Epidemiologic Data on Low-Dose Cancer Risk

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Low, but Significant, Exposures Have Become Very Common

- About 25 million patients in the US received CT exams in 2007
- Sodickson study – large representative sample of 31,000 U.S. patients receiving CT exams in 2007
- The distribution of cumulative effective doses from CT over the past 20 years showed:
  - 15% (~3.8 million) with ≥ 100 mSv
  - 4% (~1 million) with ≥ 250 mSv

(Sodickson et al, *Radiol*, 251:175, 2009)

Are the excess risks of cancer at low doses proportional to those seen at high doses?

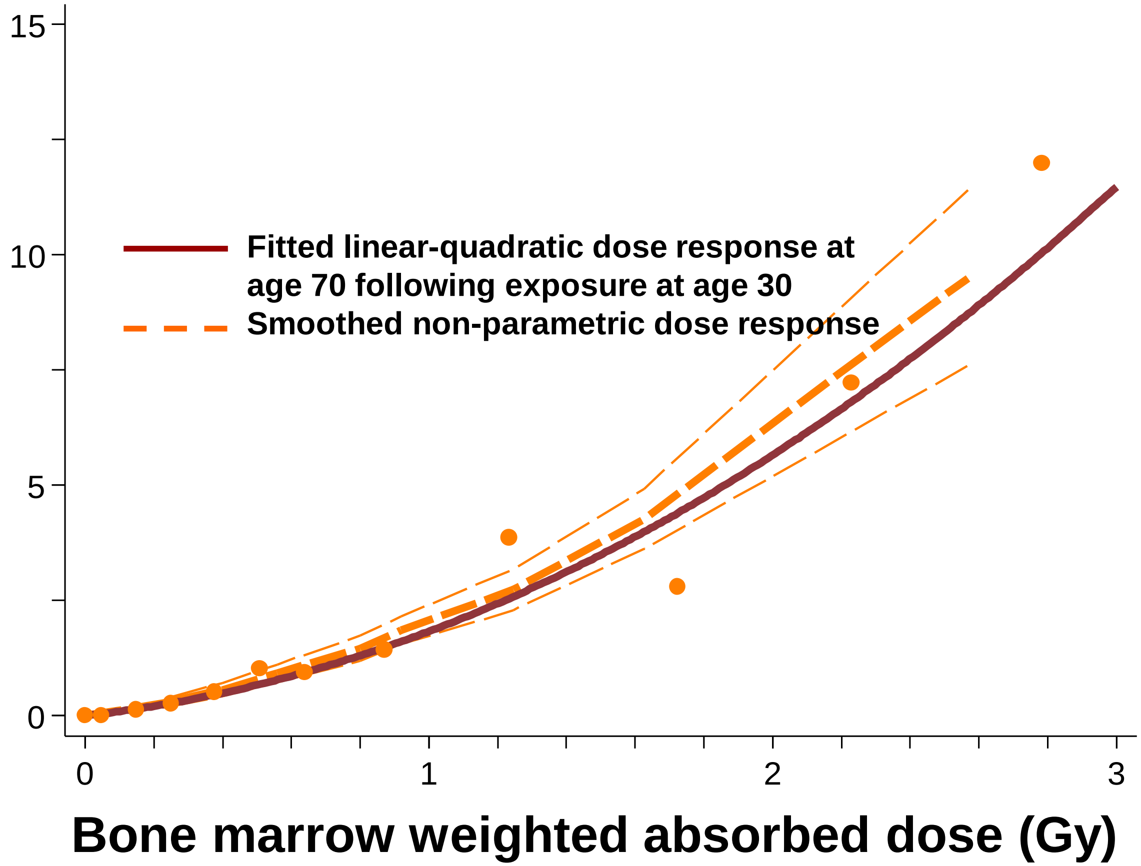
– i.e.,

Is there dose-response linearity?

higher/lower than linear risk at low doses?

or a dose threshold?

A-bomb Leukemia Dose Response

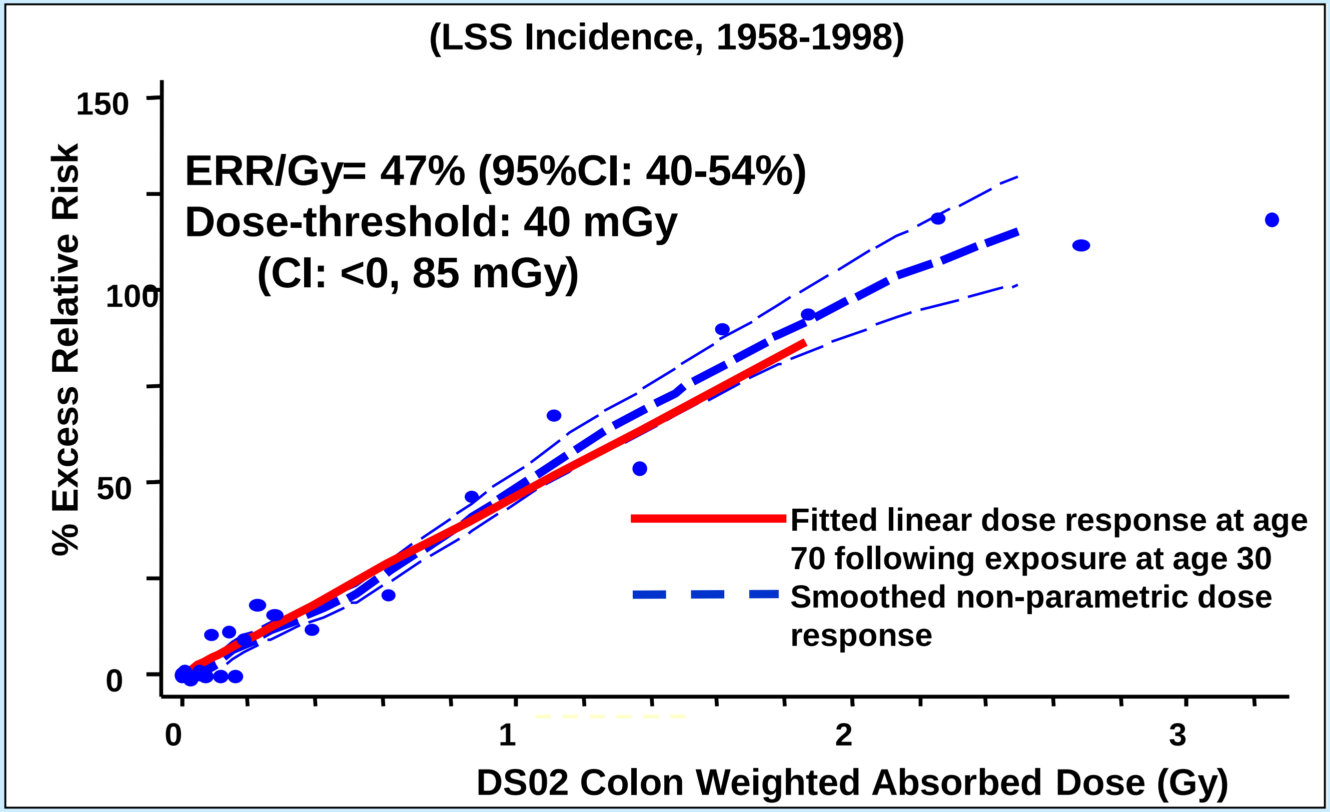


Dose-effect Threshold: 80 mGy (95% CI: 30, 190 mGy)

(Hsu et al, Submitted, 2011)

A-bomb dose response: Solid-cancer incidence

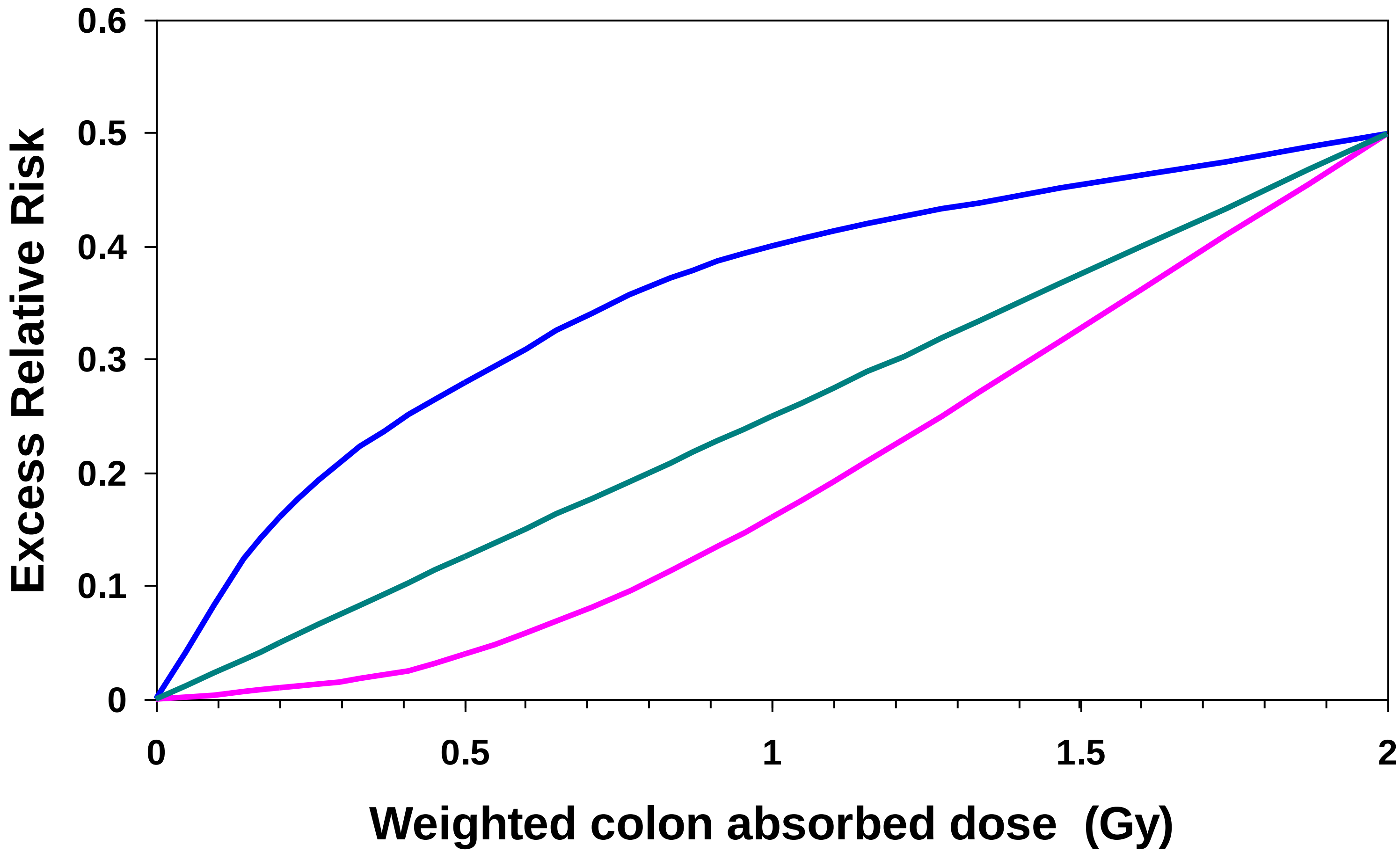
- No evidence of non-linearity in the dose response
- Significant dose response on 0-150 mGy
- Low dose-range slope consistent with full range



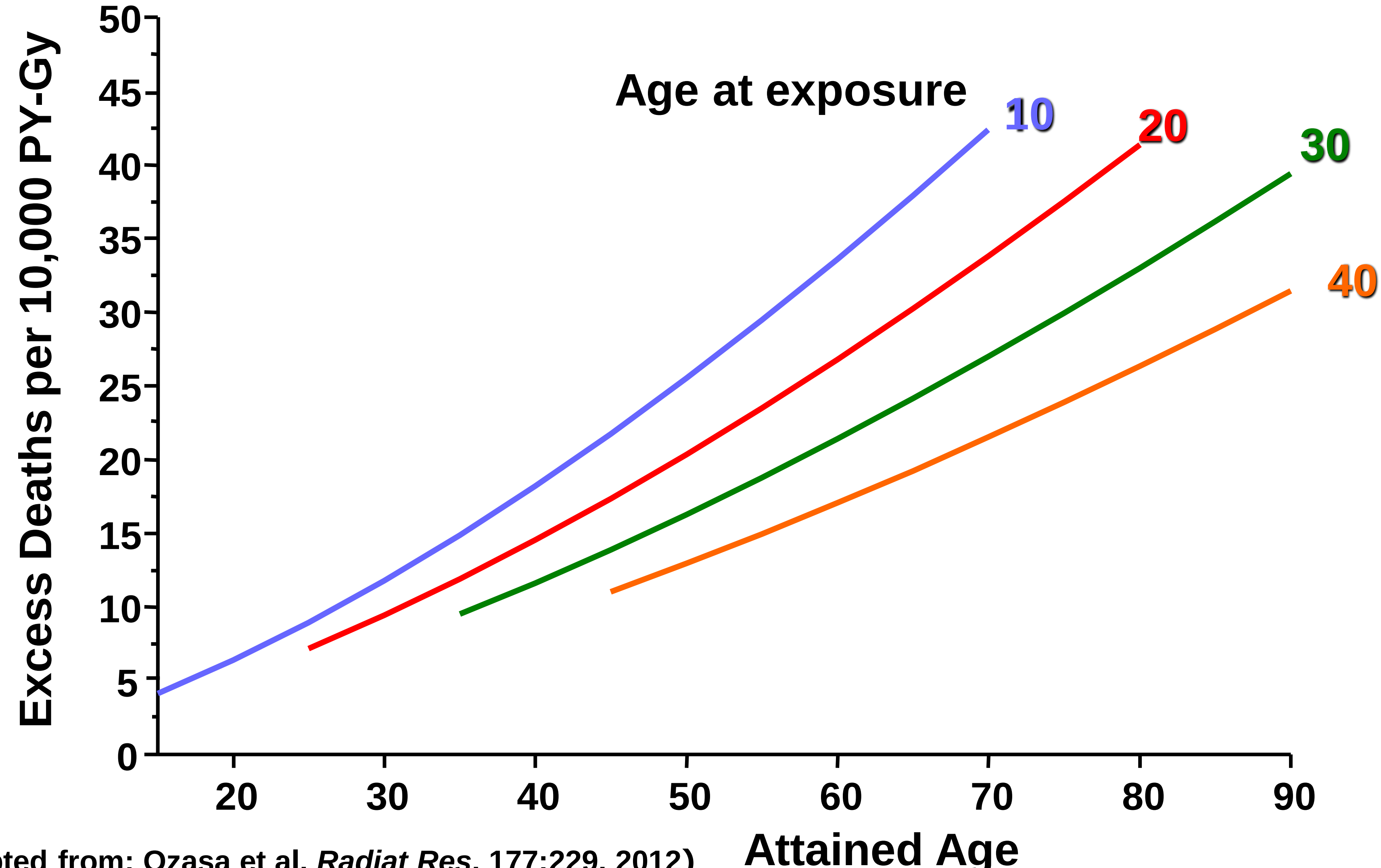
(Preston et al: Radiat Res 168:1-64, 2007)

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

Variations in Radiation Sensitivity and Shape of the Dose Response (Hypothetical Data)



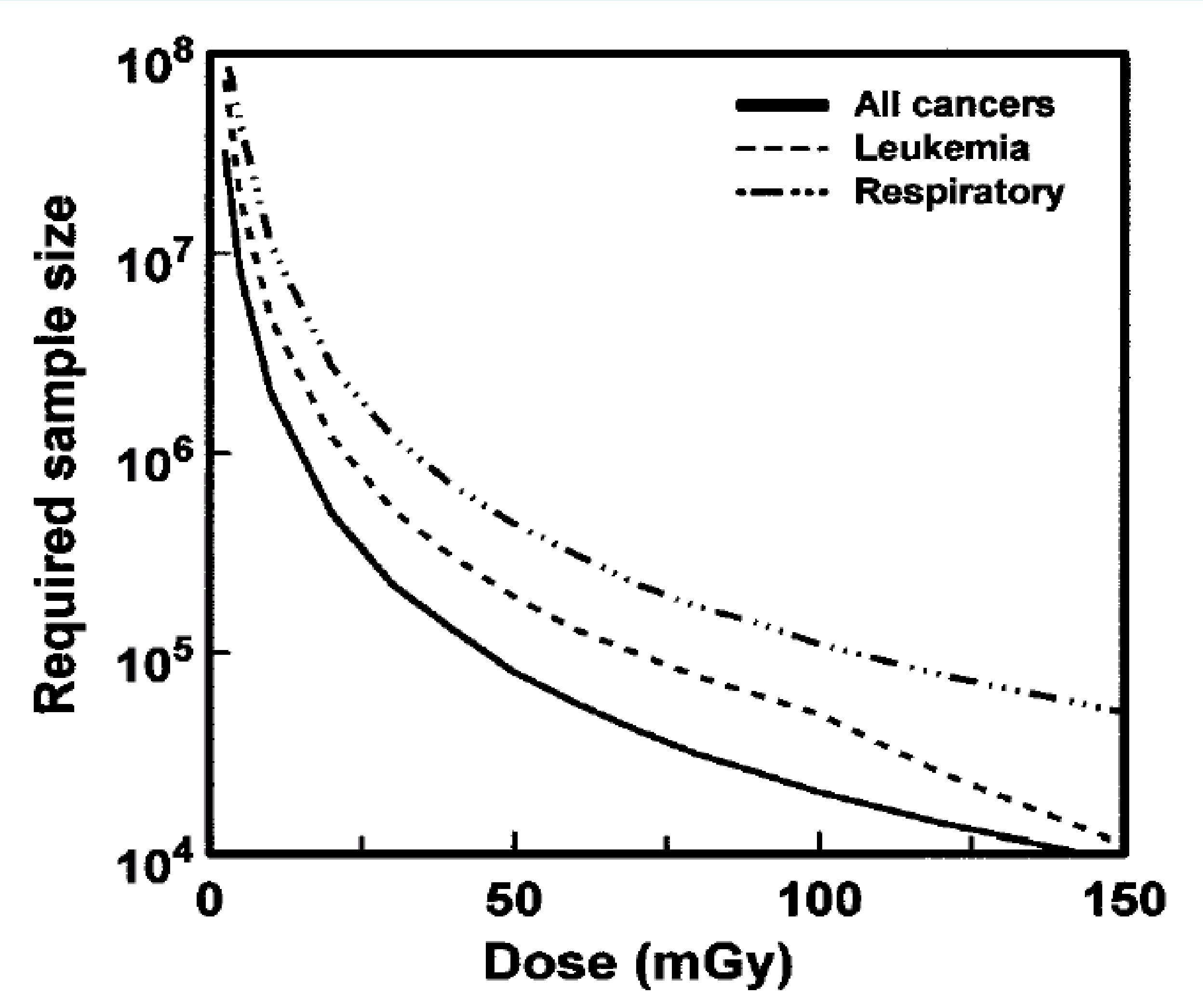
Excess Rates of Solid Cancer Mortality by Age at Exposure and Attained Age, A-bomb



(Adapted from: Ozasa et al, *Radiat Res*, 177:229, 2012)

Special Issues with Low-Dose Epidemiologic Studies

Sample Size Needed to Study Various Doses, Lifetime Risk



(Brenner et al, PNAS 100:13762, 2003)

Special Problems for a Low-Dose Study with Low Statistical Power

- **Low statistical power—null result is very likely. If the "true" effect is very small, not much more than ~5% of the time will the a risk estimate be "positive" (i.e., statistically significant), so false negative results will be common.**

  Corollaries:

  - **The risk estimates for highlighted *positive* results are likely to be biased upward (Land, *Science*, 1980)**
  - **The impact of unmeasured confounding variables is often greater in a low-dose study, because the magnitude of confounding may approach or exceed the magnitude of the dose effect.**
    - **Confounder bias can be in either direction, i.e., the uncorrected risk estimate can either *exaggerate* or *mask* the true degree of association.**
    - **However, possible confounder variable must be correlated with both exposure and the health outcome to be a confounder.**

What do the epidemiologic data show regarding risk from low, fractionated or protracted exposures?

Data from the Largest Studies of Solid-Cancer and Leukemia Risk

- To avoid choosing only a small selection of studies that support a particular (positive or negative) viewpoint, an essentially unbiased inclusion method was chosen:

  To assemble all the studies that met a chosen criterion of number of study cancers. Criteria:

  - ≥400 solid cancers
  - ≥30 leukemias

Expectations for the Tabulation of Studies with Low, Protracted or Fractionated Exposures

- **Publication bias?**
  - Nearly all major cohort studies publish results for total solid cancers and leukemia
  - Most large case-control studies also are published
- **To the degree there is an association, substantially more than 5% will be positive (i.e., statistically significant)**

Minimum Requirements for Study Inclusion

- Must have a risk estimate and have low, highly fractionated or protracted exposures
- Preferable that the risk estimate be based on the dose-response and that the risk per unit dose be reported
- However, to reduce study selection bias, studies also were included even if they:
  - lacked a dose-response based estimate,
  - were studies reporting only Standardized Incidence or Mortality Ratios (SIR or SMR),
  - were case-control studies (odds ratios)

All Solid Cancers:

Summary results of the largest studies (≥400 cancer cases) with low, fractionated or protracted exposures

Total Solid Cancers after Low, Protracted or Fractionated Exposures: Statistically Significant ("Positive") Associations

Study	Mean Dose (mSv)	No. of Cancers	RR at 1 Sv (95% CI)
Japanese A-bomb incidence (Preston '07)	230	17,448	1.47 (1.40-1.54)
UK nuclear workers (Muirhead '09)	25	10,855	1.3 (1.04-1.5)
Techa River residents (Eidemuller '10)	30	2064	1.9 (1.4, 2.5)
Mayak workers (Shilnikova '03)	810	1062	1.08 (1.03-1.14)
Chinese medical x-ray workers (Wang '02)	~240	836	1.8 (~1.5-2.1)
^{131}I for hyperthyroidism (Holm '91)	~60	789	3.0 (1.7-4.4) [A]
Semipalatinsk fallout (Bauer '05)	634	532	1.8 (1.5-2.3)

[A] Based on Standardized Incidence Ratio (SIR)

Total Solid Cancers after Low, Protracted or Fractionated Exposures: Null ("Negative") Results

Study	Mean Dose (mSv)	No. of Cancers	RR at 1 Sv (95% CI)
15-country worker study (Cardis '07)	19.4	5024	1.6 (0.9-2.4)[A]
Diagnostic ^{131}I (Holm '91) [C]	~8	3746	1.01 (0.98-1.04)[B]
Hanford workers (Wing '05) [C]	27.9	2265	1.3 (0.7-2.0)
French nuclear workers (Metz-Flamant '11)	21.5	2035	1.5 (0.5-2.5)
^{131}I for hyperthyroidism (Ron '98)	~40	1597	1.0 (1.0-1.1)[B]
Chernobyl clean-up workers (Ivanov '07)	215	1370	1.3 (0.6-2.2)
High-background area, Kerala (Nair '09)	161	1349	0.9 (0.4-1.5)
Canadian medical workers (Zielinski '09)	3.8	1205	0.8 (0.7-0.8)[B]
High-background area, China (Tao '12)	63	941	4.0 (<0.1-49)
Rocketdyne workers (Boice '11)	13.5	651	0.8 (0.3-2.7)
Multiple fluoroscopic exams (Davis '89)	~250	429	0.4 (0.3-0.7)

[A] Excluding Canada due to dosimetry problem. [B] SIR or SMR value presented, not RR at 1 Sv. [C] Total cancers.

DDREF: Crude Meta-Analysis for Solid Cancers

Type of Analysis *	RR at 1 Sv (95% Confidence Interval)
Fixed effects analysis	1.15 (1.10, 1.20)
Random effects analysis	1.37 (1.11, 1.68)

* Based on the 15 studies with estimated mean doses >10 mSv

Leukemia:

Summary results of the largest studies (≥30 leukemia cases) with low, protracted or fractionated exposures

Statistically Significant Leukemia Studies: Environmental or Occupational Protracted/Fractionated or Low-Dose Radiation Exposure

	Mean Dose (mGy)	No. of Leukemias	RR at 1 Gy (95% CI)
Japanese A-bomb mortality (Ozasa ’12)	230	318	5.3 (4.1-6.8)
Chernobyl fallout regions (Davis ’06)	~6.3	421	33 (10-85)
UK nuclear workers (Muirhead ’09)	24.9	234	2.8 (1.2-5.4)
Techa River cohort (Krestinina ’10)	300	70	5.9 (2.6-15)
Mayak workers (Shilnikova ’03)	810	66	2.0 (1.5-3.1)
Savannah River workers (Richardson ’07)	43.7	62	8.7 (2.4-21)
Chinese medical x-ray workers (Wang ’02)	244	44	5.8 (2.1-12)
US radiologists (Matanoski ’87)	~3000	33	1.7 (1.2-2.3)[A]

[A] SMR, not at 1 Gy.

Nonsignificant Leukemia Studies: Protracted/Fractionated Occupational or Environmental Radiation Exposure

	Mean Dose (mGy)	Number of Leukemias	RR at 1 Gy (95% CI)
Workers, 4 US nuclear plants (Schubauer-Berigan '07)	30.6	206	3.6 (<1-11)
15-country worker study (Cardis '07)	19.4	196	2.9 (<1-9.5)
Chernobyl clean-up workers, Russia (Ivanov '07)	107	71	5.4 (<1-17)
Idaho National Lab (Daniels '11)	13.1	52	6.4 (<1-25)
Los Alamos National Lab (Wiggs '94)	≈16	44	~1
Portsmouth Naval Shipyard workers (Yiin '05)	20	34	12 (<1-40)
Rocketdyne workers (Boice '11)	13.5	33	1.1 (0.8-1.5)
Chernobyl clean-up workers, Ukraine (Romanenko '08)	76.4	32	3.7 (<1-15)

Statistically Significant Leukemia Studies: Low-Dose or Protracted/Fractionated Medical Radiation Exposure

	Mean Dose (mGy) or [subgroup]	No. of Leukemias	Relative Risk: RR (95% CI)
Dx x-ray, childhood ALL (Infante-Rivard '03)	[≥2 x-rays]	701	1.5 (1.1-2.0)[A]
Diagnostic ^{131}I (Holm '89)	~8	119	1.3 (1.1-1.6)[B]
Diagnostic x-ray (Gibson '72)	[≥20 x-rays]	69	1.5 (1.0-2.4)[A]
Diagnostic x-ray (Preston-Martin '89)	[>20 mGy]	55	2.4 (1.1-5.1)[A]
Arthrosis/Spondylitis RT (Damber '95)	[>500 mGy]	41	1.5 (1.1-2.0)[B]
^{226}Ra for uterine bleeding (Inskip '90)	~650	34	2.9 (1.8-4.2)[C]

[A] Odds ratio, not at 1 Gy. [B] SMR or SIR, not at 1 Gy. [C] RR at 1 Gy.

Statistically Nonsignificant Leukemia Studies, Low-Dose or Protracted/Fractionated Medical Radiation Exposure

	Mean Dose (mGy) or [subgroup]	# Leukem-ias	Relative Risk: RR (95% CI)
Dx x-ray & childhood ALL (Shu ’02)	[≥3 x-rays]	1842	1.2 (1.0-1.6)[A]
Dx x-ray & childhood leukemia (Meinert ’99)	[≥4 x-rays]	1145	1.0 (0.7-1.6)[A]
Dx x-ray & adult AML (Pogoda ’11)	[>20 mGy]	412	1.6 (0.8-3.2)[A]
Dx x-ray & adult leukemia (Boice ’91)	?	316	1.4 (0.9-2.2)[A]
Dx x-ray & adult leukemia (Yuasa ’97)	?	247	0.8 (0.5-1.2)[A]
^{131}I for hyperthyroidism (Ron ’96)	42	82	<1 [B]
^{131}I for hyperthyroidism (Holm ’91)	~60	34	0.9 (0.4-1.5)[B]

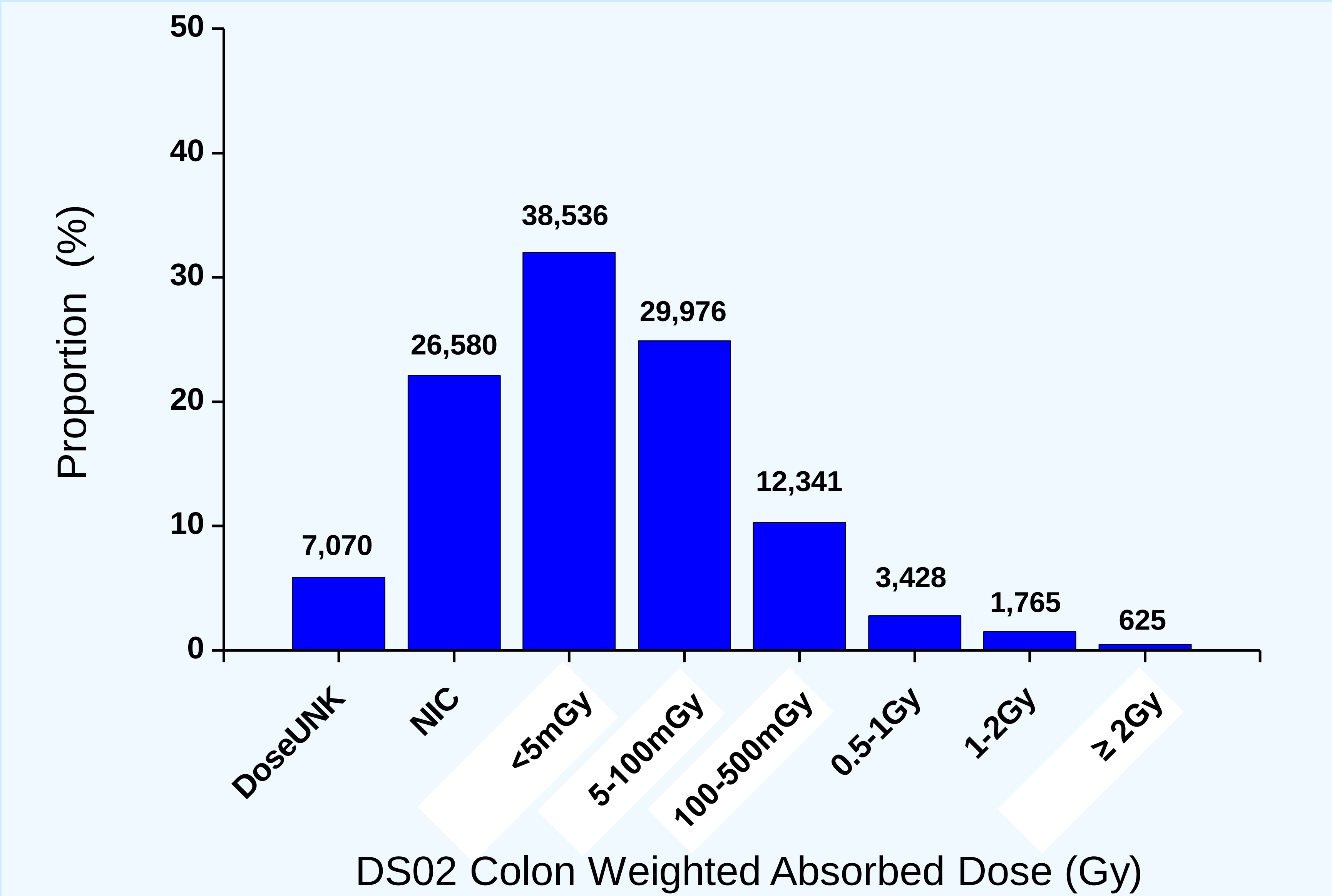
[A] Odds ratio, not at 1 Gy. [B] SMR or SIR, not at 1 Gy.

Summary

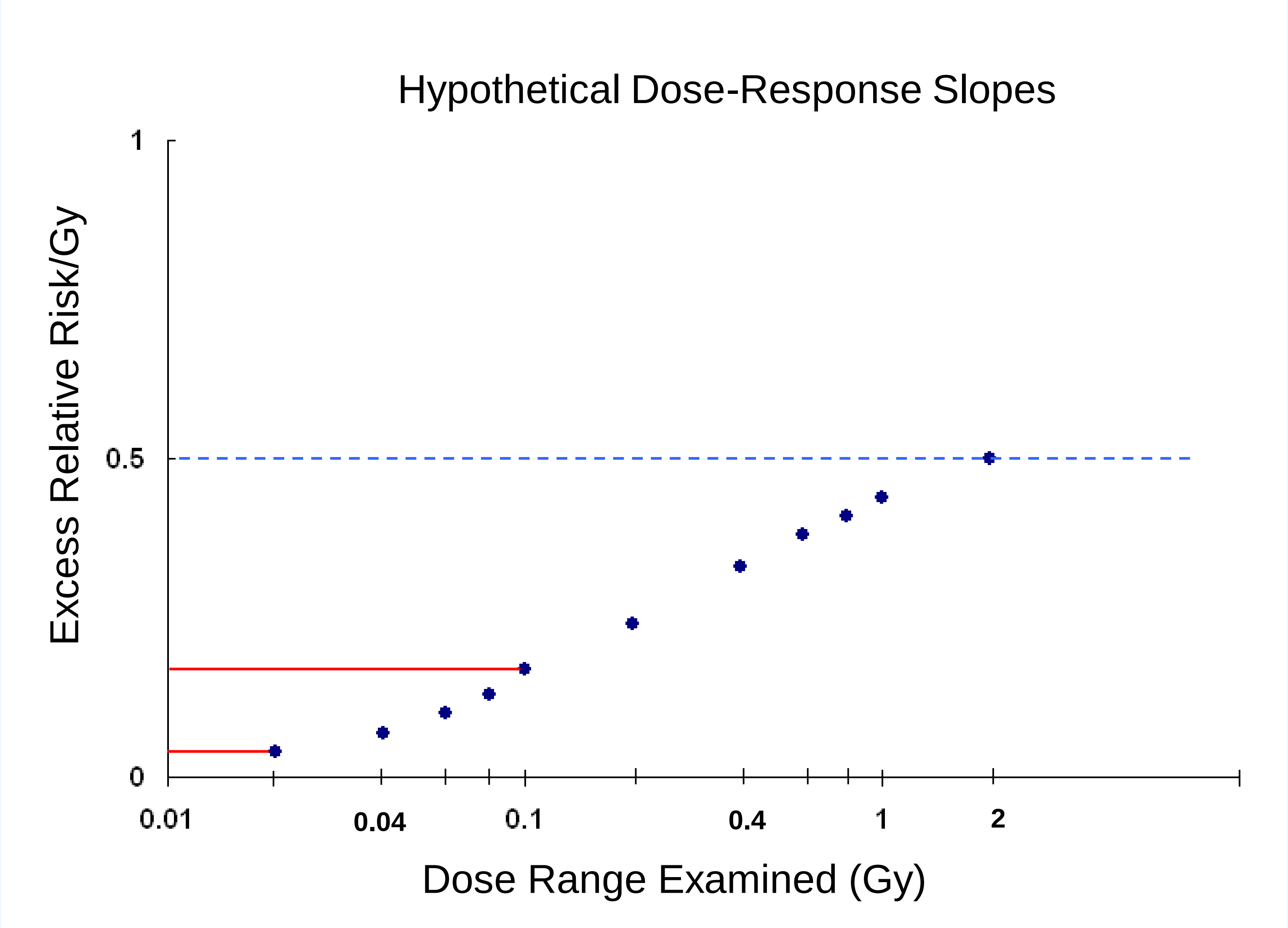
- A-bomb data show upward curvature for leukemia but little or none for solid cancers, and suggest risk at quite low doses.
- Variations in radiation-cancer susceptibility might partly account for approximate dose-response linearity.
- Certain methodological problems can be exacerbated for low-dose studies.
- Sought to have broad, unbiased look at magnitude of risk after low, fractionated or protracted (LFP) exposures
- Found evidence of solid cancer risk from LFP exposures. But too much heterogeneity to have good estimate of DDREF.
- Clear evidence of leukemia risk after LFP exposures, but can't quantify


Thank you for your attention!

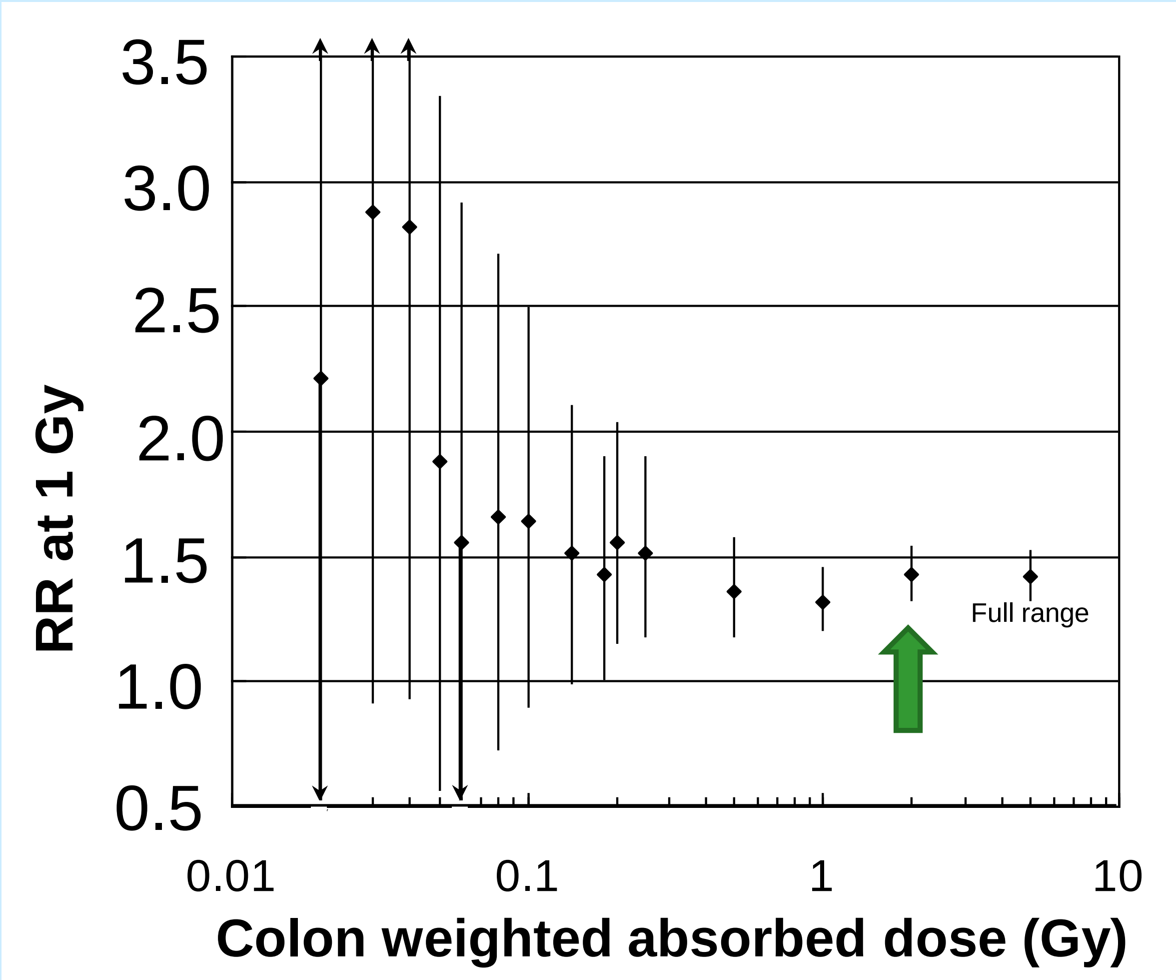
Life Span Study (LSS) Cohort
(120,321 people)



“Expected” Dose-Response Slopes for Truncated Dose Ranges



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

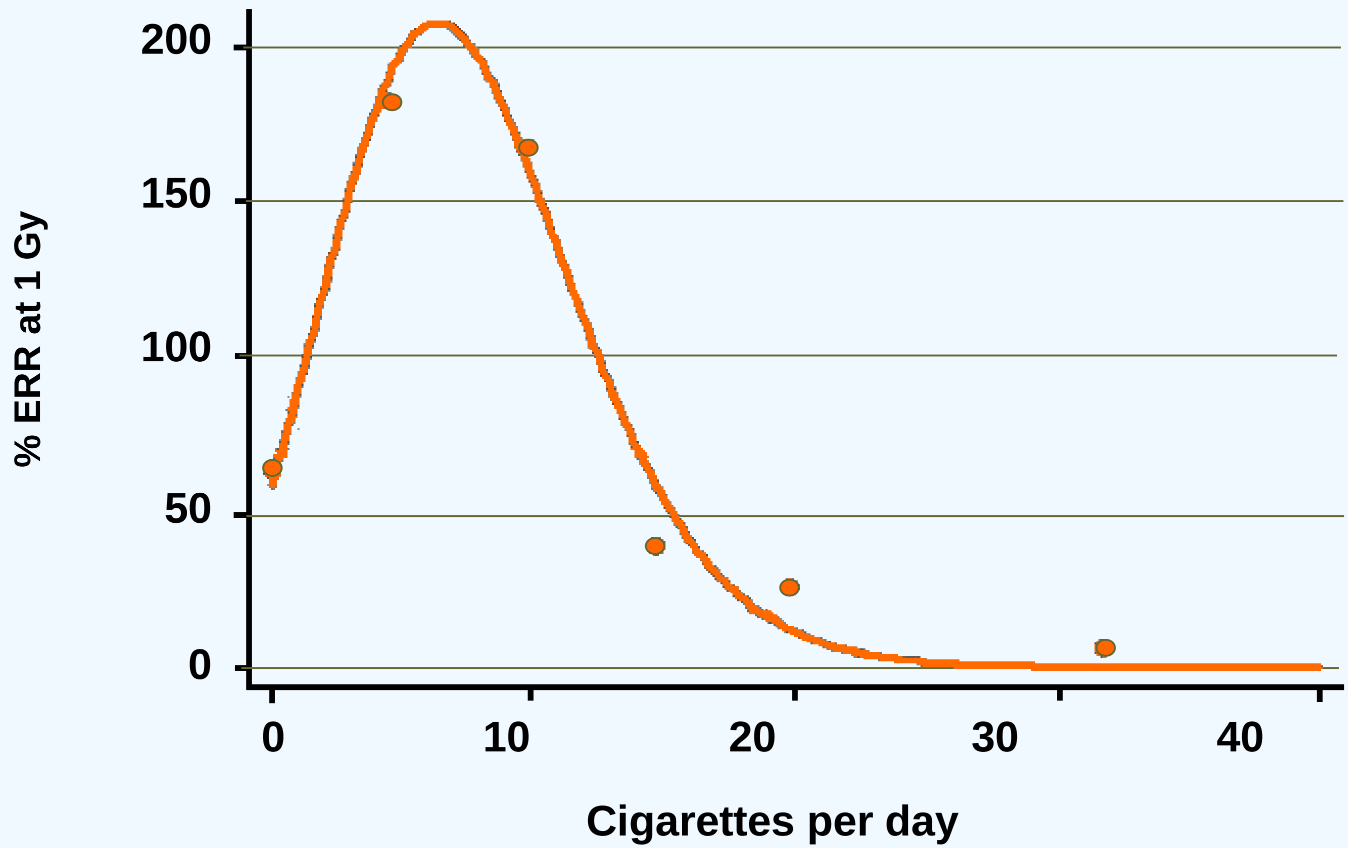


(Ozasa et al, *Radiat Res*, 177:229-43, 2012)

Special Problems for Individual Low-Dose Studies with Low Statistical Power

- **Low statistical power—null result is very likely. If the "true" effect is very small, not much more than ~5% of the time will the a risk estimate be "positive" (i.e., statistically significant), so false negative results will be common.**
  Corollaries:
  - **With low statistical power some of the "positive" results will be false-positive results**
  - **The risk estimates for selected *positive* results are likely to be biased upward (Land, *Science*, 1980)**
  - **The impact of unmeasured confounding variables is often greater in a low-dose study, because the magnitude of confounding may approach or exceed the magnitude of the dose effect.**
    - **Confounder bias can be in either direction, i.e., the uncorrected risk estimate can either *exaggerate* or *mask* the true degree of association**

Radiation Risk for Lung Cancer by Smoking Frequency, A-bomb



*Gender-averaged excess risk relative to unexposed person with same smoking history

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