

Diseases Other Than Cancer in A-bomb Survivors and Their Children

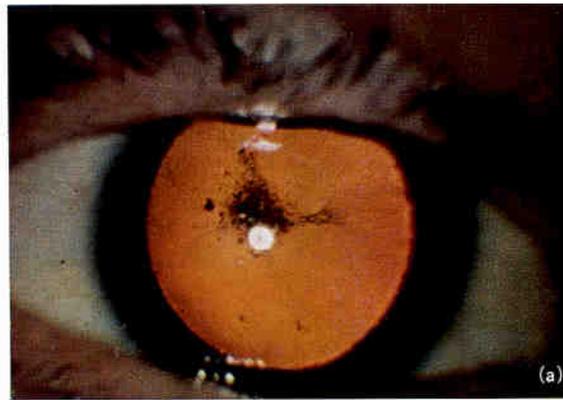
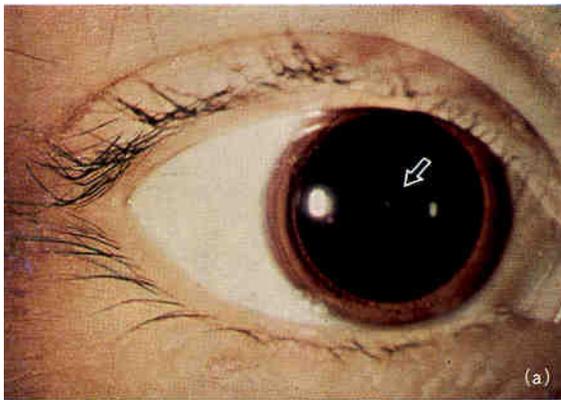
Kiyohiko Mabuchi
Radiation Epidemiology Branch, NCI
For Radiation Epidemiology Course
May 4-14, 2004

Non-cancer Diseases

- Early deterministic effects
 - Acute radiation syndrome
 - Cataract
- Mental retardation and growth impairment
 - In-utero exposure
- LSS Non-cancer Disease Risk
 - Cardiovascular disease
- Genetic effects (F1)
 - Birth defects, and other pregnancy outcomes

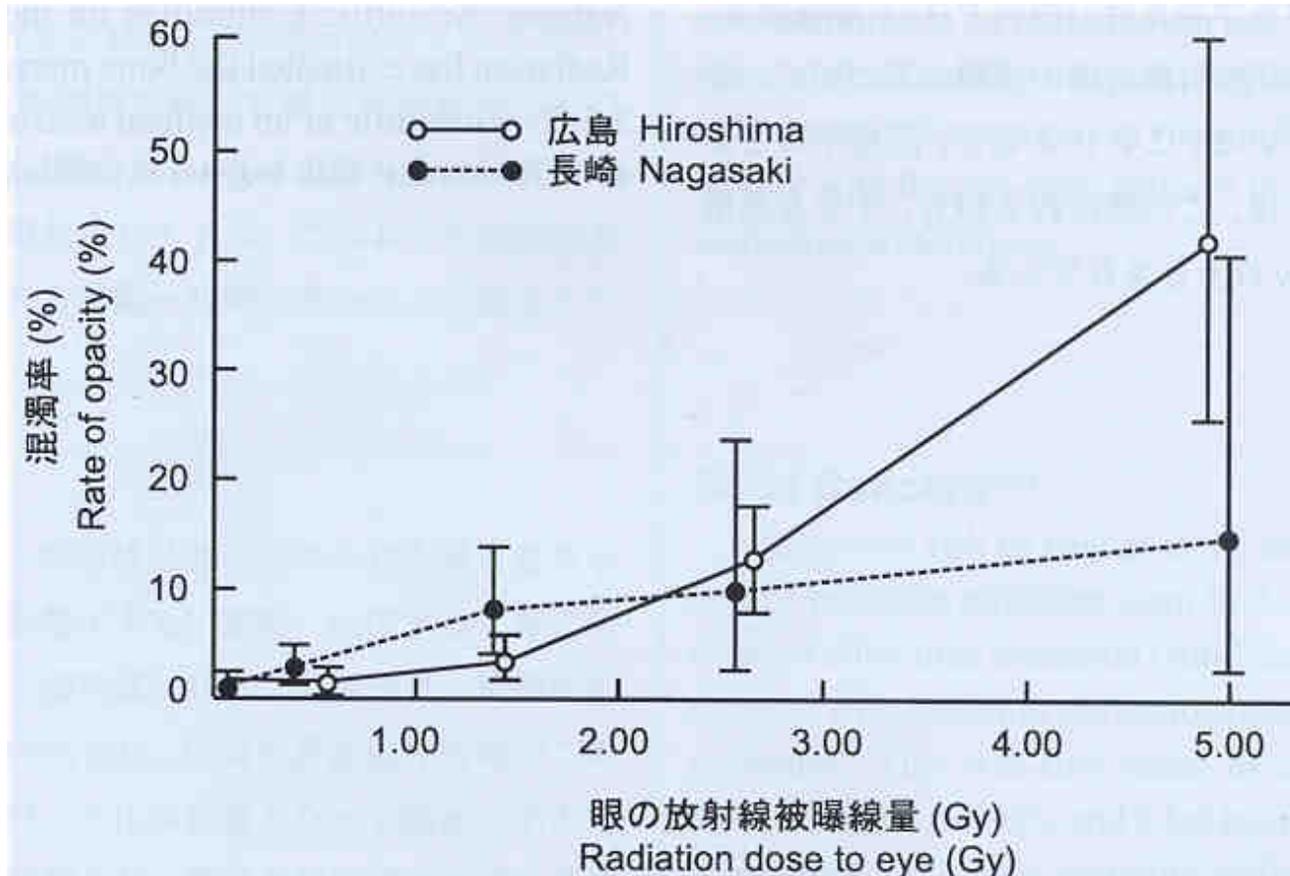
Cataract

Radiation cataract - lens opacity



- 2-3 years after exposure
- Partial opacity/cloudiness
- Most frequently posterior lenticular opacity
- Recent evidence on cortical opacity
- Rarely severe visual impairment

Cataract Dose Response



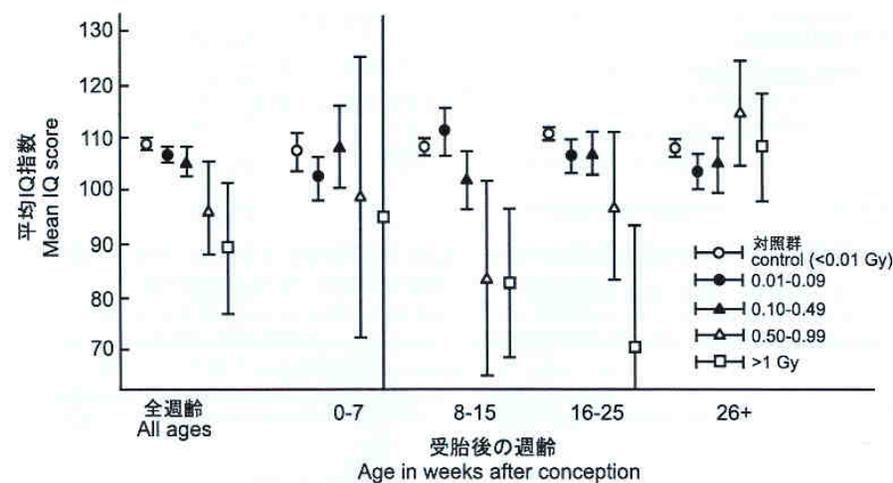
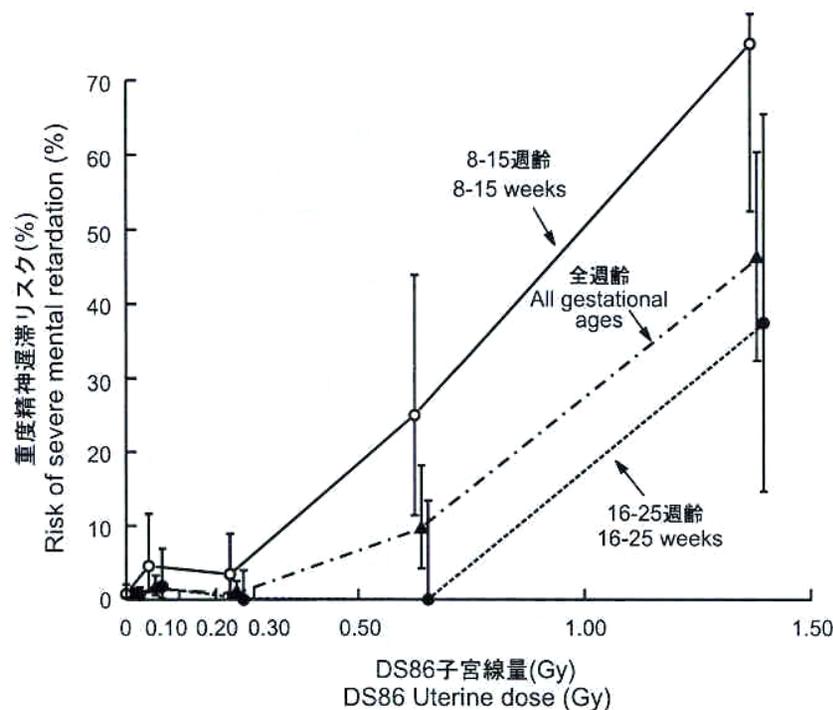
ICRP: Threshold for opacities causing visual impairment = 2-10 Gy for single low LET exposure

Mental Retardation and IQ

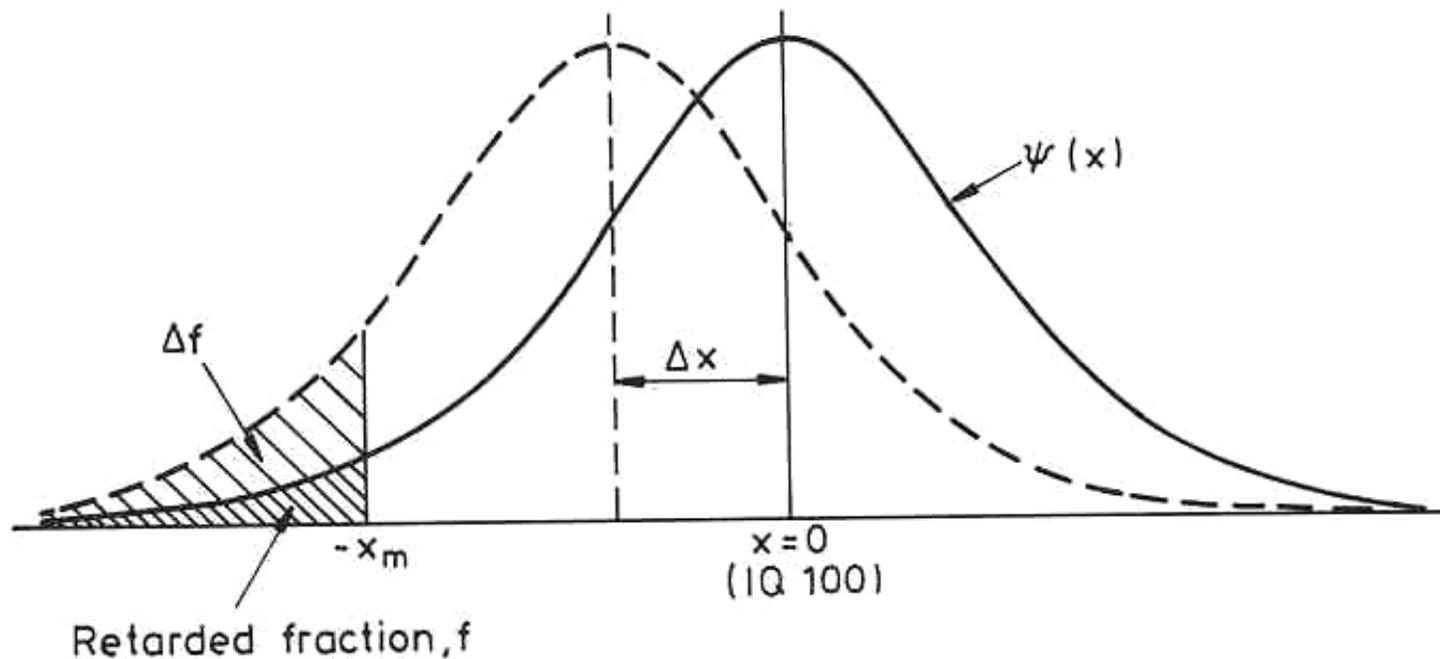
Mental retardation and IQ

In-utero exposure

- Sever mental retardation in 21 of 476 in-utero survivors >0.005 Gy
 - 8-15 weeks of gestation at exposure
- Dose-related decreases
 - school performance
 - IQ scores



IQ curve and retardation - ICRP model



Shift of IQ by 30 points per Sv

Non-cancer Disease in LSS

Noncancer Diseases in LSS

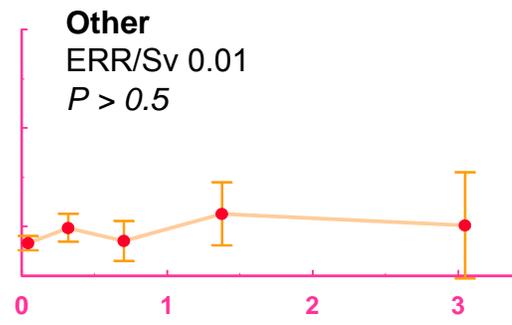
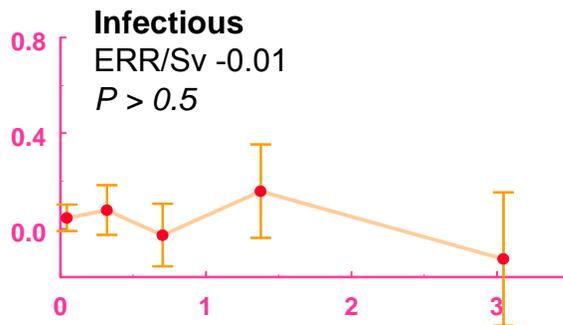
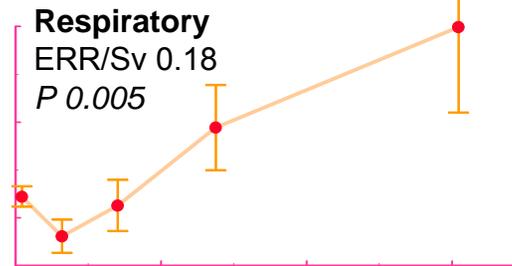
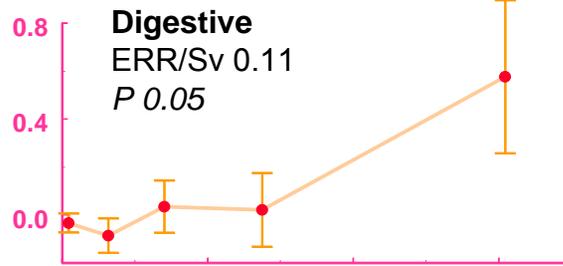
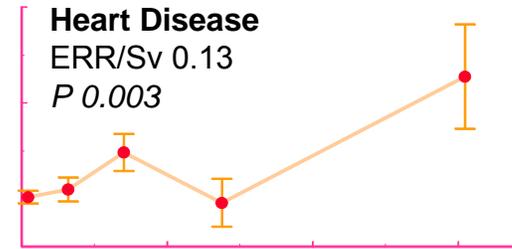
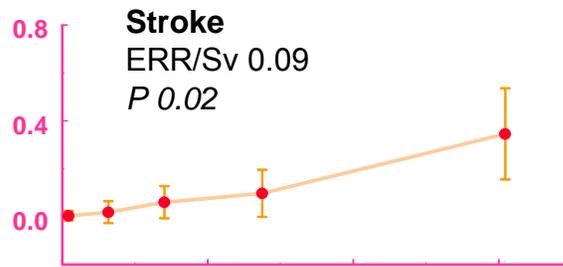
Category	No of deaths	%
Stroke	7,859	29%
Heart disease	6,826	25%
Respiratory disease	3,163	12%
Digestive disease	1,723	6%
Infectious disease	4,804	18%
Total	27,117	100%

Non-cancer Mortality 1950-97

Dose, Sv	Obs	Expected	Excess
<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

(LSS Report 13, Preston et al, 2003)

ERR



Dose (Sv)

ERR: Excess Relative Risk per Sv

Reasons for Skepticism

- Small excess relative risk (ERR) compared to cancer
 - About 10% vs. 40%
- The apparent effect seen for many disease categories
- Lack of plausible biological models

Questions

- Are the apparent radiation effects due to bias or confounding?
 - Selection effects
 - Cancer-noncancer misclassification
 - Confounding effects
- Shape of the dose response, especially at a low dose

Cohort selection

- Possible dose-related cohort selection by survival of acute effects - “healthy survivor effect”
- This effect would lower death rates but not explain dose-related *increase* in noncancer mortality - opposite of the healthy survivor effect

Causes of death misclassification

- Probability of cancer to noncancer misclassification = 22%
 - DC- autopsy comparisons
- After adjustment for this misclassification
 - Dose response remains highly significant
 - Noncancer ERR down by 20%
 - Cancer ERR up by 10-15%

	No correction	Corrected for 22% misclass.
Non-cancer % change in ERR	-	-21%
Non-cancer excess deaths	129	98
Cancer % change in ERR	-	+13%
Cancer excess deaths	354	396

Effects of Possible Confounders

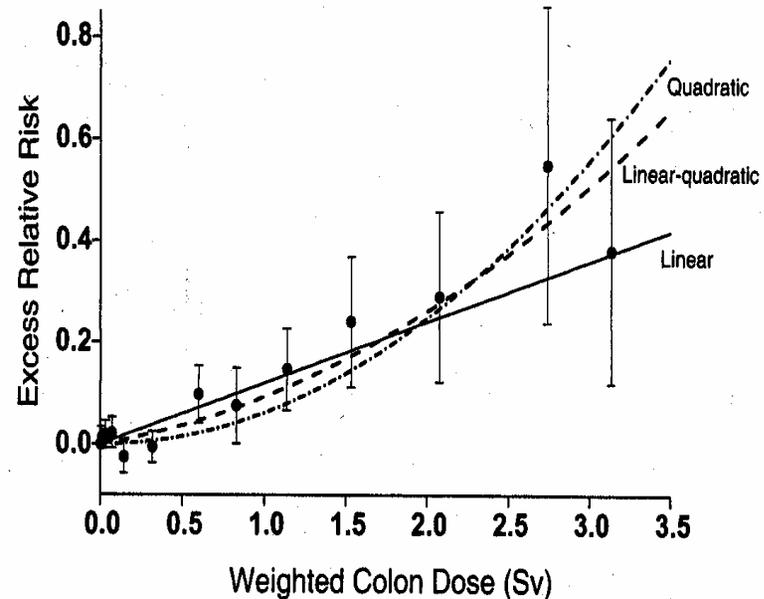
Subjects	Deaths	Noncancer ERR/Sv	
		No adjustment	Adjustment
10,308 men	1,163	0.07	0.09
13,154 women	1,121	0.14	0.14

Adjusted for

- education
- occupation
- marital status
- smoking
- house size
- Japanese-style food
- physical activity

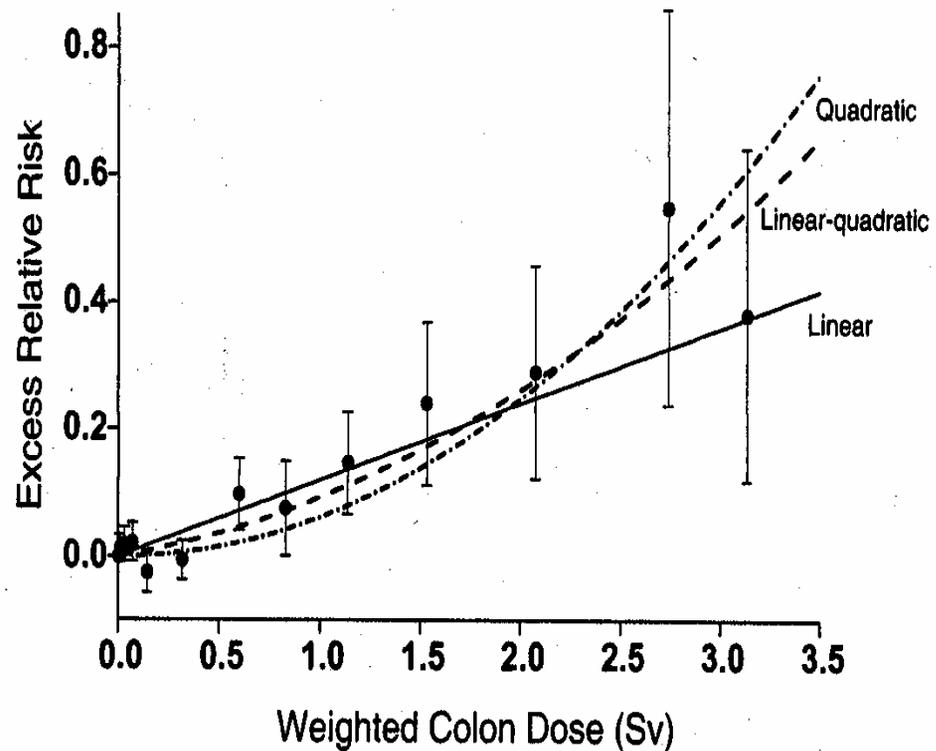
Evidence for Causality

- Clear dose response trend
- Significant dose response among survivors exposed between 900-1,200 meters from the hypocenter
 - ERR/Sv = 0.25
 - Dose: 0.35 - 5.84 Sv, mid point 1.10 Sv

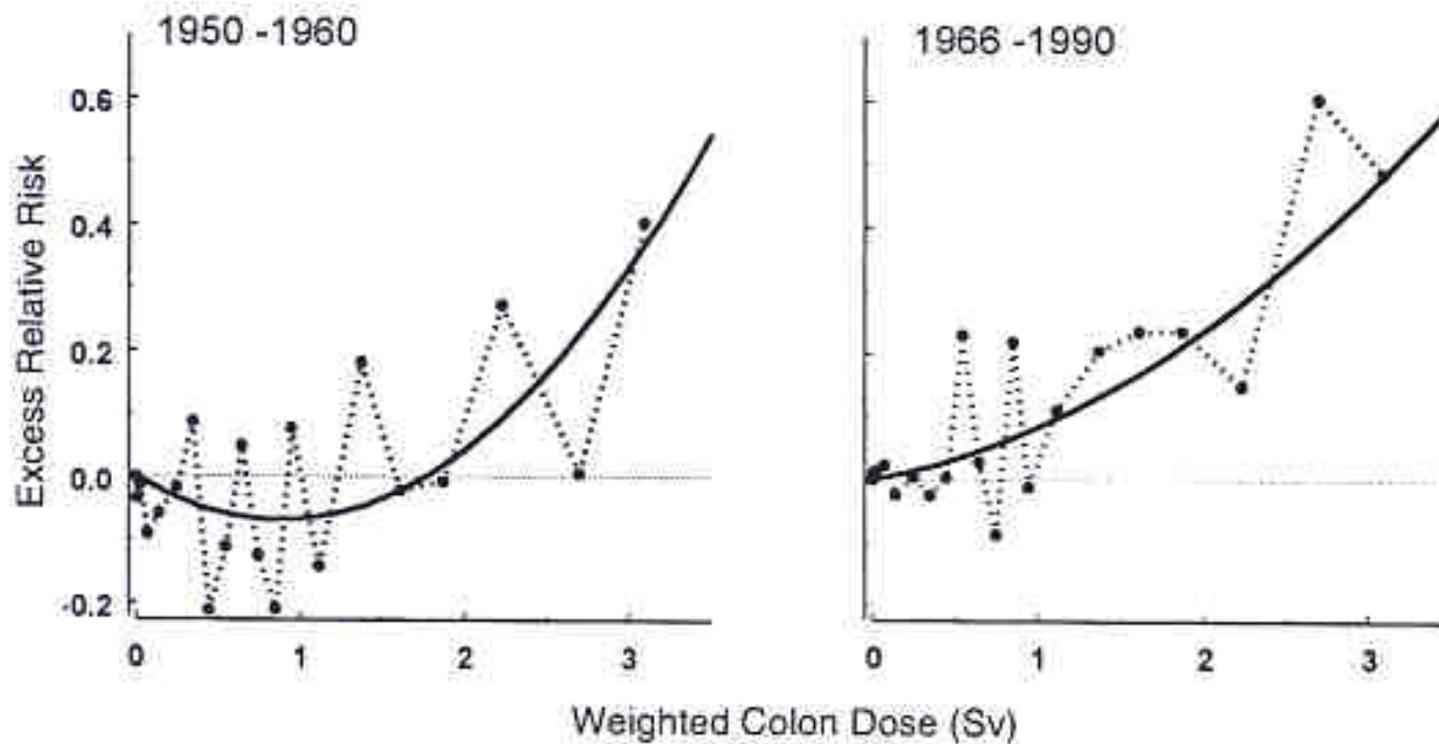


Shape of Dose-Response Curve

- Linear, linear-quadratic, pure quadratic and threshold at 0.3 Gy give comparable fits
- But little clarification of risk below about 0.5 Sv



Non-cancer Dose Response



Magnitude of Risk

	1950-1997		1991-1997	
	Deaths	Excess	Deaths	Excess
Cancer	9,335	440	1,756	114
Non-cancer	31,881	250	4,760	66

Cardiovascular Disease in Other Irradiated Populations

- Clear evidence of high-dose irradiation (i.e., >30 Gy) on heart disease, including coronary heart disease
 - Hodgkin lymphoma, breast cancer patients
- Some corroborating epidemiological data from medical and occupational studies
 - Ankylosing spondylitis and peptic ulcer patients, but not TB fluoroscopy patients
 - US radiologists and radiologic technologists, but not UK radiologists

Cardiovascular Disease Risk

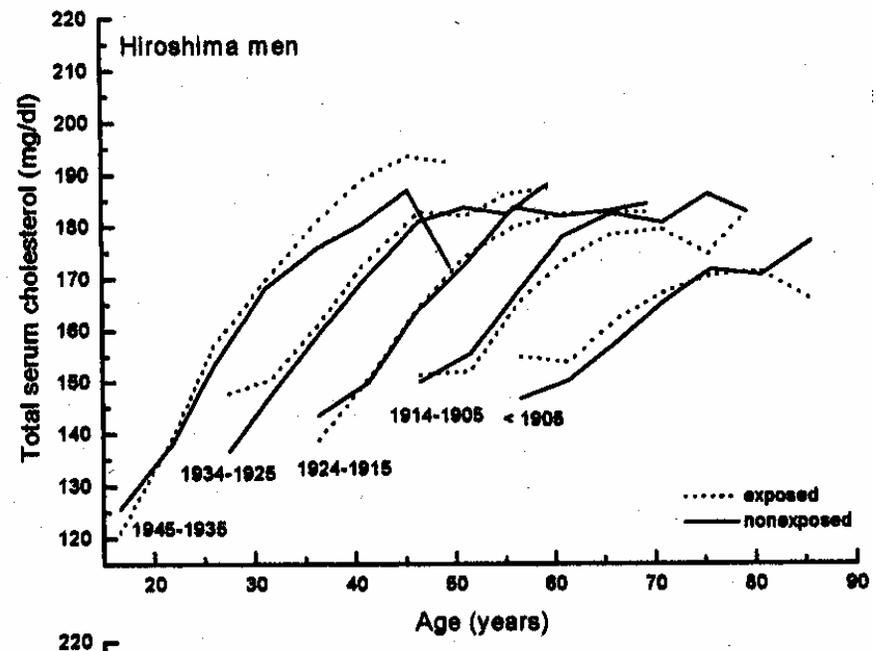
Dose	Populations	Findings
30-50 Gy High	Radiotherapy for cancer: Hodgkin's disease, breast cancer	<ul style="list-style-type: none"> • Excess myocardial infarction mortality • Dose response • Possible age / time effect
<10 Gy Moderate	Radiotherapy for benign diseases: Ankylosing spondylitis (2.5 Gy, 0-5 Gy) Peptic ulcer disease (2.2 Sv, 0.2-6 Gy) Metropathia haemorrhagica (1.3 Gy, 0-2 Gy) Mass TB fluoroscopy (0.9 G, 0-9 Gy)	<ul style="list-style-type: none"> • Excess heart disease mortality based on SMRs, except for Tb fluoroscopy cohort • Some dose response data
<1-2 Gy Low to moderate	Occupational exposures: Radiologists (UK, US), Radiologic technologists (US, Canada, China, and others)	<ul style="list-style-type: none"> • Excess heart disease mortality (US radiologists); but not in the UK cohort • Excess heart disease /stroke mortality (US rad techs) • Some dose response data
<0.5 Gy Low	Chernobyl liquidators Nuclear workers	<ul style="list-style-type: none"> • Excess heart disease mortality and dose response • Cannot rule out confounding effects

Possible Mechanisms: Radiation and Heart Disease

- Microvasculature theory
 - Especially in relation to high-dose irradiation
- Mutation theory
 - Monoclonal origin or expansion of atherosclerotic plaques
- Inflammation theory
 - Endothelial injury / dysfunction and inflammatory response

A-bomb Clinical Data -1

- Cardiovascular precursor lesions and related conditions
 - Changes in age trends for serum cholesterol levels and blood pressure
 - Increased prevalence of aortic arch calcification, isolated systolic hypertension



Wong et al, 1999

A-bomb Clinical Data - 2

- Evidence that radiation may increased inflammatory activity
 - Effect on leukocyte count, erythrocyte sedimentation rate, α -1 and α -2 globulin and sialic acid - *Neriishi et al, 2001*
 - Increased C-reactive protein and Interleukin 6 levels - *Hayashi et al, 2003*
- Atherosclerosis - an inflammatory process involving endothelial damage and dysfunction (Ross, 1999)

F1

Children of A-Bomb Survivors

Early genetic studies

- 77,000 newborns, 1948-54
 - Use of food ration program for pregnant women (>20 weeks)
 - => 90% all pregnancies in Hiroshima/Nagasaki
 - Follow-up by midwives
 - Physical examination during 2 weeks after birth
- Untoward pregnancy outcomes
 - stillbirth
 - malformations
 - neonatal death (2 weeks)

Birth Defects, 1948-53

Total major birth defects: 0.91% (n=594)

Tokyo Red Cross Hospital data: 0.92%

Mother's dose, Sv	Father's dose, Sv		
	< 0.01	0.01 – 0.49	> 0.50
< 0.01	2,257/45,234 5.0%	81/1,614 5.0%	29/506 5.7%
0.01 – 0.49	260/5,445 4.8%	54/1,171 4.5%	6/133 4.5%
> 0.50	63/1,039 6.1%	3/73 4.1%	7/88 8.0%

Blood protein mutations, 1976-

	< 0.01 Sv	> 0.01 Sv (mean 0.49 Sv)
<u>Electrophoretic protein variants</u>		
Children tested	12,297	11,364
Loci tested	589,506	544,779
New mutations	4	2
Mutation rate / 100,000	0.7	0.4
<u>Enzyme-deficient protein variants</u>		
Children tested	5,026	4,989
Loci tested	61,741	60,529
New mutations	0	1
Mutations rate / 100,000	0	2

DNA Studies in F1

- Lymphocytes from 1,000 child-parents trios:
 - 500 one or both parents exposed
 - 500 non-exposed
- Pilot on 100 families
 - minisatellite loci, 8 probes
- Two-dimensional electrophoresis
- DNA chip technology

F₁ Cancer Results

- Mortality through 1999 (Izumi et al 2003)
 - No excess cancer and non-cancer mortality
 - Hazard ratio for cancer = 0.96 (95% CI 0.59, 1.55)
 - Hazard ratio for non-cancer = 1.16 (95% CI 0.92, 1.46)
- Cancer incidence before age 20 yrs (Yoshimoto, 1990)
 - No excess for heritable and non-heritable type cancers