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

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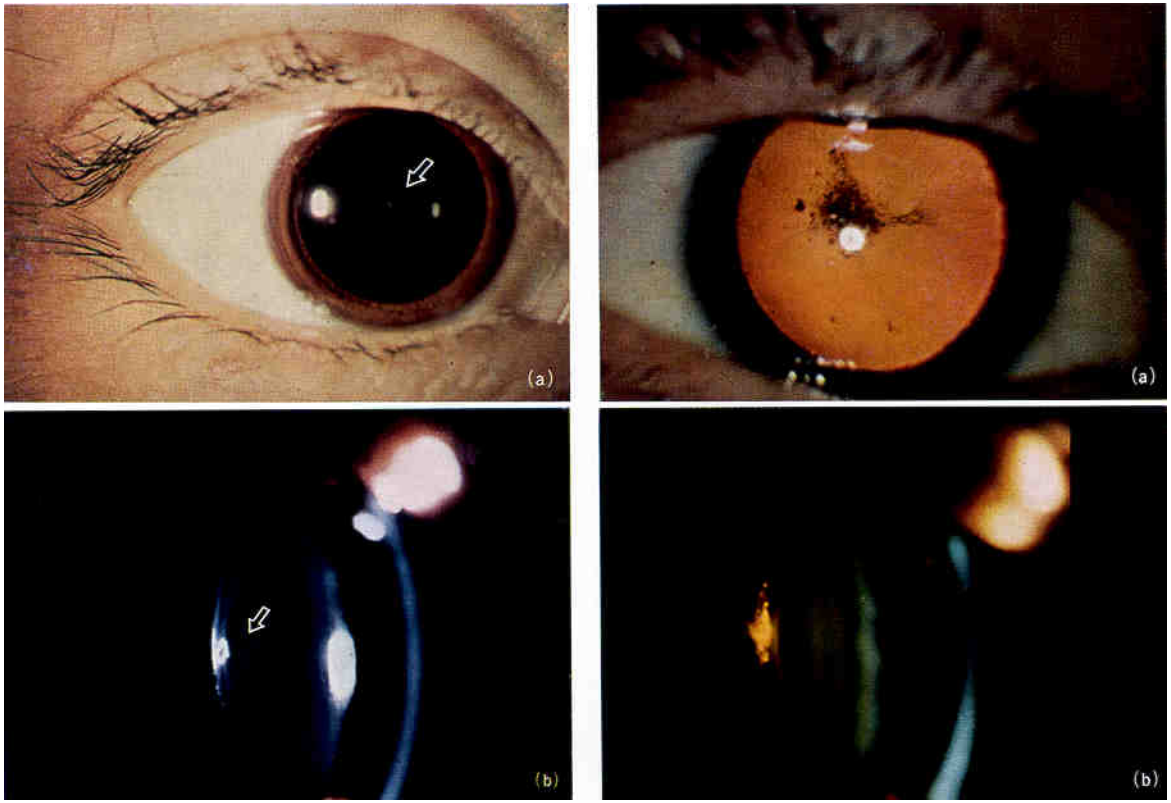
# Non-cancer Diseases

- 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

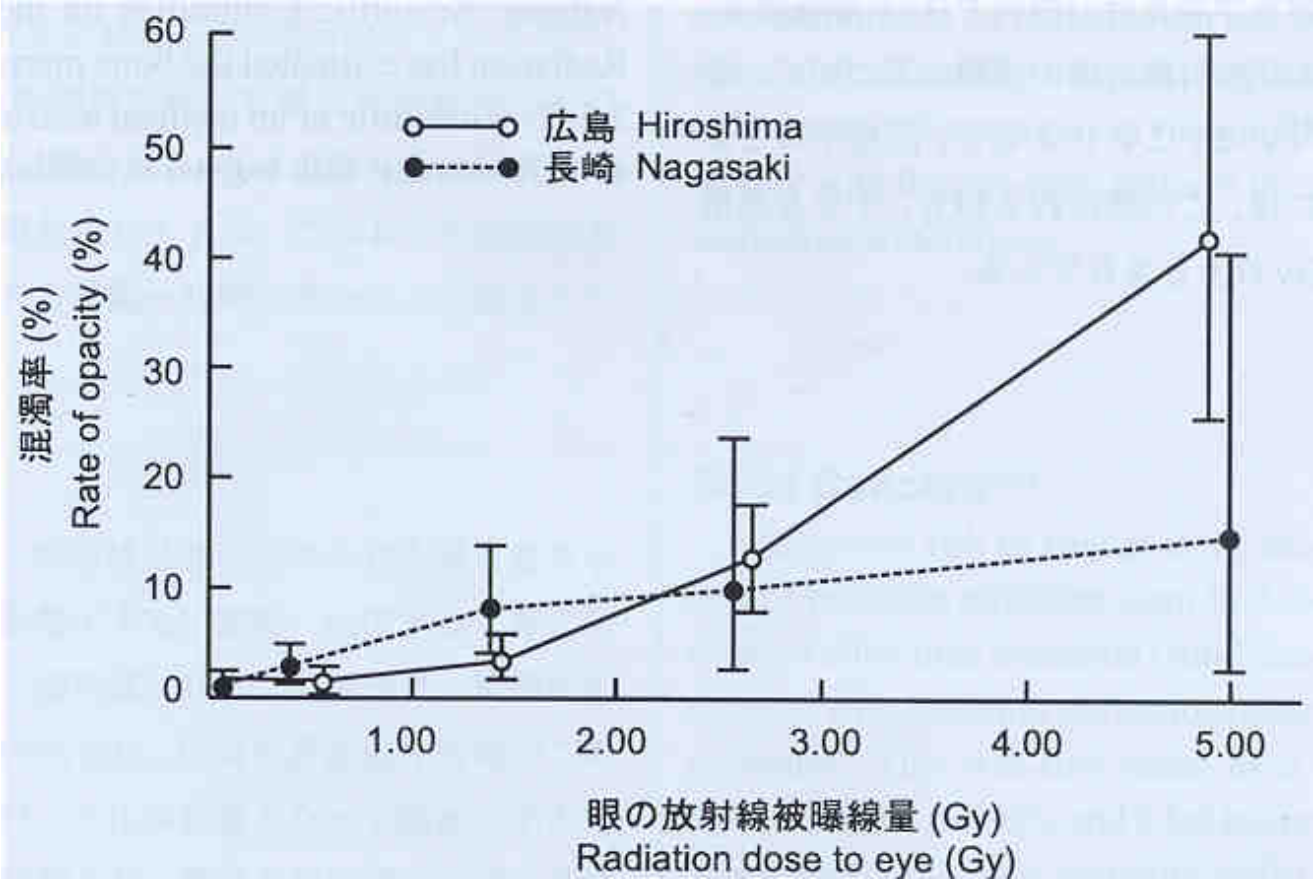
# Cataract

# 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

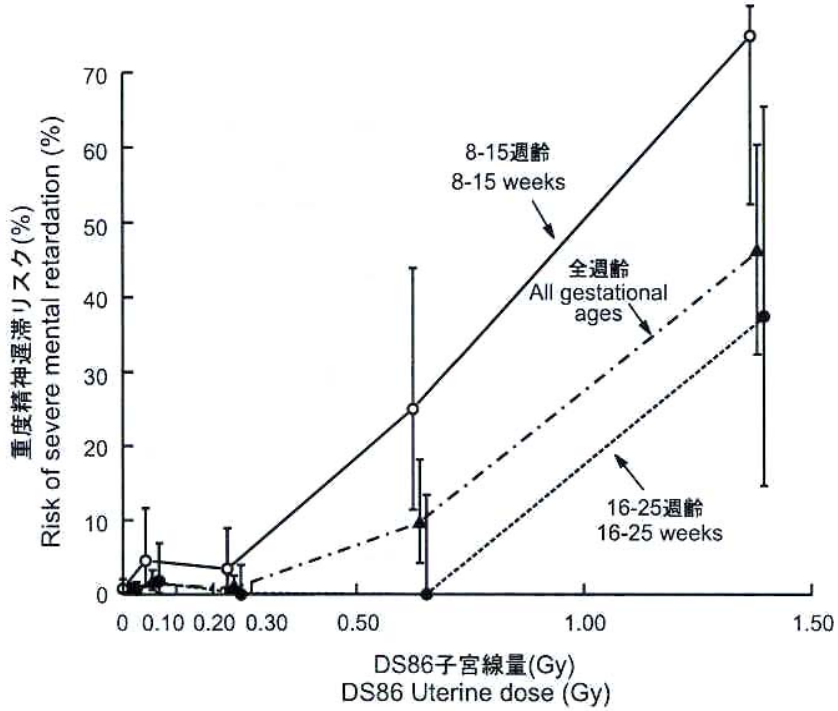


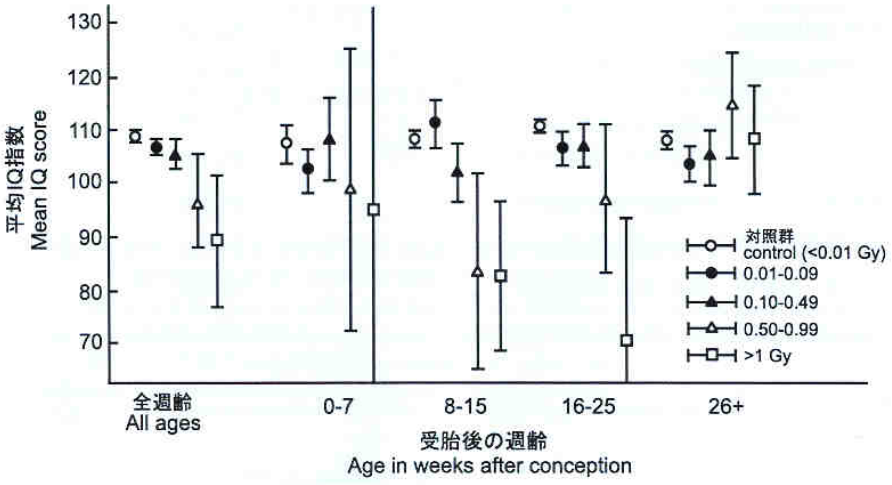

**ICRP: Threshold for opacities causing visual impairment = 2-10 Gy for single low LET exposure**

# Mental Retardation and IQ

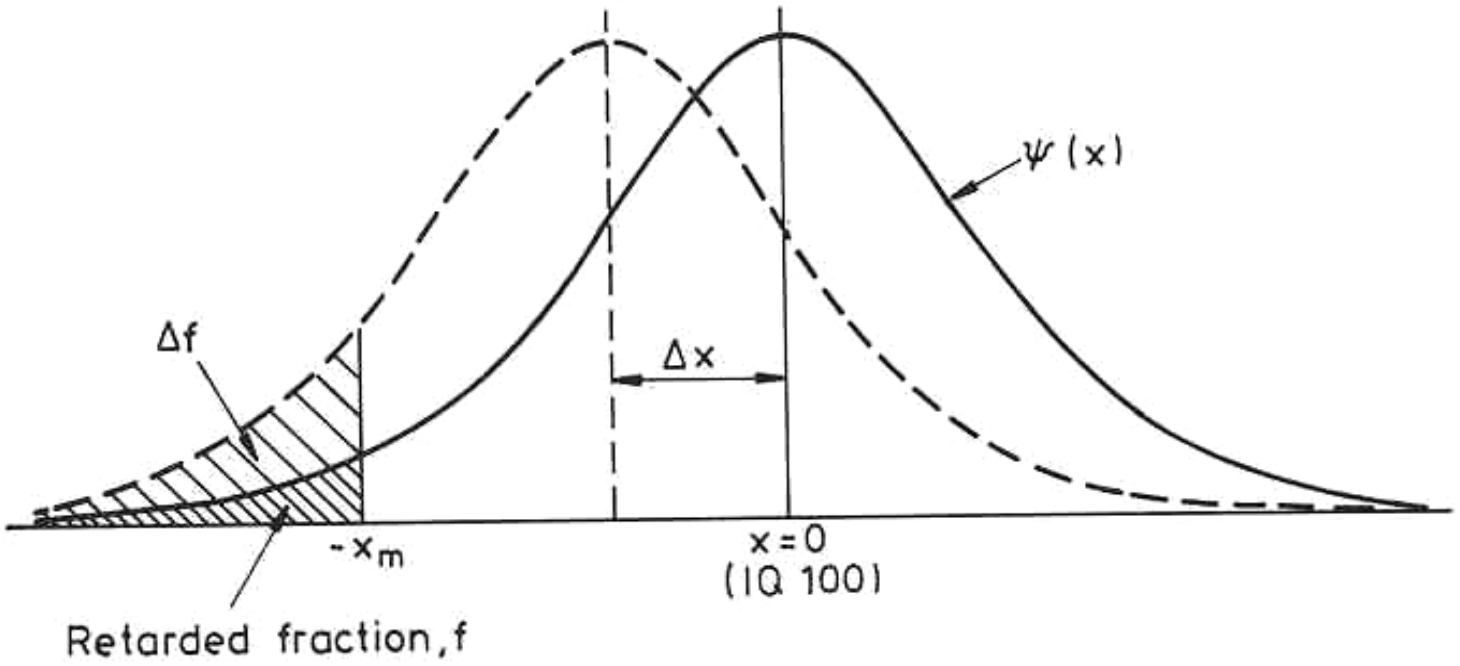
# Mental retardation and IQ *In-utero exposure*

- 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

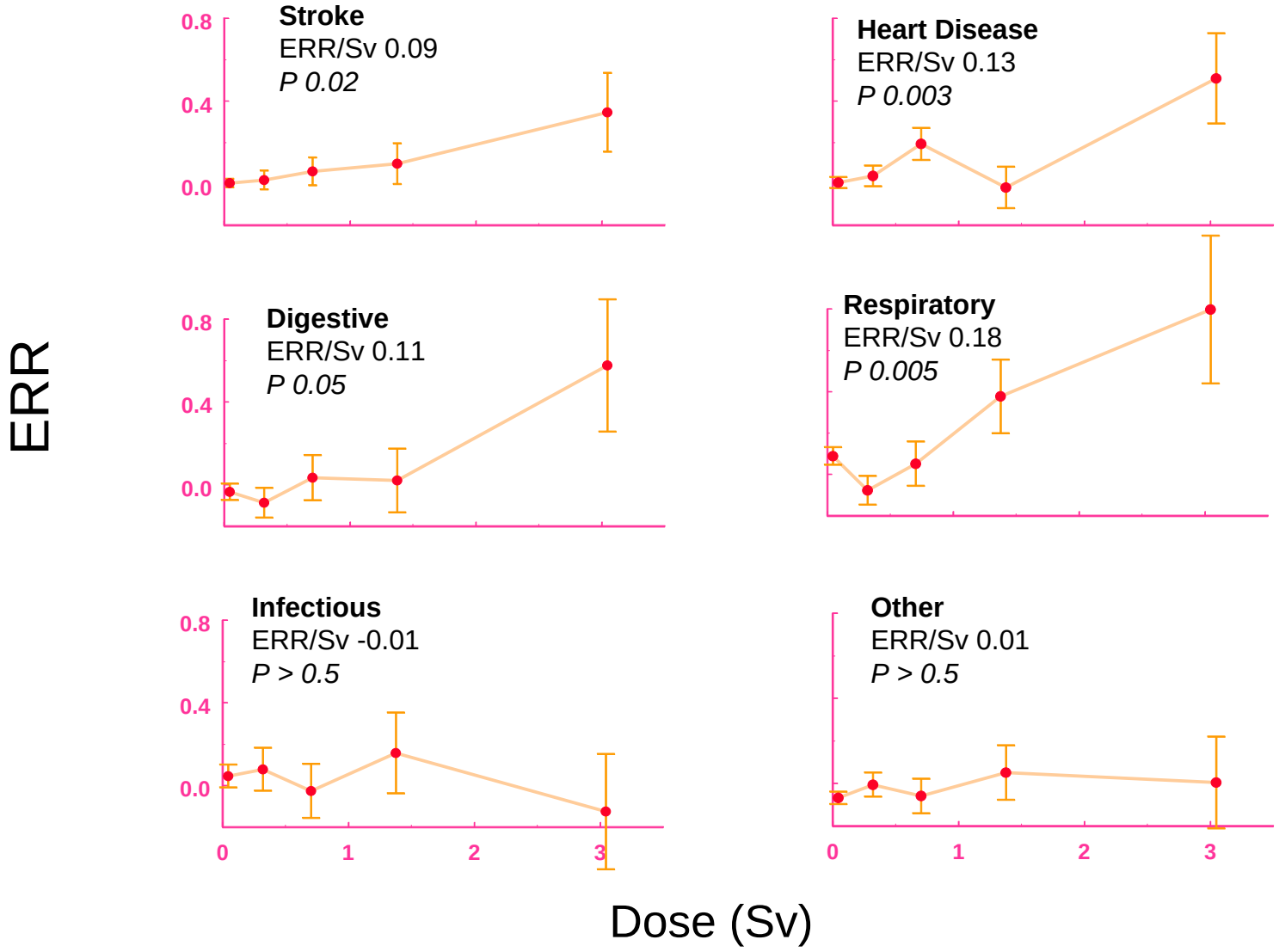
# Noncancer Diseases in LSS

| 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: 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

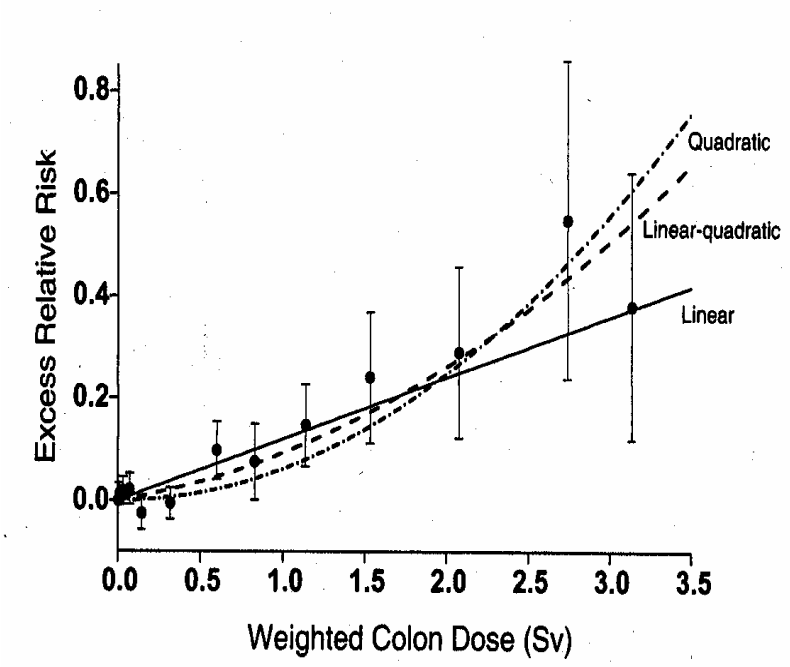
| Subjects | Deaths | Noncancer ERR/Sv | |
|---|---|---|---|
| | | No adjustment | Adjustment |
| 10,308 men | 1,163 | 0.07 | 0.09 |
| 13,154 women | 1,121 | 0.14 | 0.14 |

Adjusted for

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

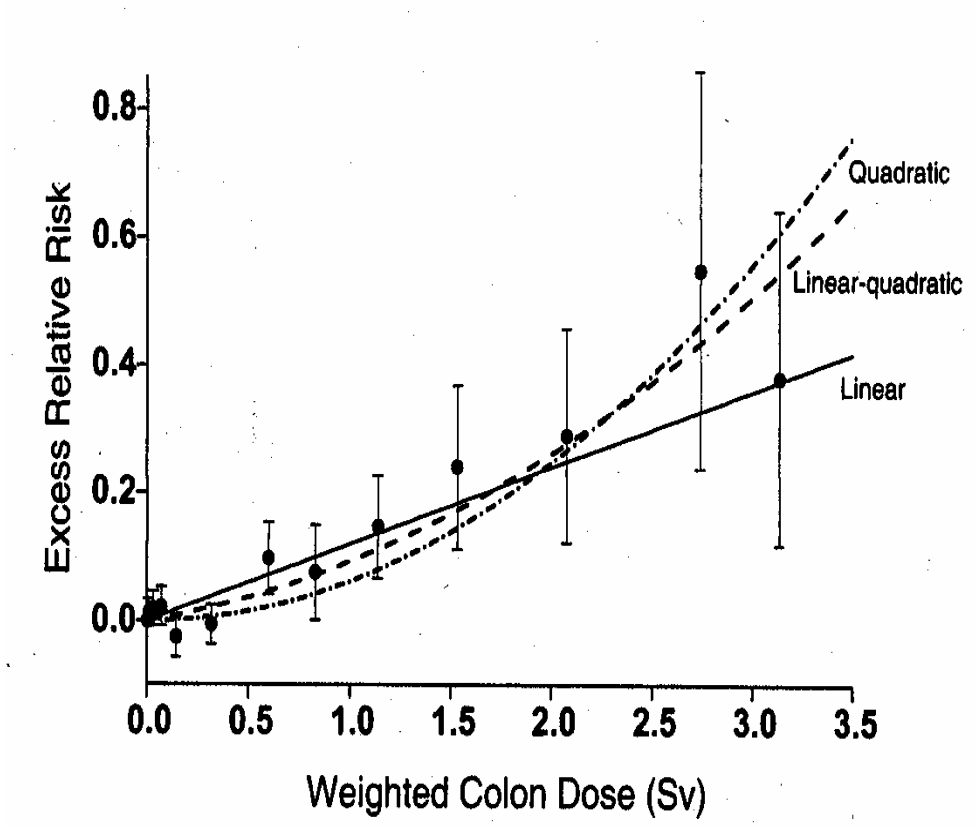
# Evidence for Causality

- 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

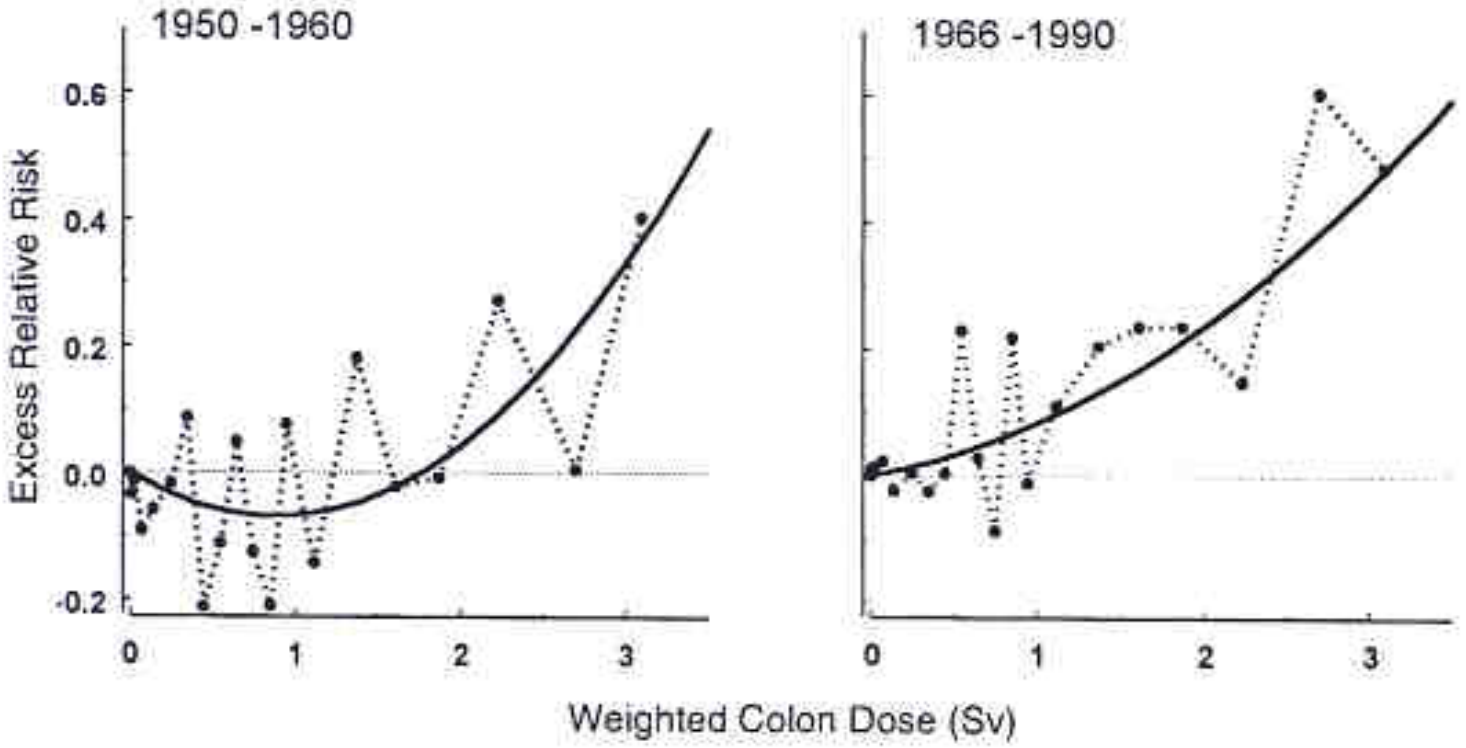


# Shape of Dose-Response Curve

- 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

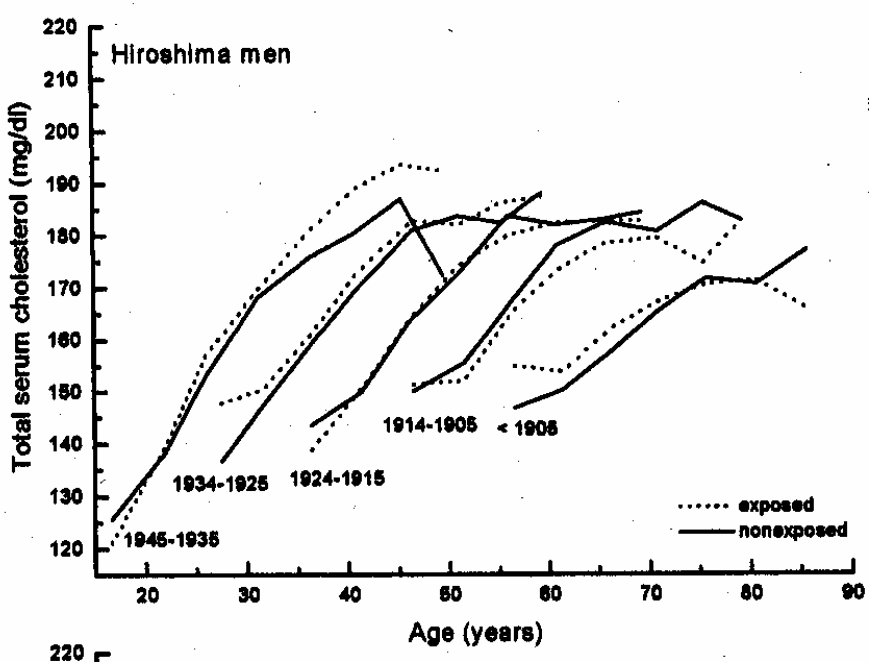
| Dose | Populations | Findings |
|---|---|---|
| 30-50 Gy<br>High | **Radiotherapy for cancer:**<br>Hodgkin's disease, breast cancer | • Excess myocardial infarction mortality<br>• **Dose response**<br>• Possible age / time effect |
| <10 Gy<br>Moderate | **Radiotherapy for benign diseases:**<br>Ankylosing spondylitis (2.5 Gy, 0-5 Gy)<br>Peptic ulcer disease (2.2 Sv, 0.2-6 Gy)<br>Metropathia haemorrhagica (1.3 Gy, 0-2 Gy)<br>Mass TB fluoroscopy (0.9 G, 0-9 Gy) | • Excess heart disease mortality based on SMRs, except for Tb fluoroscopy cohort<br>• ***Some dose response data*** |
| <1-2 Gy<br>Low to moderate | **Occupational exposures:**<br>Radiologists (UK, US),<br>Radiologic technologists (US, Canada, China, and others) | • Excess heart disease mortality (US radiologists); but not in the UK cohort<br>• Excess heart disease /stroke mortality (US rad techs)<br>• ***Some dose response data*** |
| <0.5 Gy<br>Low | Chernobyl liquidators<br>Nuclear workers | • Excess heart disease mortality and dose response<br>• 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 midwifes
  - 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<br>5.0% | 81/1,614<br>5.0% | 29/506<br>5.7% |
| 0.01 – 0.49 | 260/5,445<br>4.8% | 54/1,171<br>4.5% | 6/133<br>4.5% |
| > 0.50 | 63/1,039<br>6.1% | 3/73<br>4.1% | 7/88<br>8.0% |

# Blood protein mutations, 1976-

| | < 0.01 Sv | > 0.01 Sv (mean 0.49 Sv) |
|---|---|---|
| Electrophoretic protein variants | | |
| Children tested | 12,297 | 11,364 |
| Loci tested | 589,506 | 544,779 |
| New mutations | 4 | 2 |
| Mutation rate / 100,000 | 0.7 | 0.4 |
| Enzyme-deficient protein variants | | |
| 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

# $F_1$ 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