No indication of non-linearity in dose response
- Narrowest dose range with significant effect is 0 to 0.5/1 Gy

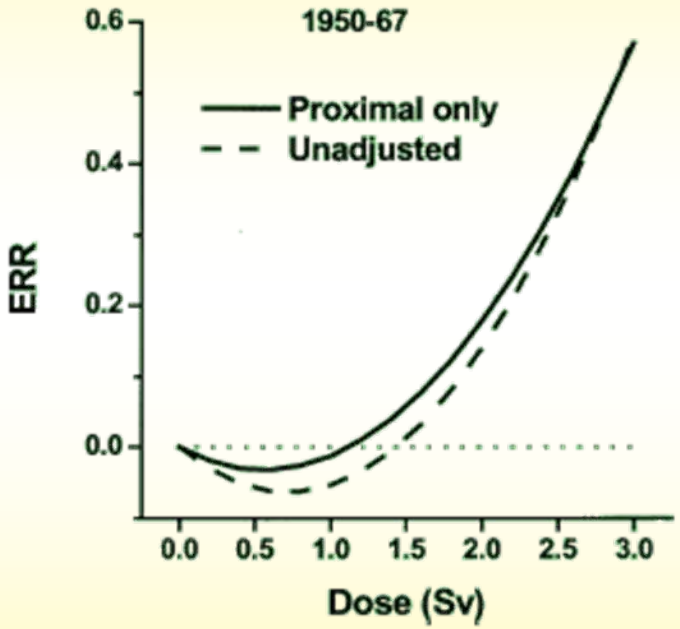
A-Bomb Survivors
Other Noncancer diseases 1968-1997



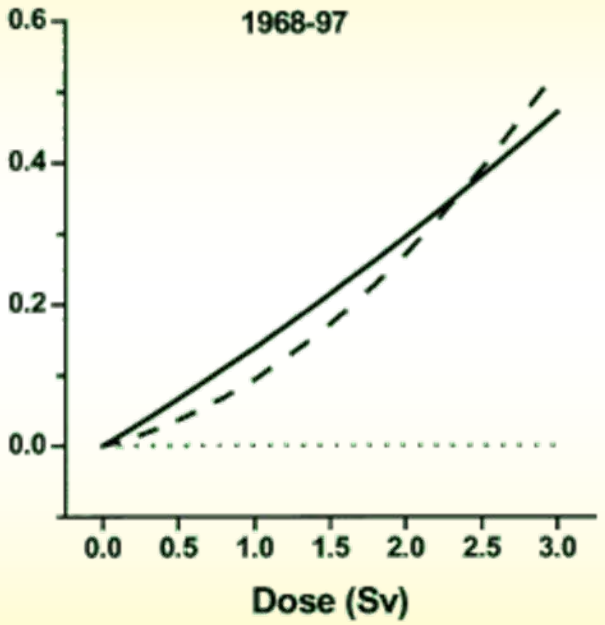
- Significant effects seen for digestive and respiratory disease but not for the infectious or other disease groups

A-bomb Survivors
Healthy Survivor Selection Effects

Early follow-up period

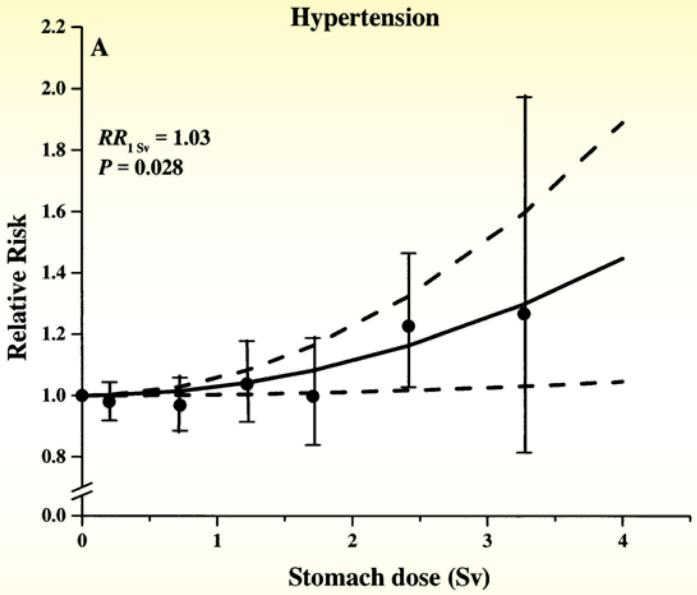


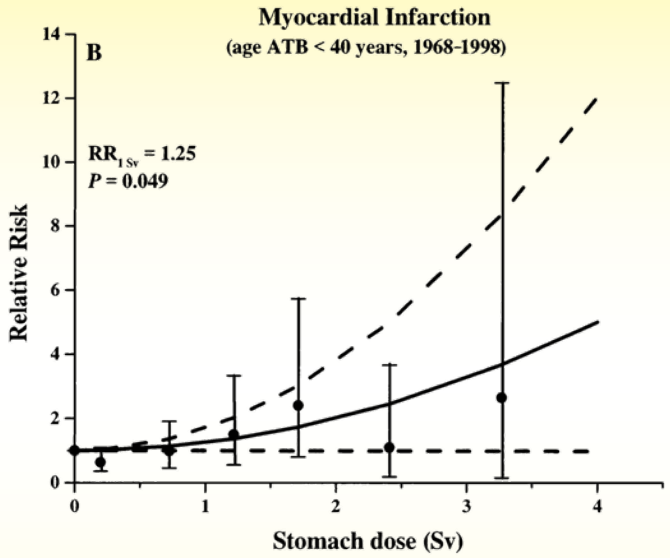
Late follow-up period



- Baseline rates ~15% lower for proximal (< 3 km) survivors in 1950
- Difference decline over time and is less than 2% by late 1960's
- Early period curvature likely to reflect selection effects

AHS Heart Disease Incidence 1958-1998





- 5,035 cases among 10,339 participants
- Significant quadratic dose response

- 117 cases
- Significant quadratic dose response

AHS Clinical Studies
Subclinical changes

Radiation effects on various circulatory disease risk factors

- Changes in age trends for serum cholesterol and blood pressure
- Increased prevalence of isolated systolic hypertension, aortic arch calcification, pulse wave veolcity
- Increased inflammatory response markers elevated C-reactive protein levels

LSS Circulatory Disease Risks
Updated analyses

- Follow-up 1950-2003 (6 additional years
- 19,000 circulatory disease deaths
  - 51% stroke, 45% heart disease
- Significant dose response for heart disease and stroke
- ERR estimates similar to earlier analyses
- Suggestion risk heterogeneity for heart disease subtypes
  - Possibly lower for ischemic heart disease than other types

Shimizu, Kodama et al in progress to appear 2008/9

LSS Circulatory Disease Risks

- Radiation doses below 2 Gy are associated with increased heart disease risks
  - Contribute a significant proportion of radiation-associated mortality
- Cannot rule out linearity, but
- No clear indication of risks below about 0.5 Gy

Other “Low” Dose Studies

- About 45 potentially useful cohorts (<4-5 Gy)
  - Cancer radiotherapy (4)
  - Non-cancer radiotherapy (14)
  - Diagnostic radiation (3)
  - Occupational exposure (24)
- 29 report circulatory disease results

Circulatory Disease Analyses

- Some dose response analysis (16 studies)
  - 8 with significant radiation effects (6 from occupational studies)
  - 8 with no significant effects (6 from occupational studies)
- Internal comparisons (6 studies)
  - 2 with significant effects
  - 4 with no significant effects
- External comparison (SMRs, O/E ratios) (5 studies)
  - One with significantly elevated SMR
  - 4 with no significant differences
- Not presented (18 studies)

Ankylosing Spondylitis Patients

- 1,400 with a single course of x-ray therapy
- 2.5 Gy mean cardiac dose; 0.04-4.75 (10-90% range)
- Cerebrovascular disease O/E = 1.14
- Other circulatory disease O/E = 1.25
- Relative risk (compared to a separate un-irradiated spondylitic cohort) = 0.66 for stroke, 0.97 for other circulatory disease

Darby, 1987; McGale 2005

Benign gynecological disease patients

1930-40s, uterus and ovaries irradiated for abnormal bleeding

Scottish metropathia hemorrhagica (Smith, 1976) (n= 2,068)

Bone marrow dose, Gy	Coronary heart O/E
<1.25	0.70
1.25-1.49	1.27
≥1.5	1.17
Trend	Borderline significance

New England BGD patients (Inskip, 1989) (n = 4,483)

Bone marrow dose, Gy	Circulatory O/E
0.01-	0.8
0.26-	1.0
0.51-	1.0
≥0.76	1.0
Unknown	1.1

Cautions: underlying hyper-estrogenic status; cell-killing effects of RT on ovaries

Other Medically Irradiated Cohorts

- Massachusetts TB fluoroscopy (repeated exams)
  - 3,351 patients; mean lung dose = 0.91 Gy
  - Circulatory disease SMR
    - 1.0 (exposed women), 1.0 (exposed men)
    - 1.1 (unexposed women), 1.1 (unexposed men)
  - No dose response analysis
- Scoliosis patients (repeated radiographic exams)
  - 5,573 women; mean lung dose = 0.41 Gy
  - Significant dose response

Peptic Ulcer Disease

Weighted cardiac dose, Gy	In-field* dose, Gy	Coronary heart disease RR
0	0	1.00
0.1 – 1.9	0.86 – 9.1	1.00
2.0 – 2.5	9.2 – 11.7	1.23
2.6 – 3.0	12.0 – 13.9	1.54
3.1 – 7.6	14.4 – 35.6	1.51

- 1,859 patients irradiated between 1940 and 1960's
- Significant trend with dose

* 5% of heart in the radiation field

Carr, 2005

Nuclear Worker Studies

- IARC 15-country study (Vrijheid 2007)
  - 275,000 workers, ~8 years follow-up per person
    average dose 21mSv
  - No significant effects but risk estimates consistent with LSS
- UK NRRW (Muirhead, 1999)
  - 125,000 workers
  - No significant trend
- Chernobyl liquidators (Ivanov, 2006)
  - 61,000 workers
  - Large ERR estimates, but concerns about biases
- No consistent patterns across numerous studies

Radiologists and X-Ray Techs

- UK radiologists (Berrington, 2001)
  - SMR comparisons to general population or other type of practitioners provide no indication of increased risk
  - No dose information
- US radiologists (Matanoski, 1984)
  - SMR comparisons to other physician specialists suggest higher cardiovascular disease rates especially later in life
  - No dose information
- US X-ray Techs (Hauptman, 2003)
  - Higher SMR's for earlier (higher dose) subcohort
  - No dose estimates (yet)

Current State of Knowledge

- A-bomb survivor evidence compelling for moderate doses (e.g. 0.5 – 2 Gy), unclear at lower doses
- No consistent indications from other studies
- Unconsidered in many populations
- Follow-up often limited
- Power often low
- Mechanisms uncertain
  - A-bomb survivor results increased interest

Mechanisms?

- Inflammaotry/Microvasculature theory
  - Possible signature changes in microvasculature, e.g., fibrosis
  - Endothelial injury / dysfunction and inflammatory response
    - Possible long-term radiation effects on immune system
- Mutation theory
  - Monoclonal origin of atherosclerotic plaques (G6PD)
    - Transformation of smooth muscle cells in atherogenesis pathway?
  - Oncogene activation, LOH, and microsatellite instability

What Next?
Epidemiology

- Can expect updated / new results
  - A-bomb survivors
    - More information on younger survivors, temporal patterns etc.
    - Type-specific risk estimates
  - New and updated worker studies (Sellafield, Mayak., …)
  - Dose response analyses in US XRT cohort
- None of these are likely to provide definitive answers, but should help to reduce uncertainties

What Next?
Radiation Protection

- Increasing attention to potential risks
  (e.g. UNSCEAR, 2008, Little 2008, Schultz-Hector, 2007)
- Uncertainty inhibits direct impact on guidelines now
- Increased pressure for consideration is likely
  - Difficult to incorporate in current framework
  - Need better ways to allow for uncertainties about risk and incorporate them into risk assessment

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