National Cancer Institute

Non-Cancer Diseases in Atomic Bomb Survivors

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Topics

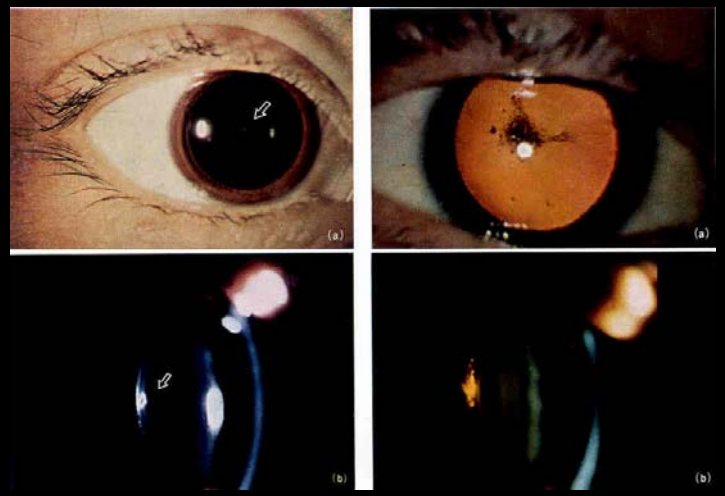
- Atomic-bomb survivors
  - Acute radiation effects
  - Late effects
    - Cataract
    - Growth and development, hyperparathyroidism
    - Cardiovascular and other adult-onset diseases
- In-utero exposure
- F1 – second generation

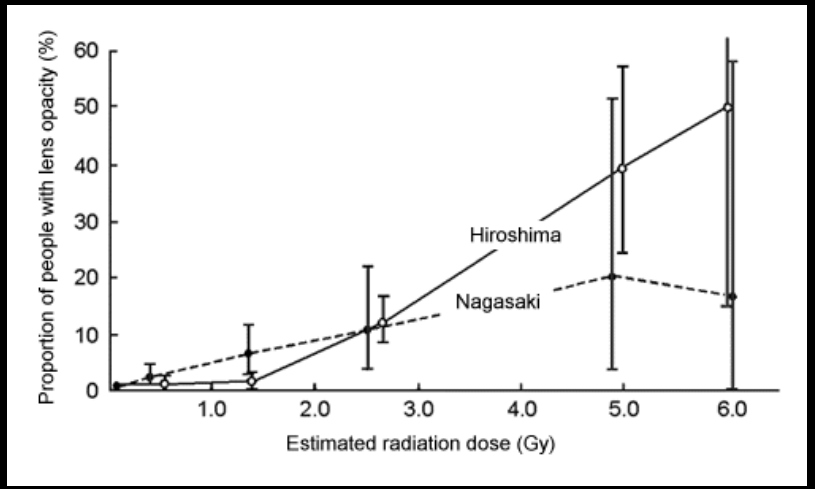
Acute Death & "Acute Radiation Syndrome"

- Acute radiation syndrome
  - Vomiting, diarrhea, bleeding, hair loss
  - Damage to the intestine, bone marrow, hair-root cells
- Acute death (within 2 months):
  - 50% acute mortality at 1-1.2 km (Hiroshima) and 1-1.3km (Nagasaki) from the hypocenter
  - UNSCEAR estimate of 50% lethal dose at 60 days (LD50/60) ~ 2.5 Gy; >5 Gy if full medical care available

Lens Opacity (Cataract)

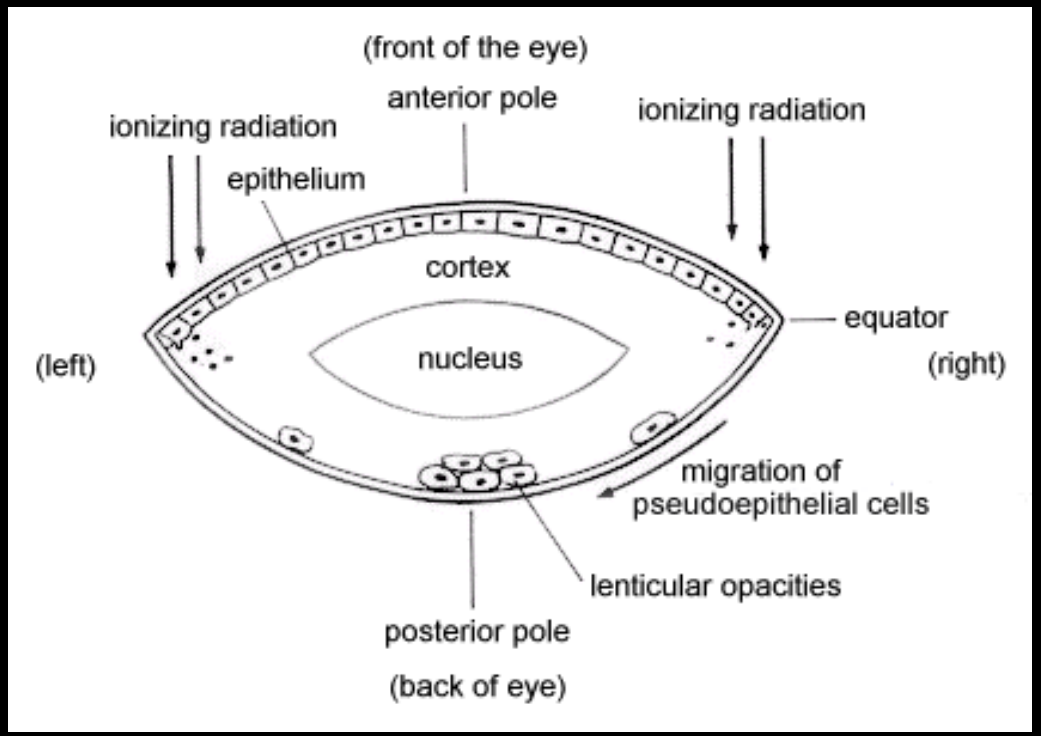
- An early radiation effects appearing 2-3 years after exposure
- Partial opacity, most often of posterior lens, detected by slit-lamp exams; rarely causing severe visual impairment
  - Possible “threshold” dose level ~ 1.5 – 2 Sv





Posterior Lenticular Opacity Possible Mechanism

- Radiation especially harmful to dividing cells, at the equator
- Damaged cells move toward the rear of the lens before converging on the center



Lens Opacity As Late Effect

- Emerging evidence of long-term effect on aging-related cataract (cortical cataract)
- Lower or absent threshold dose level

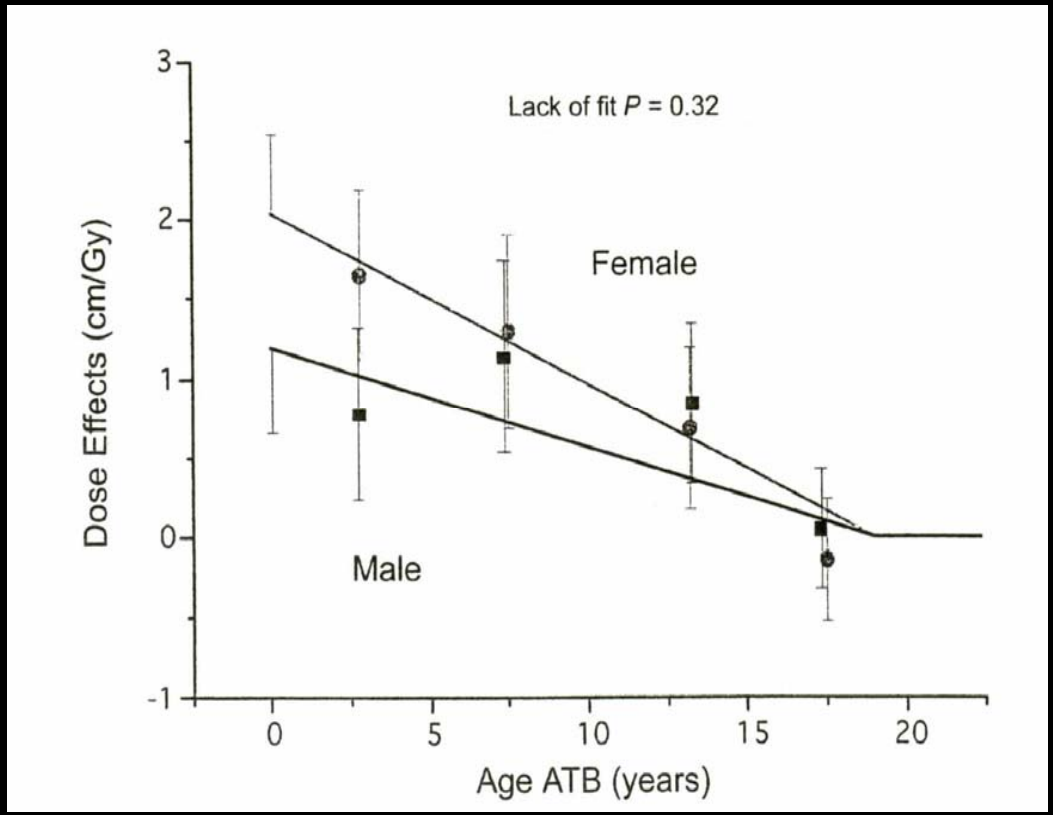
Lens Opacity Classification System II (LOCSII) for grading opacity
AHS, 2000-02

	Odd Ratio per Sv	p
Nuclear color	1.01	ns
Nuclear opacity	1.07	ns
Cortical cataract	1.30	0.002
Posterior sub-capsular opacity	1.44	<0.001

(Nakashima et al, 2006)

Development and Fertility

- Growth retardation
  - Reduction in height and weight, ages 19-27 yrs, among those exposed at <10 yrs *(Otake, 1994)*
  - Apparent gender and age-at-exposure effect *(Nakashima, 2002)*
- No radiation effect on age at menarche or fertility



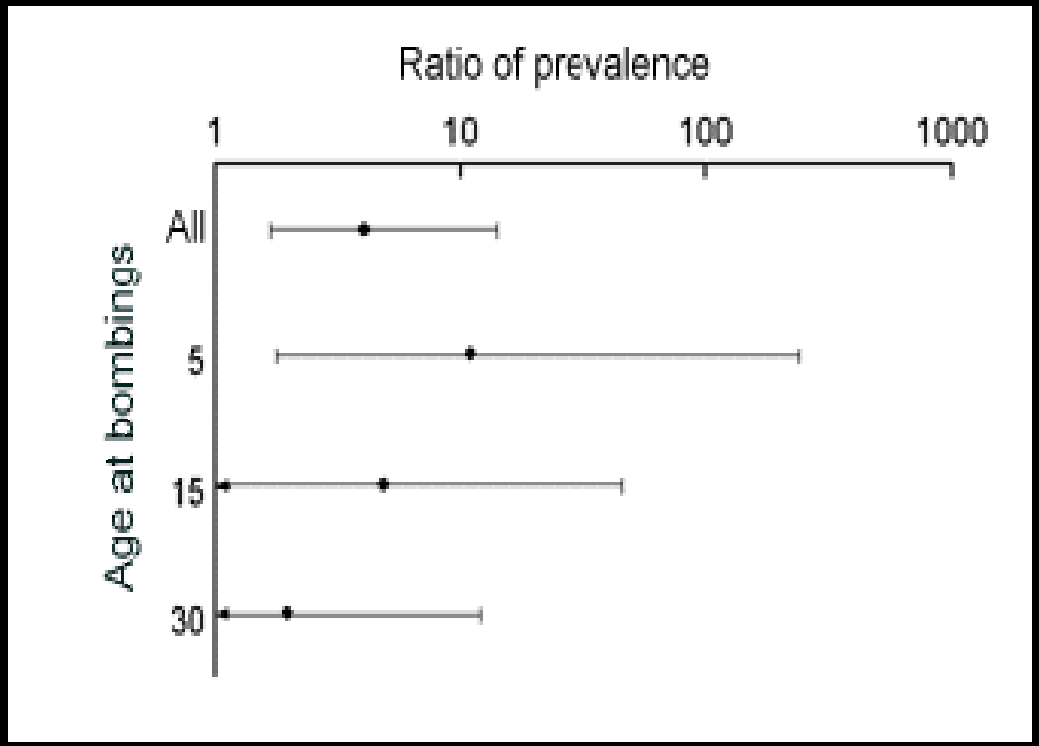
(Nakashima, 2002)

Benign Tumors

- Excess risk of benign tumors or tumor precursors for some known sensitive tumor sites
  - Thyroid: Nodule
  - Breast: Proliferative disease, atypical hyperplasia
  - Neural: Schwannoma
  - Salivary glands: Warthin's tumor
  - Stomach: Polyps
- Intriguing sites/tissues
  - Hyperparathyroidism
  - Uterine myoma

Hyperparathyroidism

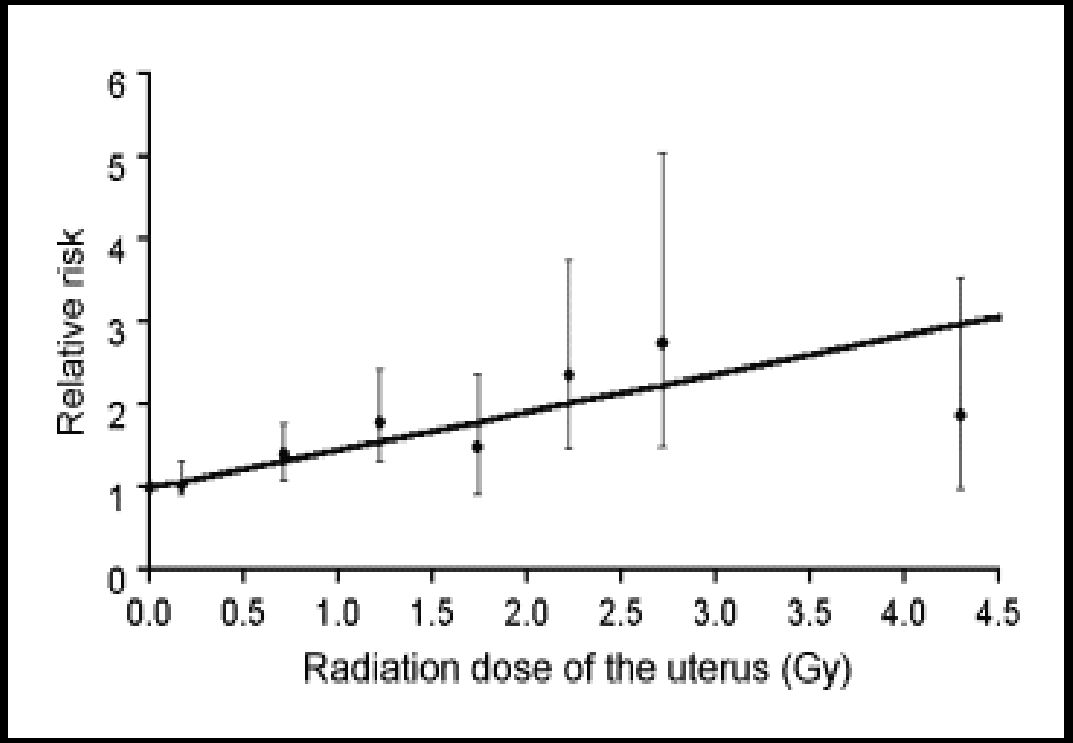
- Hyperparathyroidism
  - Results from increased parathyroid hormone due to:
    - Adenoma
    - Hyperplasia
    - Cancer
- Suggestion of age-at-exposure effect



(Fujiwara et al, 1992)

Uterine Myoma

- Often called "fibroids"
  - Originates from uterine muscle tissue
  - Highly estrogen-dependent growth



(Wong et al, 1993)

Effects on Immunity

- Acute (short-term) effects
  - 150,000 acute deaths and acute radiation syndrome
- Long-term effects
  - Became apparent in 1980s
  - Slight reduction in T-cells (10% per Gy) accompanied by slightly increased B-cells
  - No effect on innate immunity function, e.g., natural killer cells

Late Immunity Effects
Health Implications

- Reduced clearance of hepatitis B virus in the carriers *(Fujiwara, 2002)*
- Increases in chronic inflammation markers
  - Sedimentation rate, α-1 and α-2 globulin and sialic acid (*Neriishi, 2001)*
  - C-reactive protein and Interleukin 6 (*Hayashi, 2003)*
  - Reason for excess risk of cardiovascular and some other chronic diseases ?
- No increased risk for tuberculosis or autoimmune diseases (rheumatoid arthritis, autoimmune thyroiditis)

Aging

- No dose response for physiological markers of aging
  - Skin elasticity, vision, breathing capacity, etc
- No radiation effects on certain specific aging-related diseases
  - Alzheimer disease
  - Osteoporosis

Psychological Effects

- Anxiety and somatization symptoms compatible with PTSD seen in the survivors 17-20 years after the bombings – *(Yamada, 2002) :*
  - Increased ORs for anxiety (1.73) and for somatization (1.99) associated with acute radiation syndromes
    - Anxiety – nervousness, fatigue, getting up tired in morning, etc
    - Somtization – pain, GI and psychoneurological symptoms
  - ORs increasing with increasing distance from hypocenter, but independent of disease history
- Inverse dose response for suicide morality in LSS

Cardiovascular and Other Chronic Diseases in LSS

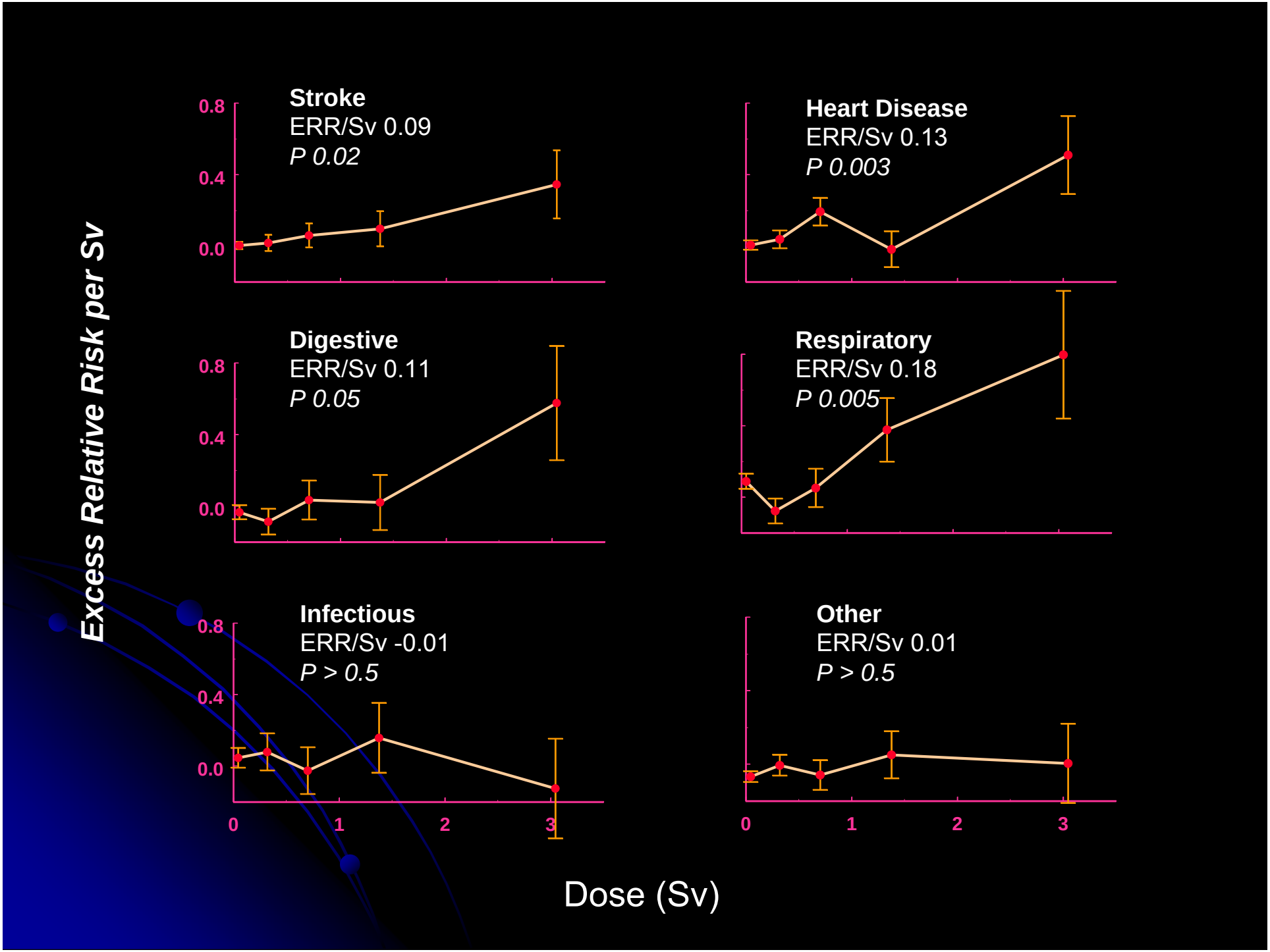
- Emerging evidence on radiation effects on heart disease, stroke and other adult-onset chronic diseases
  - Small relative risk, but
  - Large absolute risk because of high background rates
  - Increasing evidence of a linear dose response

LSS Non-cancer Mortality - 1950-97

Dose, Sv	Obs	Exp	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*

Solid cancer deaths: 1,335 (440 excess) *(Preston, 2003)*

Solid


Excess Relative Risk per Sv
Stroke
ERR/Sv 0.09
P 0.02
Heart Disease
ERR/Sv 0.13
P 0.003
Digestive
ERR/Sv 0.11
P 0.05
Respiratory
ERR/Sv 0.18
P 0.005
Infectious
ERR/Sv -0.01
P > 0.5
Other
ERR/Sv 0.01
P > 0.5
0.8
0.4
0.0
0
1
2
3
Dose (Sv)

Confounding Does Not Explain the Dose Response

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

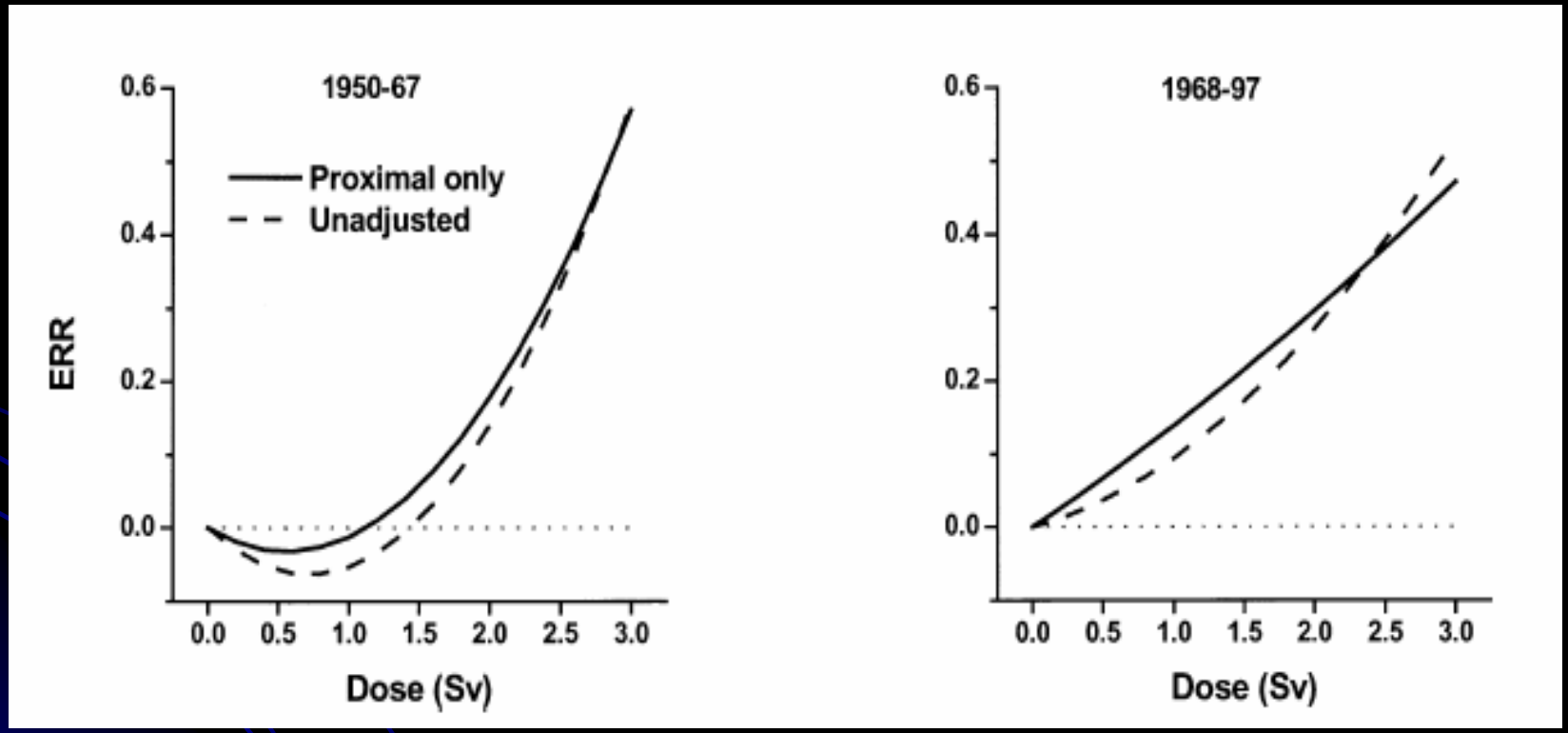
Confounding factors used for adjustment:

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

"Healthy Survivor Effect" and Urban-rural Difference Complicating Non-cancer Dose Response Analyses

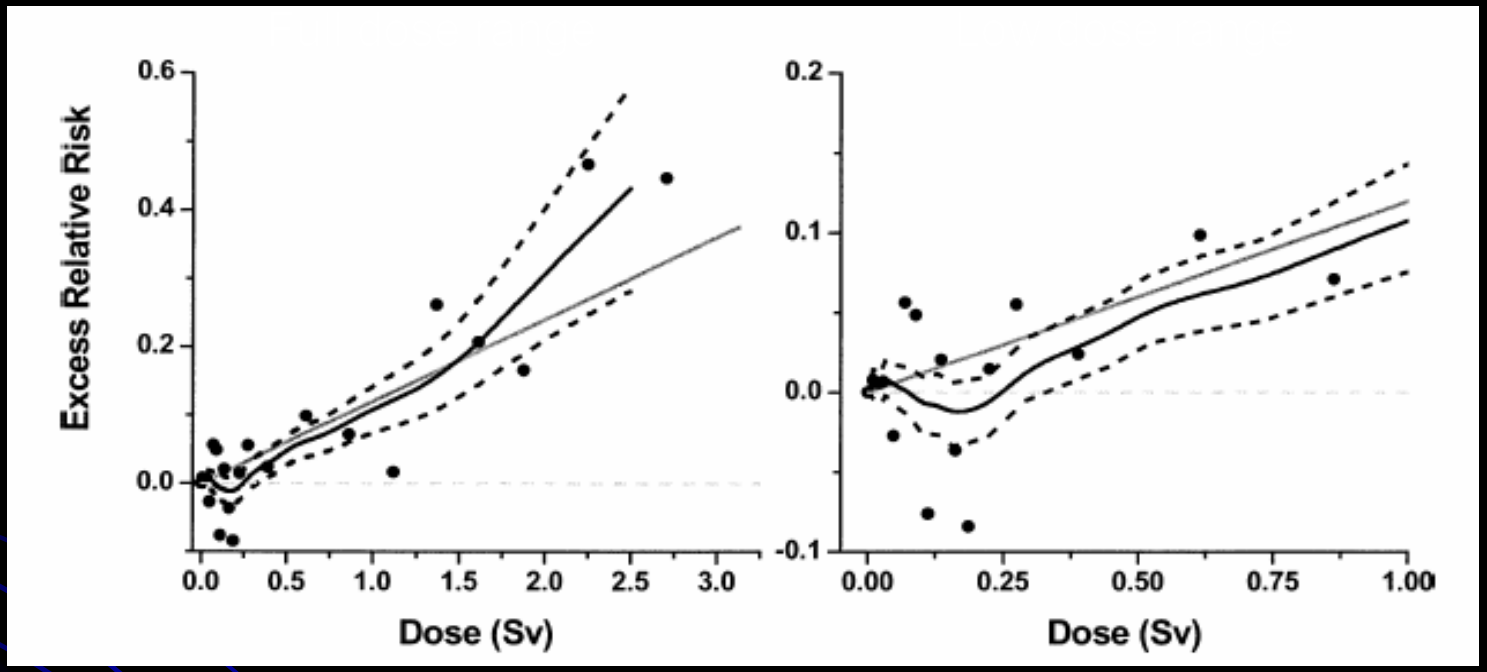
Early follow-up period

Late follow-up period



Proximal survivors: <3 km from hypocenter.
Unadjusted: full cohort.

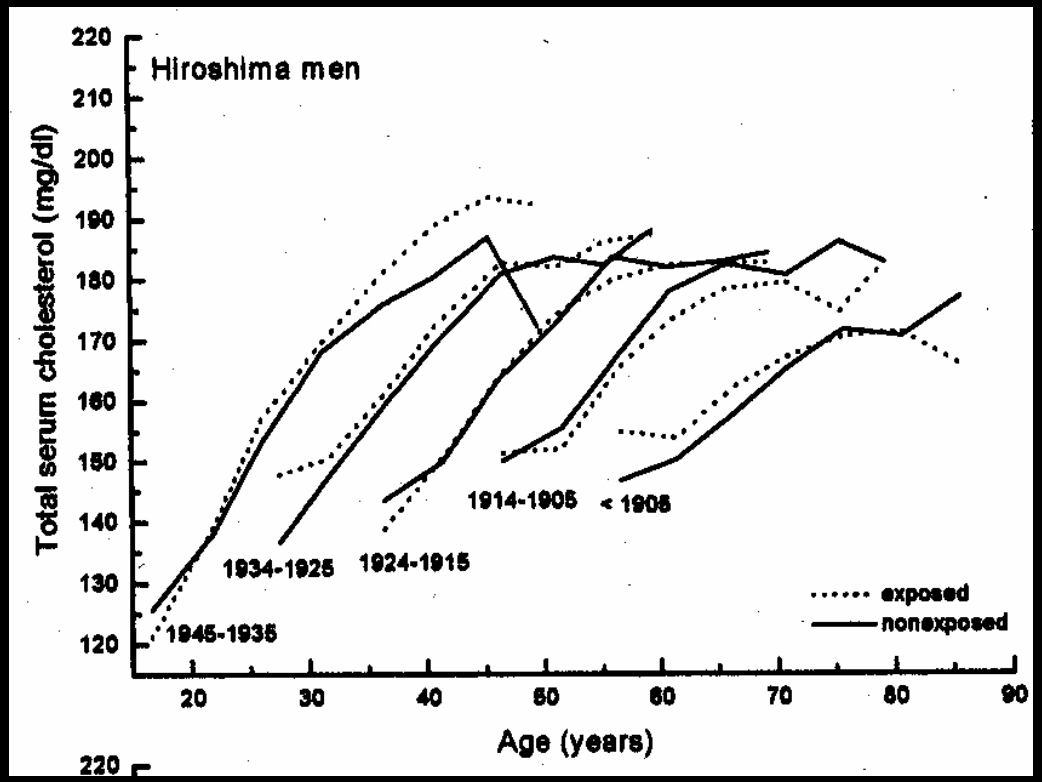
Dose Response at Low Doses: 1968-97



Best described by a linearity but consistent with a non-linearity.
The risk below 0.5 Gy is uncertain.

Serum Cholesterol and Precursor Lesions

- 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

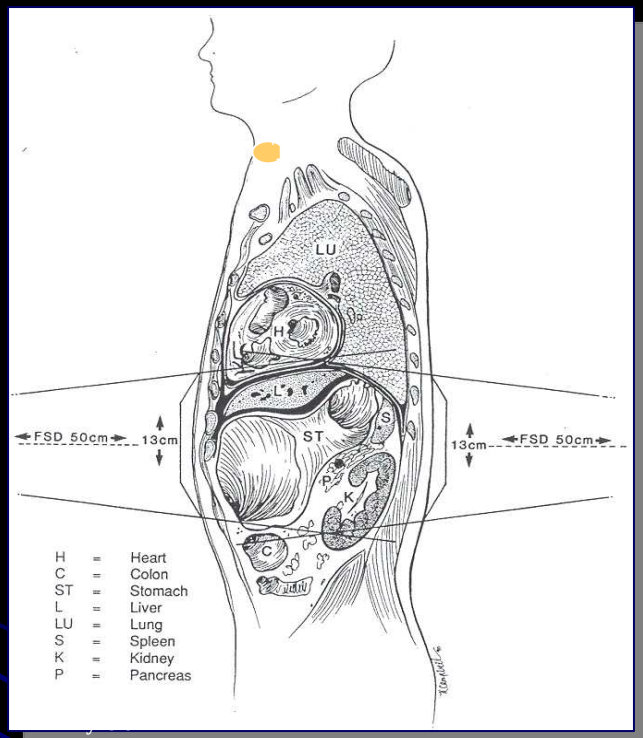


Wong et al, 1999

CVD - Other Irradiated Populations

- High-dose radiotherapy (Hodgkin lymphoma, breast cancer at >30-40 Gy) increases heart disease risk; doses are localized.
- Evidence of increased heart disease risk from some but not all medical and occupational studies
  - Ankylosing spondylitis but not TB fluoroscopy patients
  - US radiologists and radiologic technologists but not UK radiologists
  - Localized exposures
  - Few dose response data
- Varying results from low-dose occupational studies
  - Low statistical power
  - Lacking smoking and confounder information

Peptic Ulcer Disease Cohort



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**

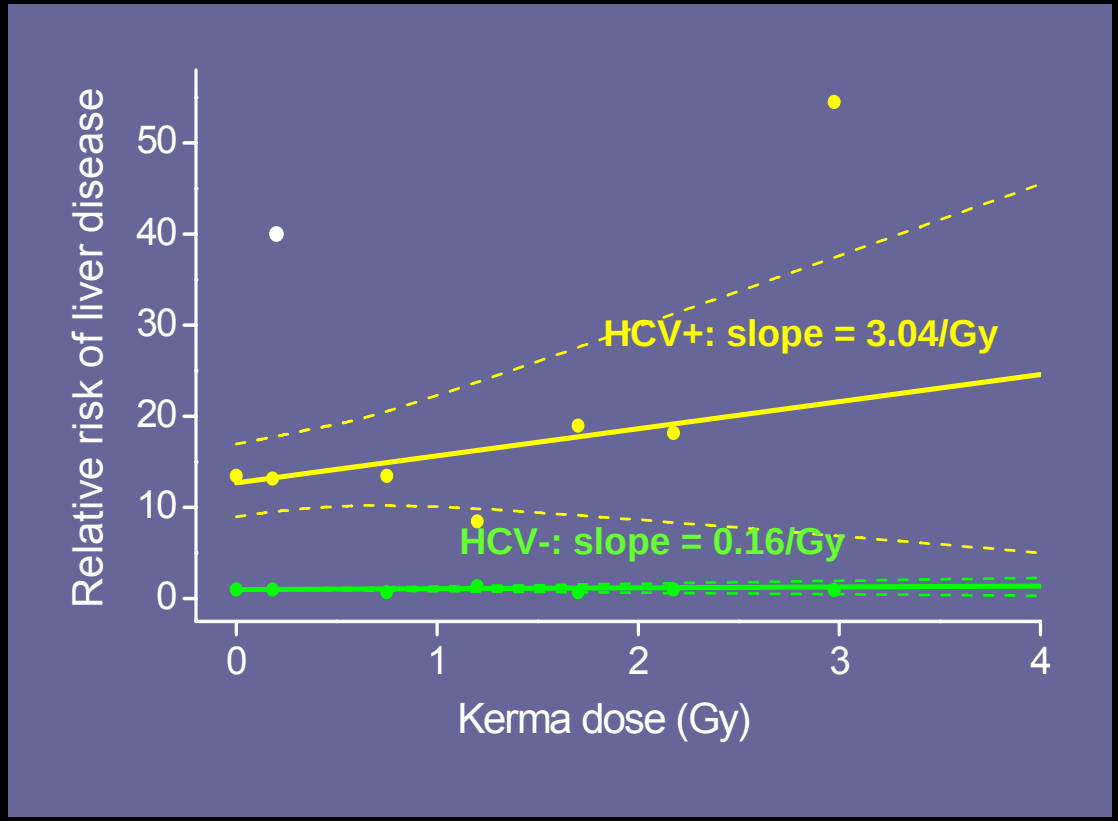
Best supporting low-dose data
Marked dose heterogeneity

* 5% of the heart (apex) in the radiation field

(Carr et al, 2005)

Liver Disease and Hepatitis C Virus

- Chronic hepatitis and liver cirrhosis
- No relationship between radiation dose and HCV sero-positivity
- Dose response for liver disease differs by HCV status



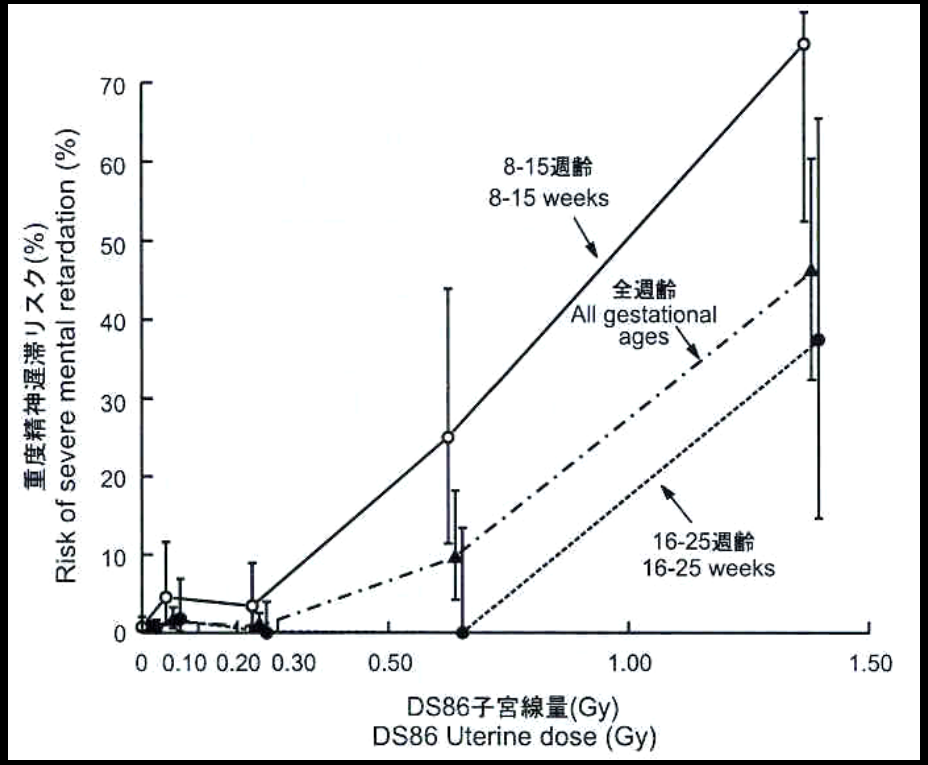
(Fujiwara et al, 2002)

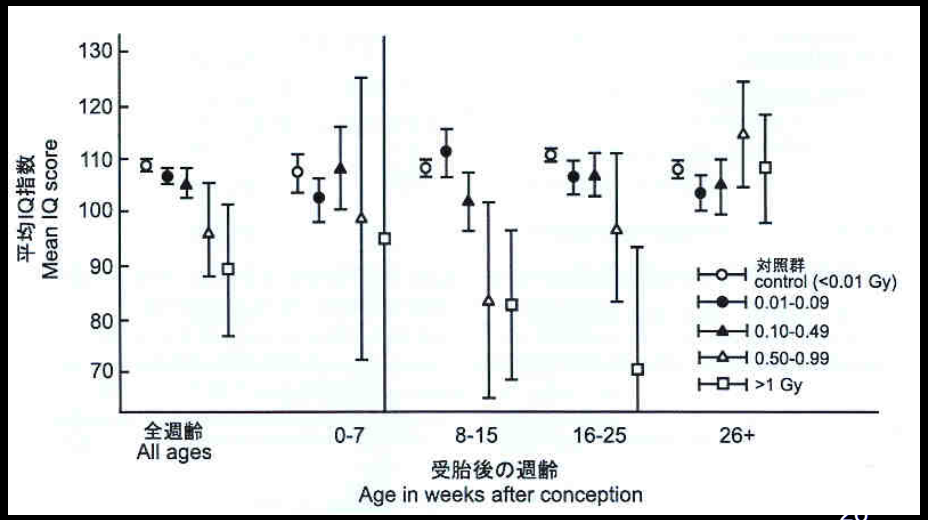
In-Utero Cohort

- Mortality, cancer incidence and clinical (subset) follow-up of 3,600 exposed and unexposed subjects
  - Impaired mental and physical growth development - the major health effects
  - More recently, increased risk of solid cancer at young adult ages
  - Follow-up for non-cancer diseases to continue

Effects of In-Utero Exposure

- **Severe 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**
- Reduction in **height & weight** at age 18
  - No effect of gestational period

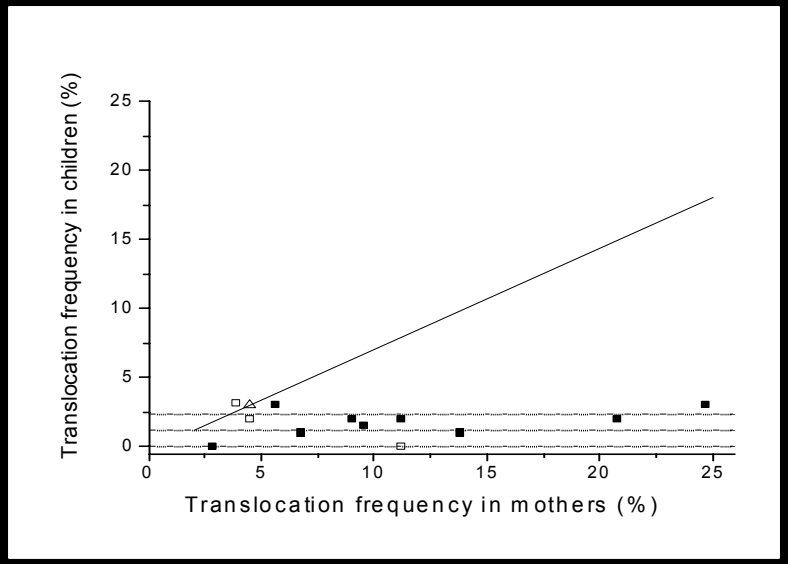


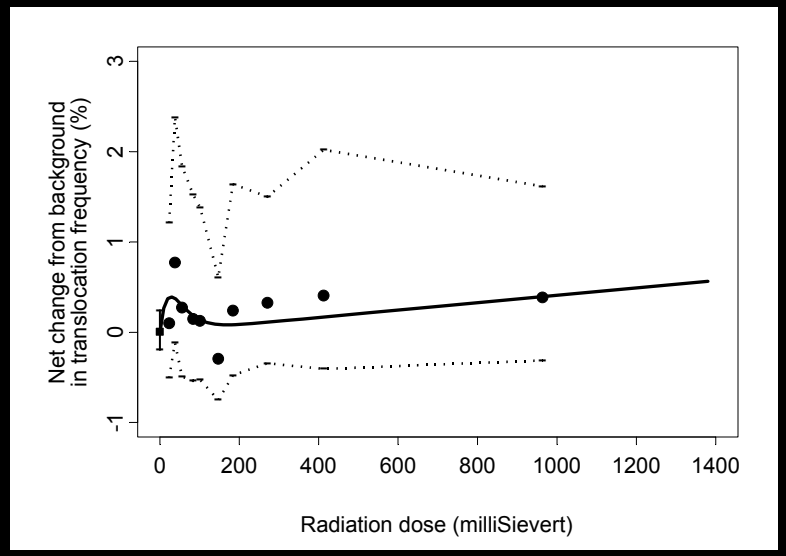


In-utero Exposure and Chromosomal Damage

- Lower translocation frequency from in-utero exposure – mother-child comparison
- Apparent sensitivity at a low dose
- Suggestion of two sub-populations in lymphoid precursor cells in fetuses

(Ohtaki, 2004)





Somatic Effects – Conclusions (1)

- Acute deaths occurred from thermal, mechanical and radiation injuries, especially due to bone marrow depletion - acute effects on immunity
- Emerging evidence of long-term radiation effects of on immunity - characterized by subtle functional and quantitative abnormalities involving T- and B-cells.
  - Possible implications for some non-cancer disease risks
  - E.g., liver disease interacting with viral infection; cardiovascular disease through inflammatory process

Conclusions (2)

- Increasing evidence of a linear dose response, suggesting the low-dose radiation effect on cardiovascular and a variety of other chronic adult-onset diseases.
- Developmental effects are especially pronounced from exposure in utero or during early childhood.
  - Possible long-term effects and
  - Implication for future cardiovascular and other disease risks
- Low-dose radiation effects observed for a wide range of non-cancer diseases are subtle, long-term and interacting with a variety of other risk factors
  - Difficulty in corroboration from other studies

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)
- Sex ratio

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	5.0%	5.0%	5.7%
0.01 – 0.49	4.8%	4.5%	4.5%
> 0.50	6.1%	4.1%	8.0%

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 and Non-cancer Risk

- Mortality through 1999 (*Izumi, 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

F1 Current and Future Studies

- Re-analysis of malformation and pregnancy outcome data using the latest dose estimates (DS02) - underway
- Question on risk for multi-factorial diseases (cancer, cardiovascular disease, diabetes, etc) through continued mortality and cancer incidence follow-up and sub-cohort clinical follow-up - underway

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