Japanese A-bomb Survivor Data and Studies of Low-Dose Effects

Beebe Symposium

National Academy of Sciences

December 1, 2010

Roy Shore,

K. Ozasa, Y. Shimizu, K. Kasagi, K. Furukawa, W-L. Hsu, D. Preston, K. Neriishi, A. Suyama, K. Kodama

shore@rerf.or.jp

Why is the A-bomb cohort considered a benchmark for assessment of radiation risks?

RERF A-bomb Related Cohorts

Residents in Hiroshima and Nagasaki at Explosions : ≈500,000

Residents at 1950 National Census
A-bomb survivors : ≈280,000

Life Span Study
120,000 (1950-)

Adult Health Study
17,000 (1958-)

In Utero Exposed
3,600

In Utero Clinical
1,600 (1978-)

F1:
Offspring of Survivors
77,000

F1 Clinical
12,000 (2002-)

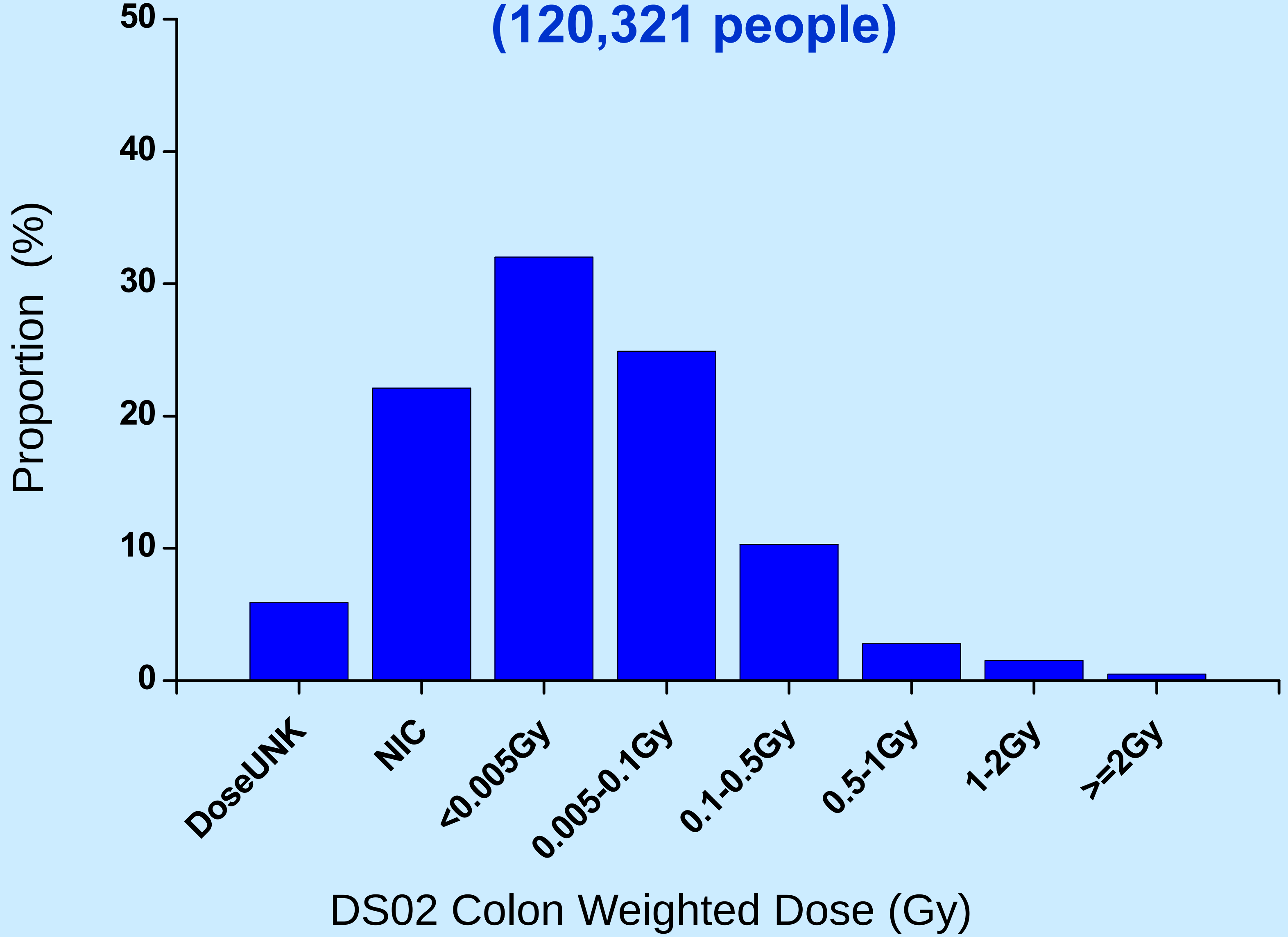
A-bomb Studies as a Benchmark for Radiation Risk Assessment

Characteristics of the radiation-exposed cohort:

- **Large, prospective cohort (~120,000) consisting of all ages at exposure and both sexes**
- **Wide range of radiation exposure with relatively accurate estimated dosimetry**
- **Cohort is unselected with respect to medical conditions, occupational fitness, etc.**
- **High rates of follow-up and disease ascertainment for ~60 years**
- **Information on potential confounding risk factors**
- **Adult Health Study – biennial clinical examinations and biospecimen collection for a subset of about 17,000 – study correlates and mechanisms of radiation-related disease through biomarkers, etc.**

Life Span Study (LSS) Cohort

(120,321 people)

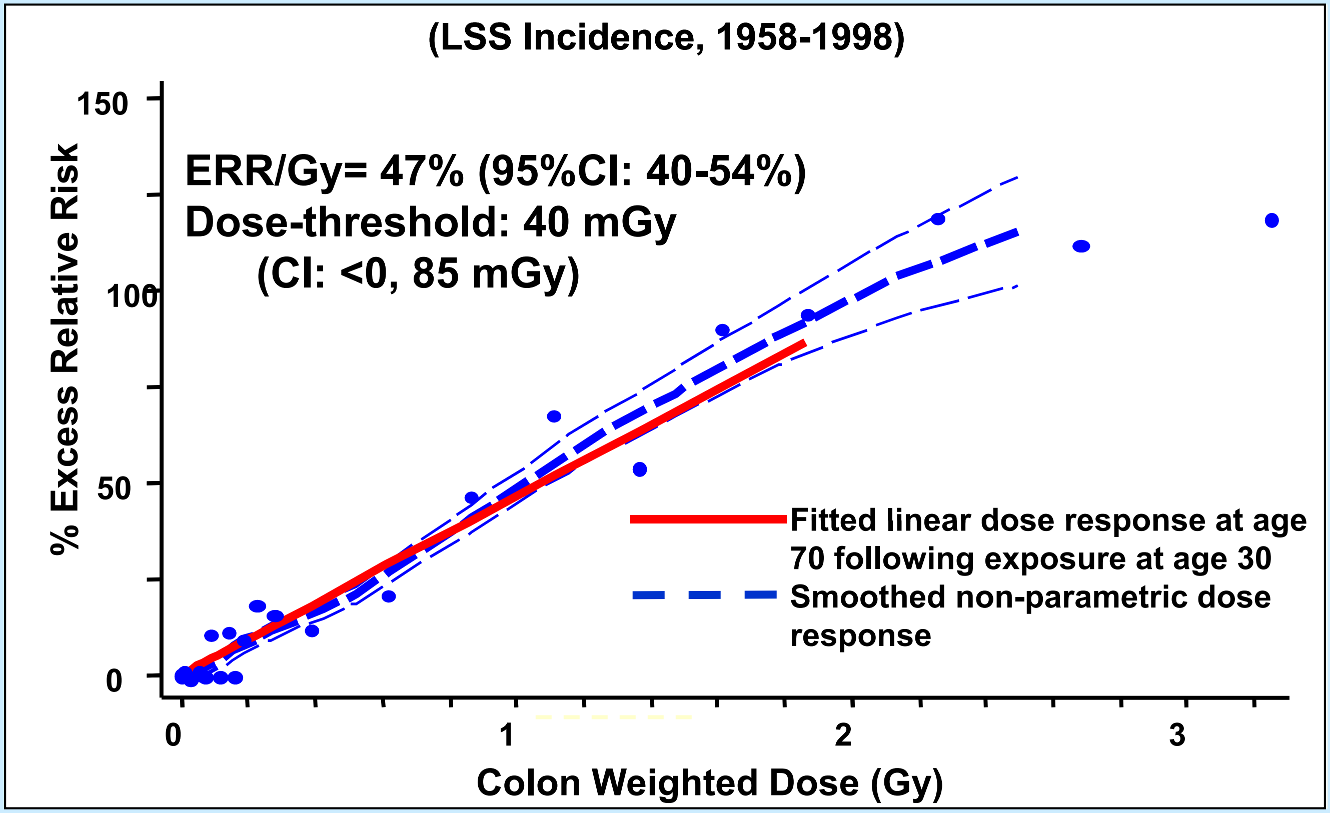


Are the excess risks of cancer at low doses proportional to those at high doses? – i.e.,

Is there dose-response linearity,
less-than or more-than linear risk at low doses,
or a dose threshold?

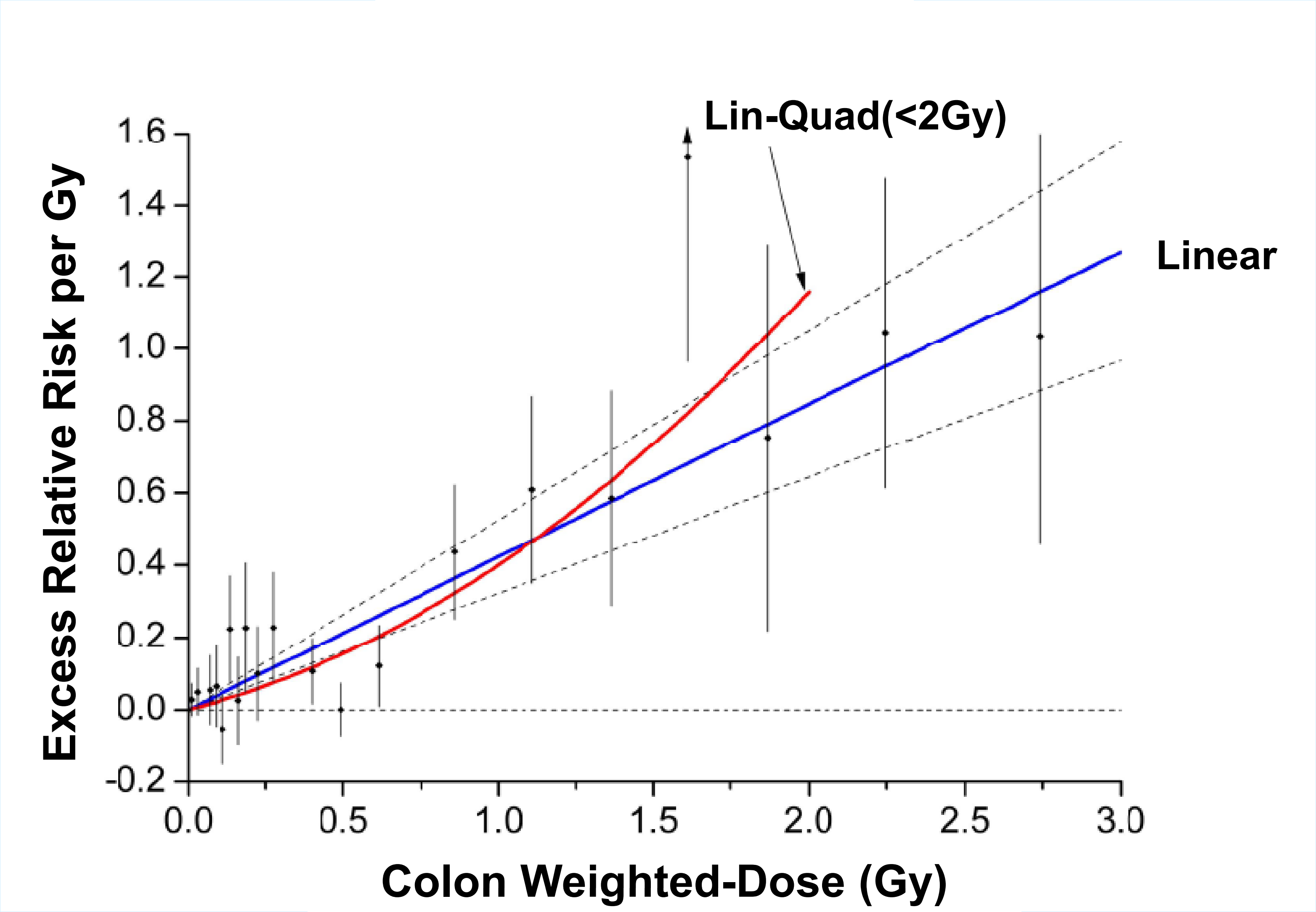
LSS dose response: Solid-cancer incidence

- No evidence of non-linearity in the dose response
- Significant dose response on 0-150 mGy
- Low dose-range slope consistent with full range



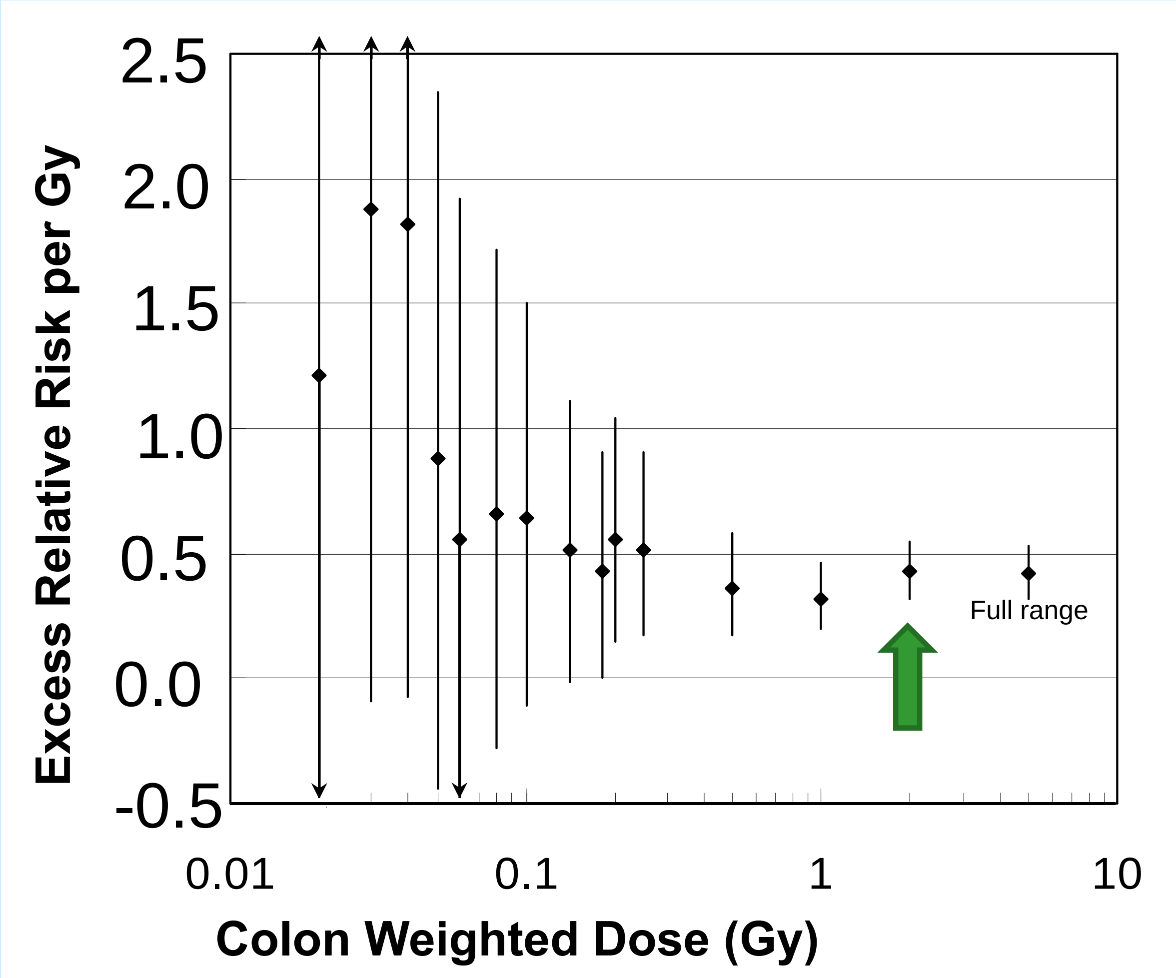
(Preston D et al: Radiat Res 168:1-64, 2007)

LSS Dose-Response for Solid Cancer Mortality, 1950-2003



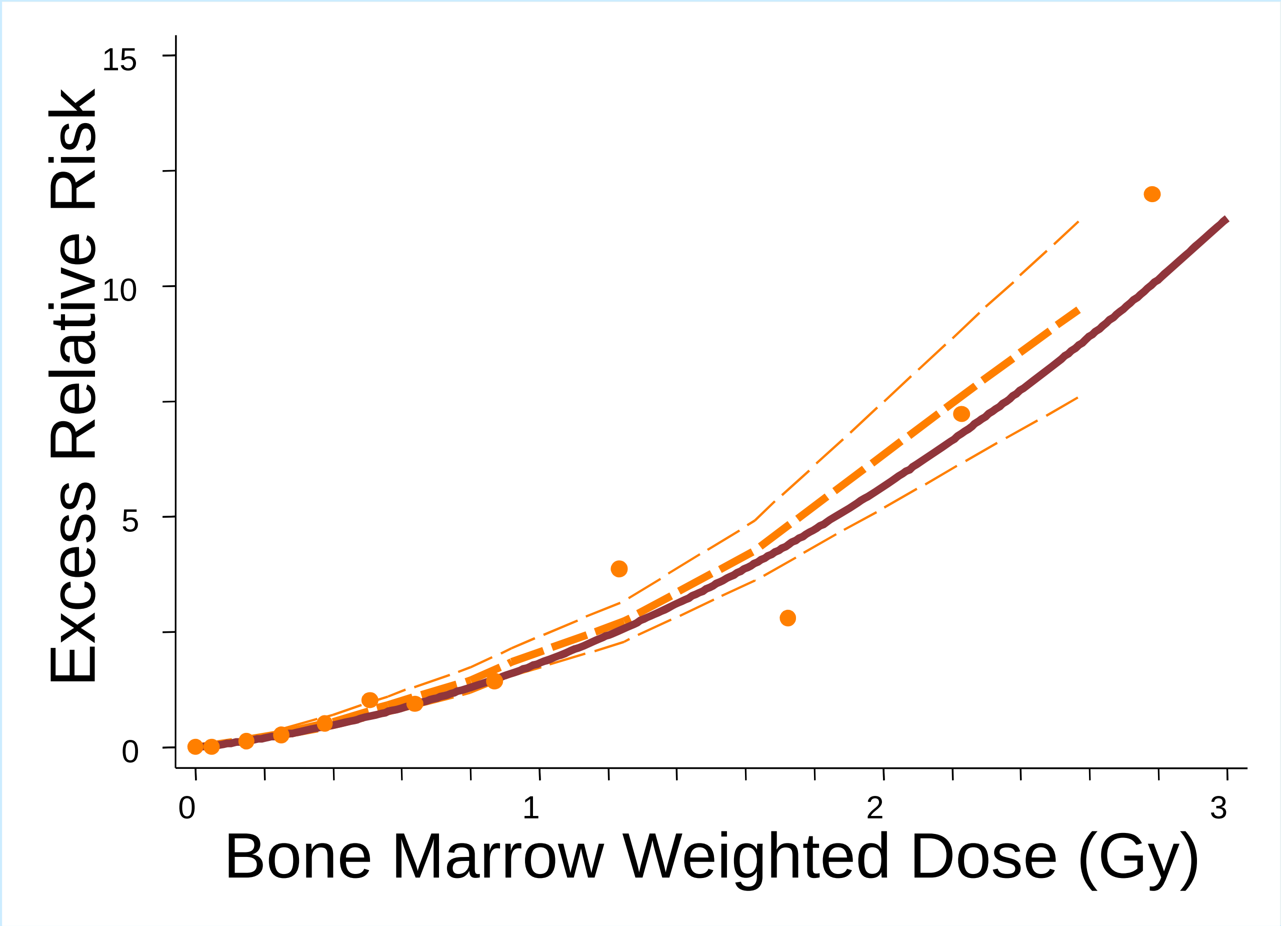
(Ozasa, Shimizu, et al, Unpublished, 2010)

LSS Mortality Estimates of Relative Risk at 1 Gy for Various Dose Ranges (0 to Plotted Dose)



(Ozasa et al, Unpublished, 2010)

LSS Leukemia Dose Response



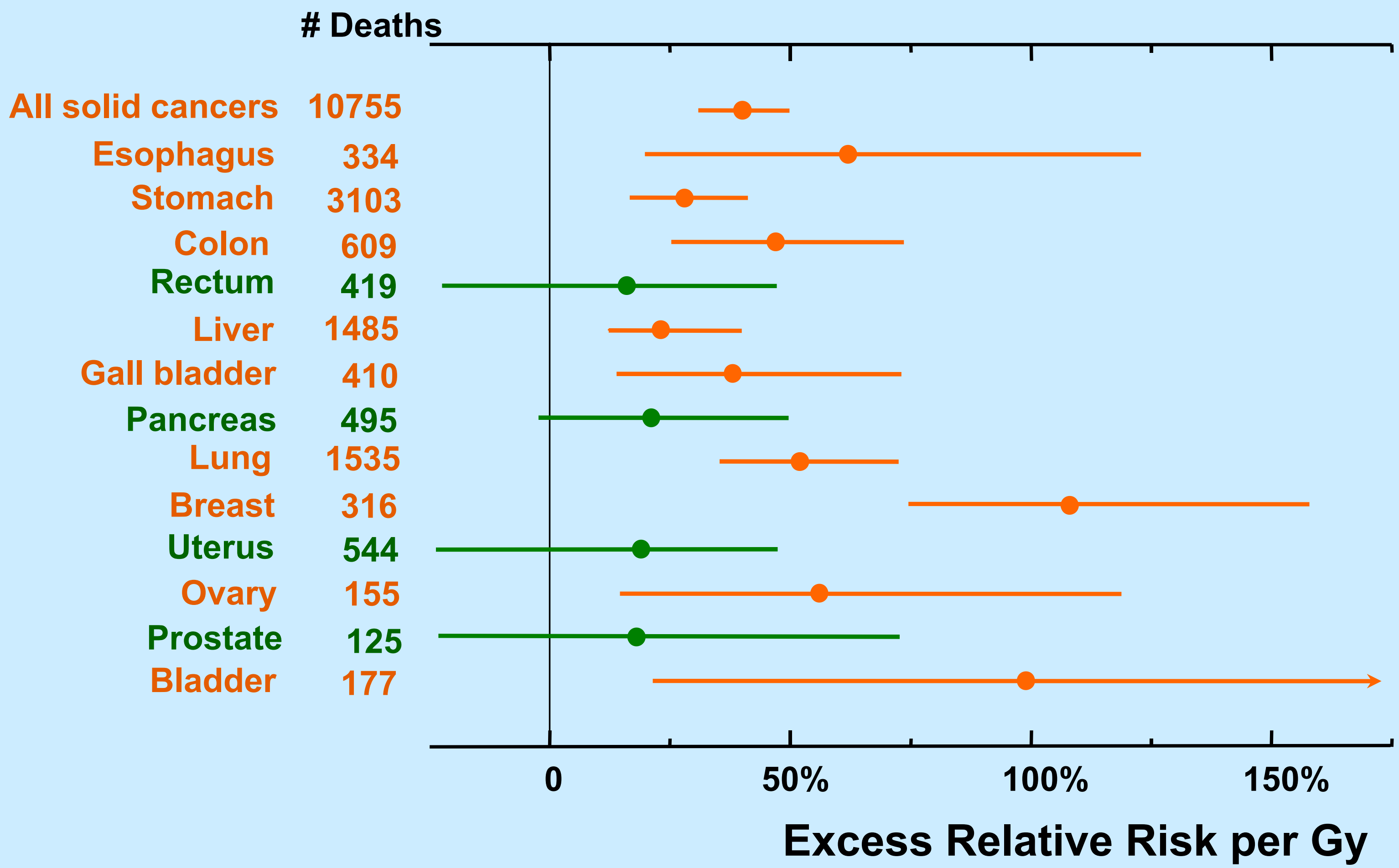
Linear-quadratic fits better than Linear model.

Dose-threshold estimate: 80 mGy (95% CI: 30, 190 mGy)

(Hsu et al, Unpublished, 2010)

Which organs are at risk of radiation-related cancer?

Excess Relative Risk (ERR) per Gy for Various Solid Cancers (LSS Mortality, 1950-2003)

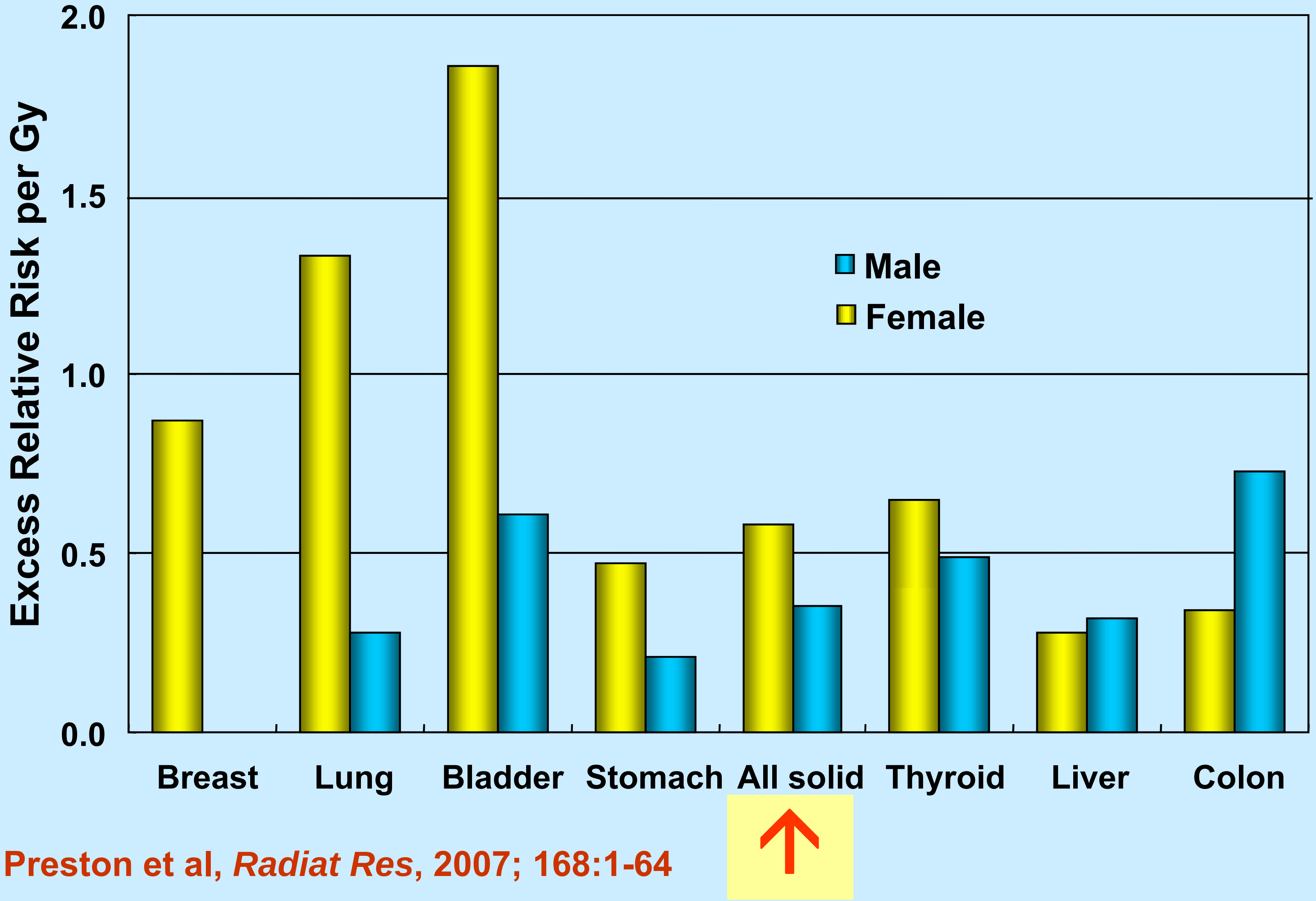


Note; Estimates standardized to age 70 after exposure at age 30
and averaged, where appropriate, over sex.

(Ozasa, Shimizu et al, Unpublished, 2010)

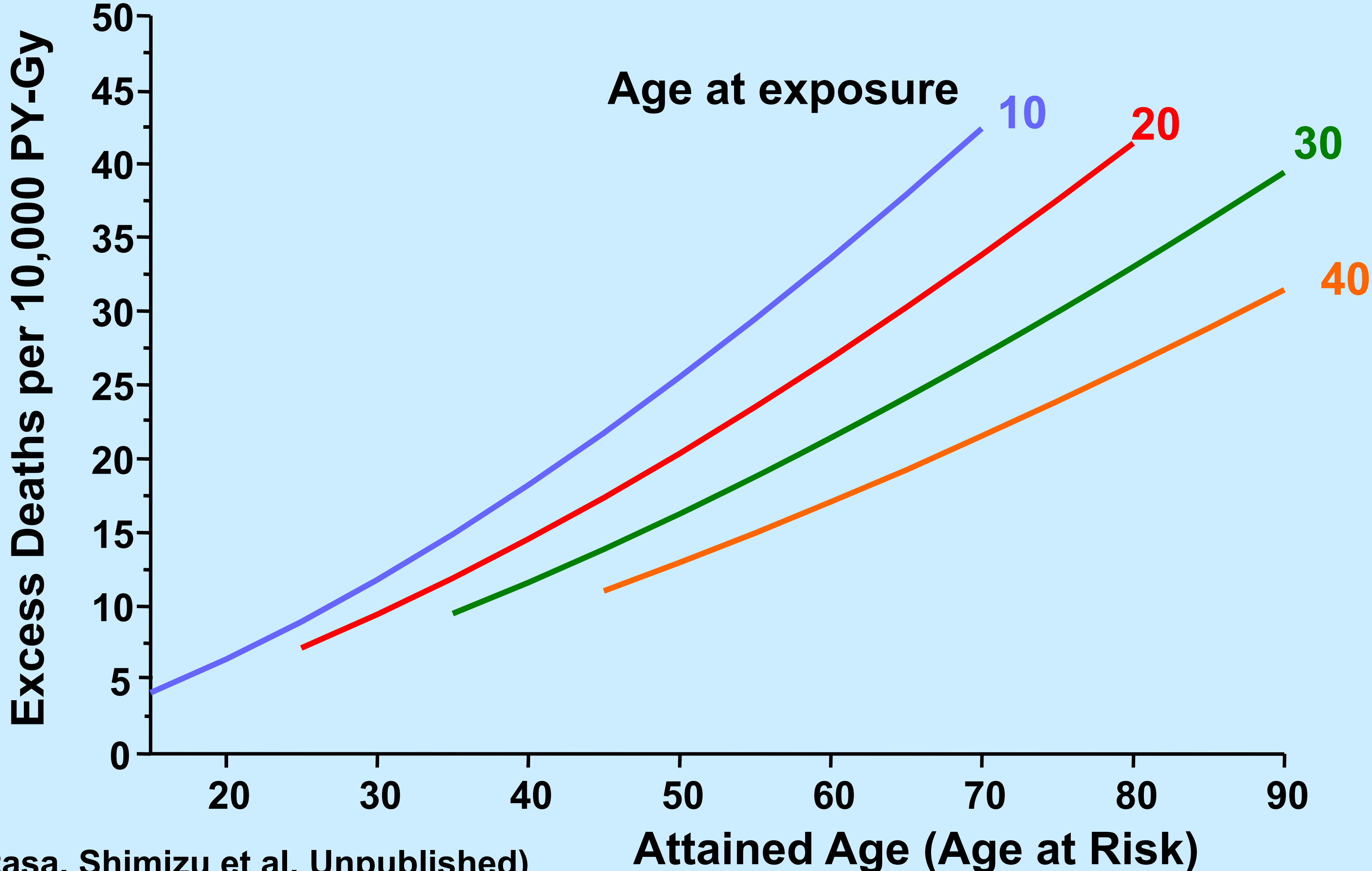
Do certain subgroups have greater risk of cancer from radiation exposure?

LSS Cancer Incidence: Site-specific Excess Relative Risk (ERR) Estimates by Gender



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

Excess Rates of Solid Cancer Mortality by Age at Exposure and Attained Age



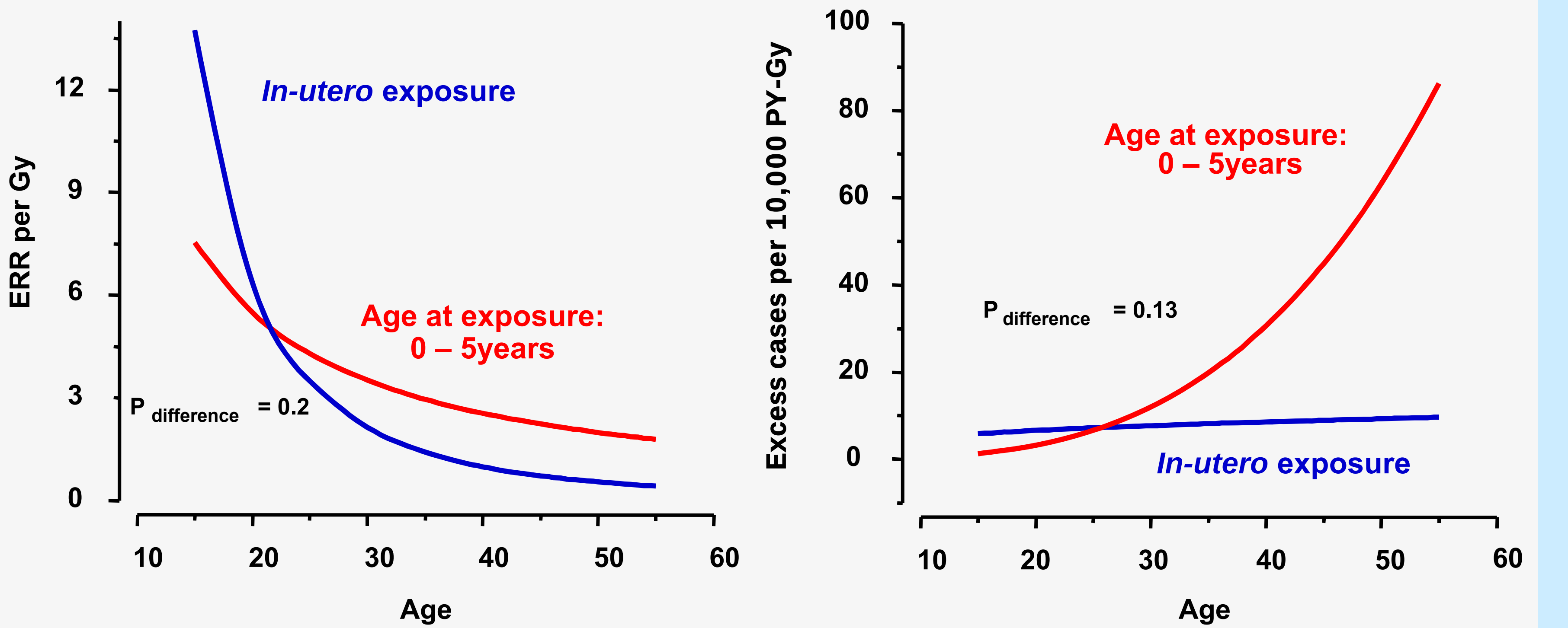
(Ozasa, Shimizu et al, Unpublished)

How great is the cancer risk following *in utero* exposure?

Very large risks from *in utero* exposure have been predicted

- Based mostly on the large Stewart-Kneale case-control study of fetal radiation exposure and childhood cancer, it was predicted that an additional 6% of persons would die from cancer after 1 Gy of *in utero* radiation.
  (Doll & Wakeford, *Br J Radiol*, 70:130-39, 1997)
- 6% lifetime cancer mortality risk per Gy is:
  - ~3 times as large as the corresponding estimated A-bomb risk after exposure at age 10, or
  - ~6 times as large as estimated risk after exposure at age 30. (Preston et al, *Radiat Res*, 160:381-407, 2003)

Solid Cancer Risk Patterns for *In Utero* and Childhood Exposure, A-bomb Survivors



In utero ERR/Gy= 1.0 (95%CI: 0.2, 2.3)

(Preston et al, *J Natl Cancer Inst*, 2008; 100:428-36)

Leukemia after *In Utero* or Childhood A-bomb Exposure

Childhood exposure, ages 0-5

- 39 cases, 22 with estimated bone marrow doses >500 mGy
- Steep dose response (ERR/Gy = 15, 95%CI: 6, 36)

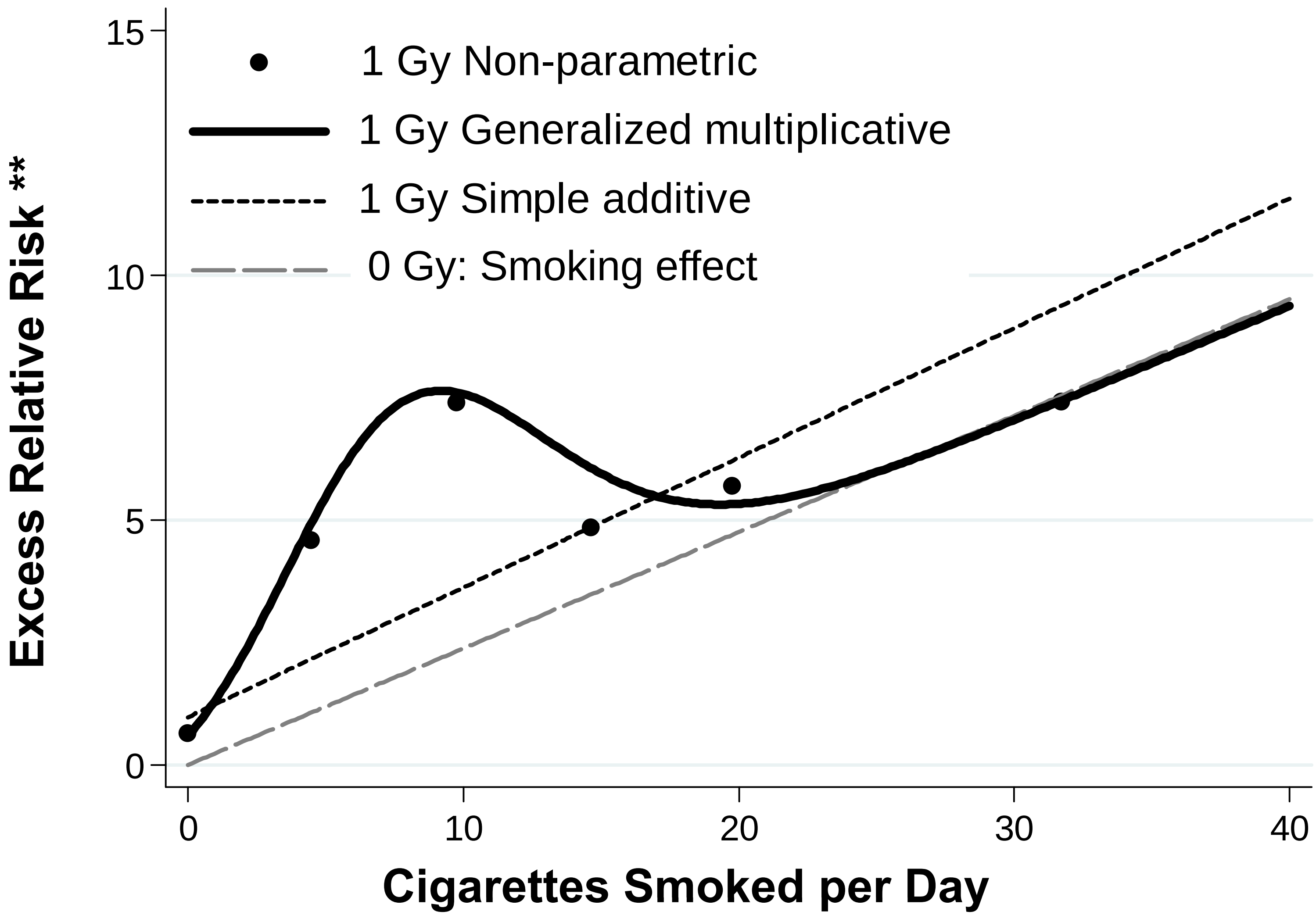
In Utero Exposure

- 4 cases, all with estimated bone marrow doses <40 mGy
- No dose response (ERR/Gy = 0, 95%CI: <0, 7)

(Kasagi, Ozasa, et al, Unpublished, 2010)

Is the magnitude of radiation risk altered by other environmental exposures?

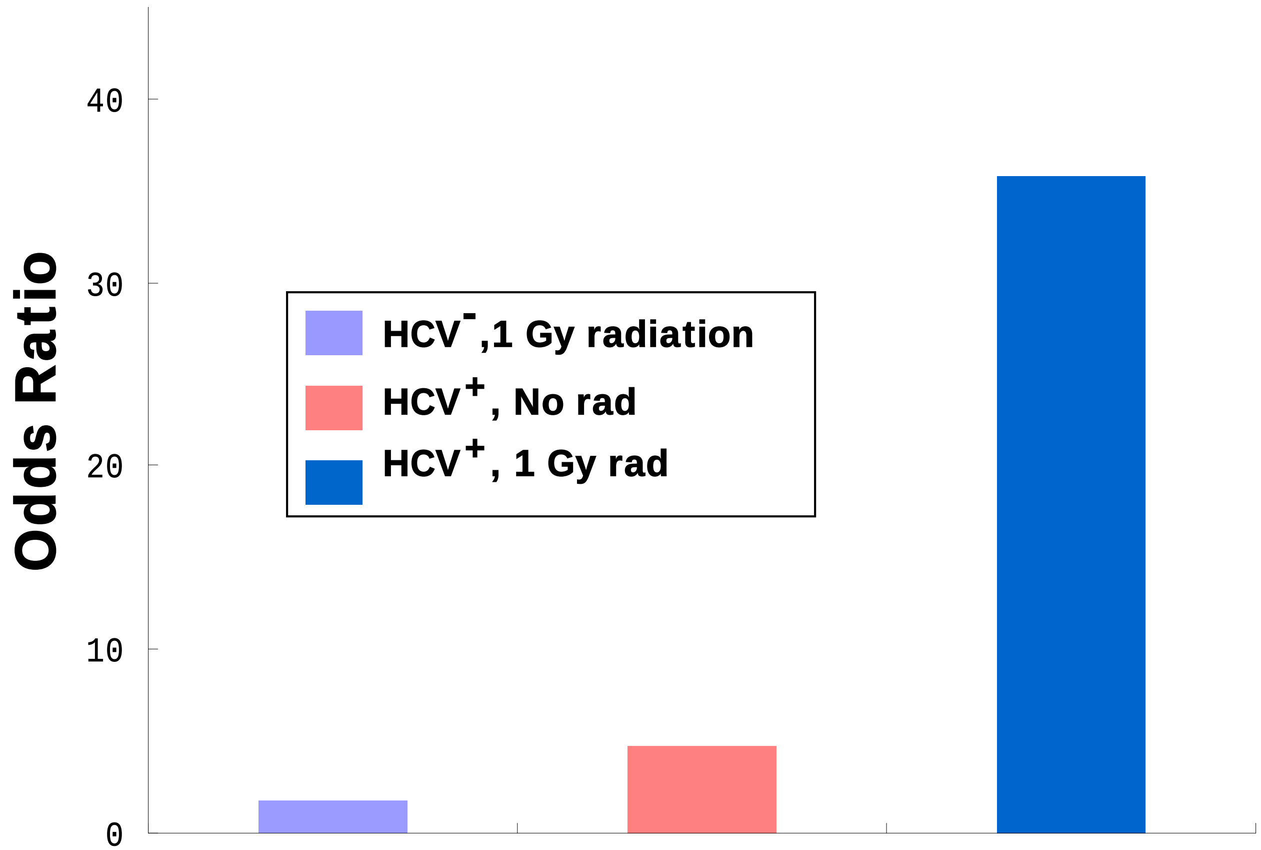
Models of Lung Cancer Risk: Radiation Dose and Smoking



** Gender-averaged excess risk relative to unexposed never-smokers

(Adapted from: Furukawa et al, *Radiat Res*, 174:72-82, 2010)

Liver Cancer Risk from Hepatitis C Virus (HCV) and Radiation

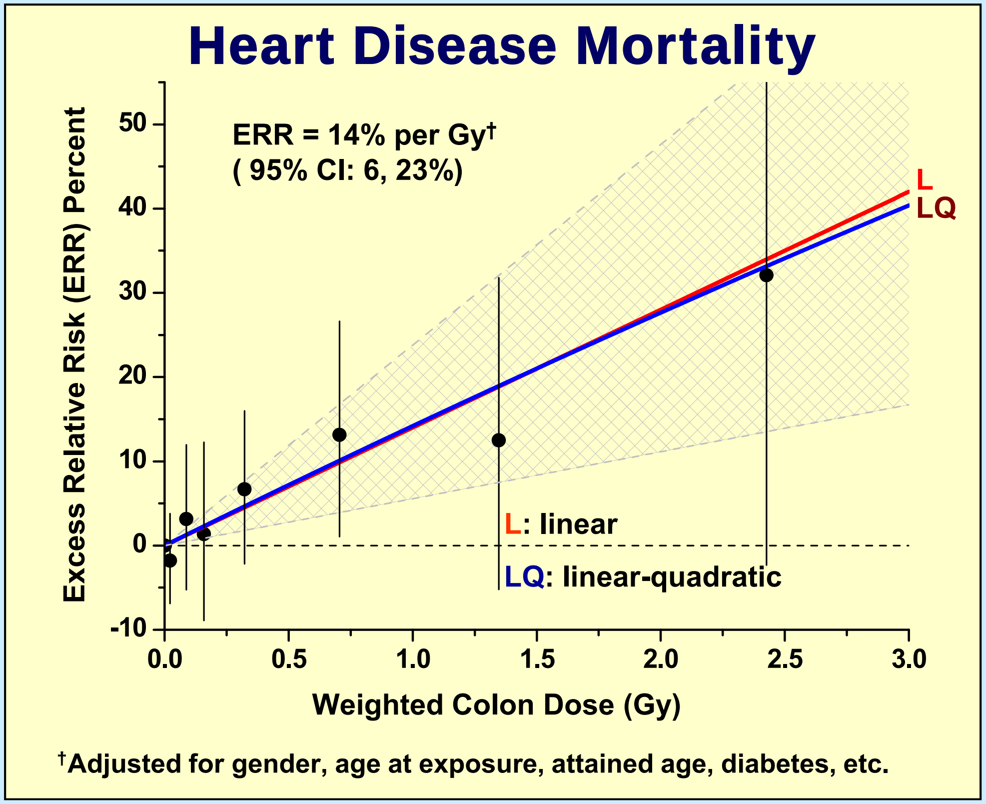


(Sharp et al, *Int J Cancer*, 103:531-37, 2003)

Are there noncancer risks from radiation exposure at low doses?

Radiation and Heart Disease Mortality

- **Clear evidence of heart disease risk at doses below 4-5 Gy**
- **Dose-response for heart disease mortality appears linear, but there is considerable uncertainty below about 0.5 Gy.**



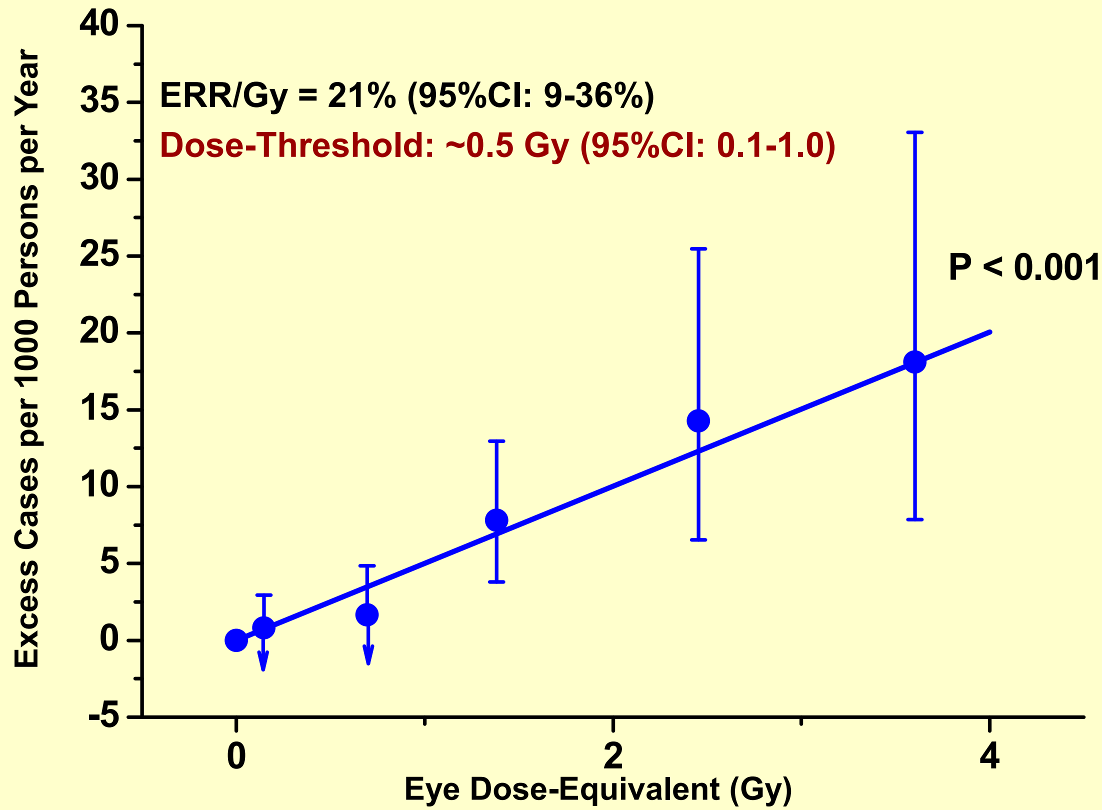
(Shimizu et al, *Br Med J*, 340:193, 2010)

Corroborative Clinical Evidence for Radiation Effects

- ↑ Circulatory system inflammation – numerous markers of inflammation are ↑
- Blood lipids – ↑ total cholesterol, triglycerides; ↓ HDL cholesterol
- Cardiovascular risk factors – ↑ blood pressure and calcification of arteries

Cataract-Surgery Incidence, 1986-2005

• Radiation protection agencies had long believed there was no risk for vision-impairing cataracts below about 5 Gy and set safety standards accordingly. More protective safety standards for the eye are now being considered.



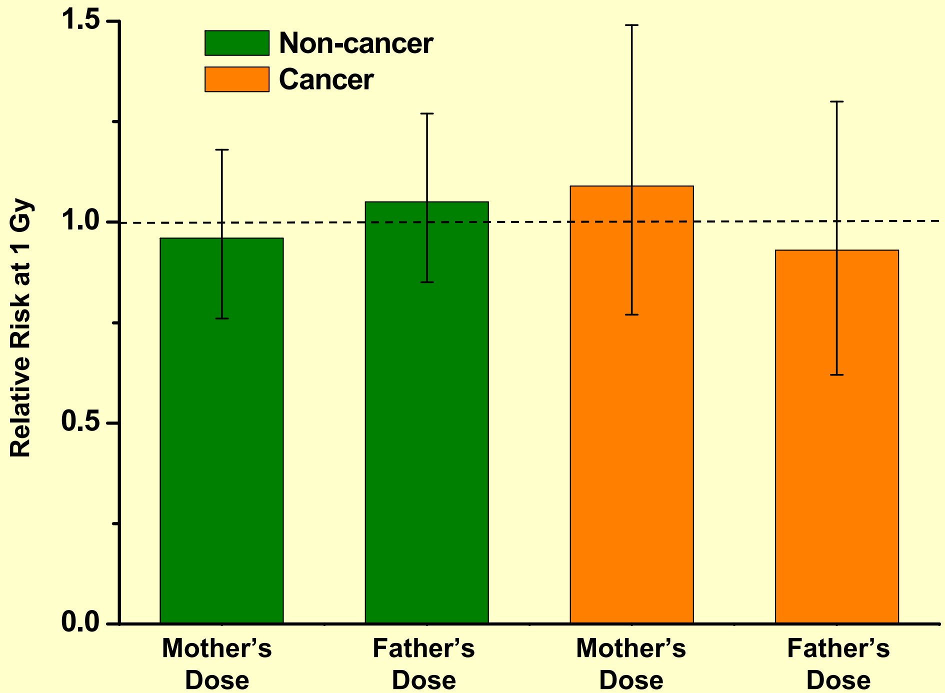
(Adjusted for city, gender, age at exposure, attained age and diabetes)

(Nakashima, Neriishi et al, Unpublished, 2010)

How large is the risk to offspring from parental gonadal irradiation?

Relative Risk for Non-cancer and Cancer Mortality in 41,000 Offspring of Atomic Bomb Survivors, 1946-2003

- To date, the frequencies of cancer and other diseases in the offspring are unrelated to parental radiation dose, but 20-30 more years of follow-up are needed to provide definitive evidence.



*Adjusted for potential confounding factors: Age, gender, city, birth year, parent's ages at exposure and childbirth order

(Suyama, et al, Unpublished, 2009)

Thank You