

New Information on Radiogenic Cancer Risks Since BEIR VII

Is it time for BEIR VIII?

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David Pawel

Radiation Protection Division

U.S. EPA





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The views expressed during this presentation are the author's, and do not necessarily reflect the views of EPA.

Outline

- How risks for exposures to low levels of IR were calculated in BEIR VII (2006)
 - Models for most cancers derived from atomic bomb survivor Life Span Study (LSS)
- “Indirect” information from the LSS with the greatest potential for affecting “BEIR VIII” risk projections
 - Curvature of dose response in LSS (used to determine DDREF)
 - Risk models for specific types of cancer (most notably lung cancer)
 - Time patterns in risk, e.g., risks from childhood exposures
- Low dose and dose rate issue: Is there “direct” information on risks from chronic exposures/low doses from other epidemiologic studies?

Basic Background About BEIR VII

- Comprehensive document: “Health Risks from Exposure to Low Levels of Ionizing Radiation” (2006), 406pp.
 - Chapters that reviewed Radiobiology, Heritable Genetic Effects
 - Chapter on Epidemiology: Life Span Study of Atomic Bomb Survivors
 - Chapters on Epidemiology: Medical, Occupational, Environmental Studies
 - Chapters on Risk Assessment
- ***Risk models for most cancer sites were derived from Atomic Bomb Survivor Lifespan Study data***

Basic Terminology and Concepts

- Radiation Risk Model: Function that relates disease risk to exposure (dose) and factors that might modify this risk.
- ***Incidence and Mortality Rates*** approximate the probability that a person will develop or die from a disease in a year.
- Compare incidence and/or mortality rates in exposed vs. unexposed populations (or in different dose groups)

EAR & ERR Risk Models

- **Excess absolute risk (EAR):** increase in cancer rate from exposure to radiation
 - EAR adds to the baseline cancer rates
 - Is radiation risk about equal in Japan & U.S.?
- **Excess relative risk (ERR):** fractional increase in cancer rate from radiation: radiogenic cancer rate divided by the baseline rate in the population. (Rad-risk proportional to baseline rates).

BEIR VII Cancer Risk Projections for the U.S.

(most cancer sites)

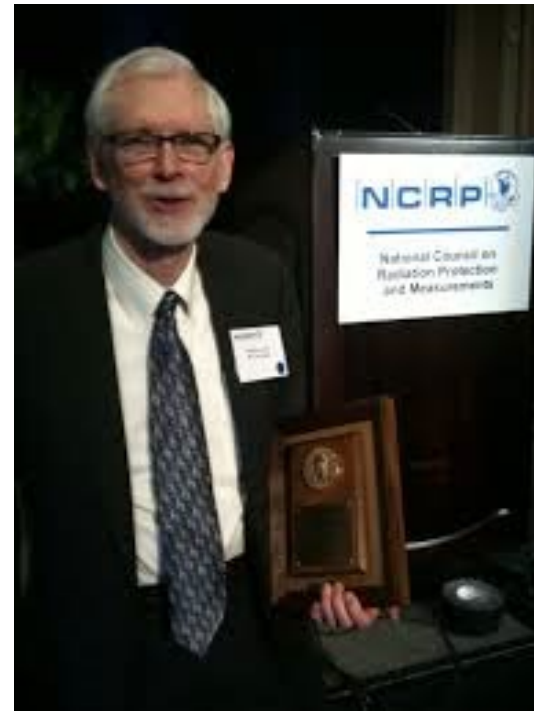
- Fit ERR and EAR risk models to atomic bomb survivor Lifespan Study (LSS) data.
 - Many with high, acute doses
 - Direct estimates of risk for low-LET, acute exposures to a Japanese population.

Extrapolations

- To the U.S. Population (different baseline rate)
- To low-doses, dose rates using a dose and dose rate effectiveness factor (DDREF)
- To different types of radiation (RBE)

Why Use Such a Convoluted Approach!

- Estimating Cancer Risks from Low Doses of Ionizing Radiation:
“Precise direct estimation of small risks requires impracticably large samples.”
 - Land (1980)
- Example: Cohort study requires about 100 million w/ 20 y follow-up to detect effects of 1 rad to breast (typical mammography dose at that time)



Much Larger Studies Now Possible

- Pearce et al (2012) and Mathews et al (2013) on cancer risk from CT scans

- **But is Sample Size the Whole Story?**

- **NO!***

- *“Subtle sources of bias ... may be comparable in effect to exposure. Increasing sample size cannot compensate for such bias, and may in fact add to difficulties ... On the other hand, when the excess risk due to radiation is high, such biases often can be ignored.”* (Land 1980)

*Marel Marceau, “Silent Movie”

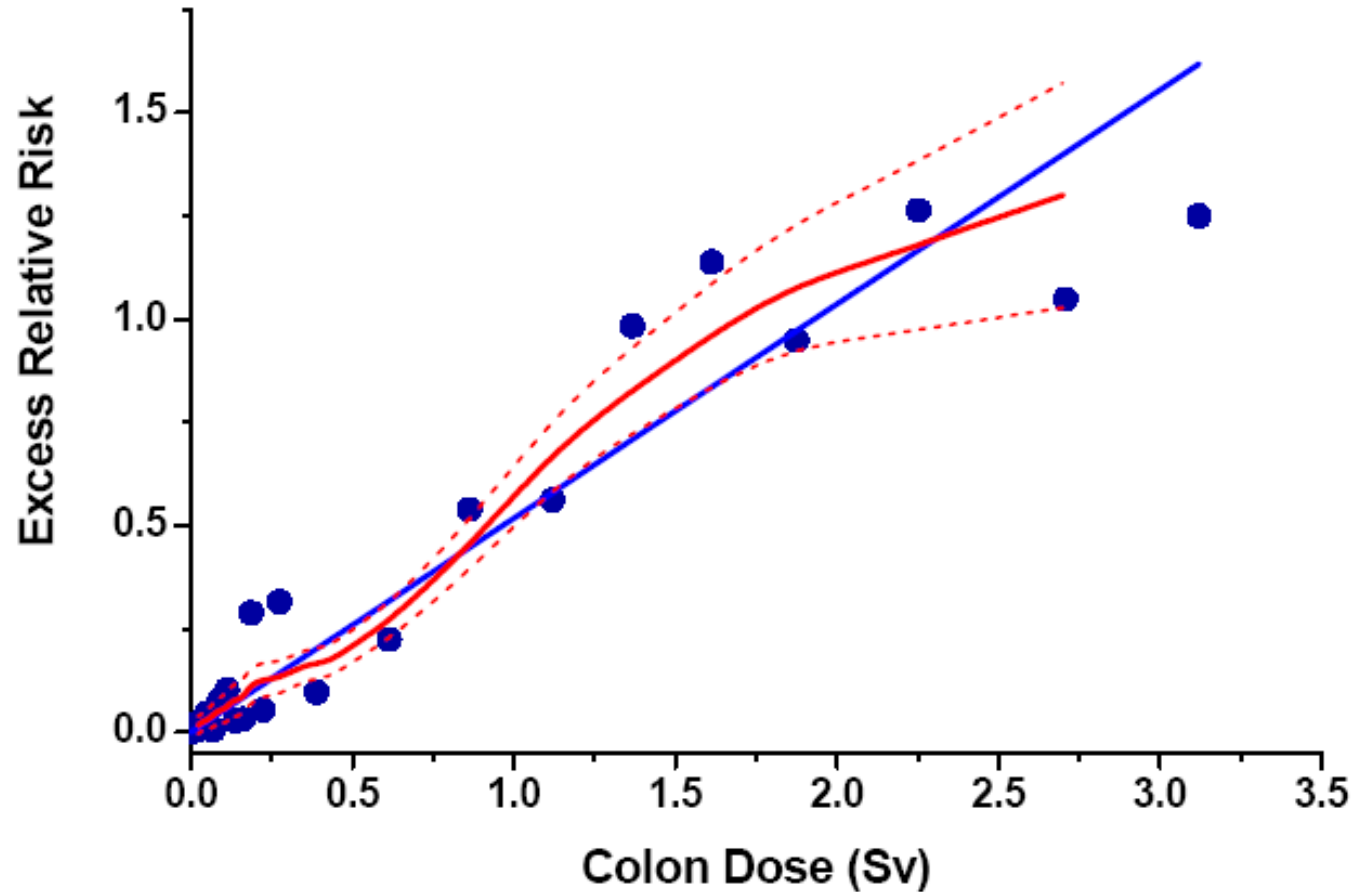
Atomic Bomb Survivors



Lifespan Study (LSS) of Japanese A-Bomb Survivors

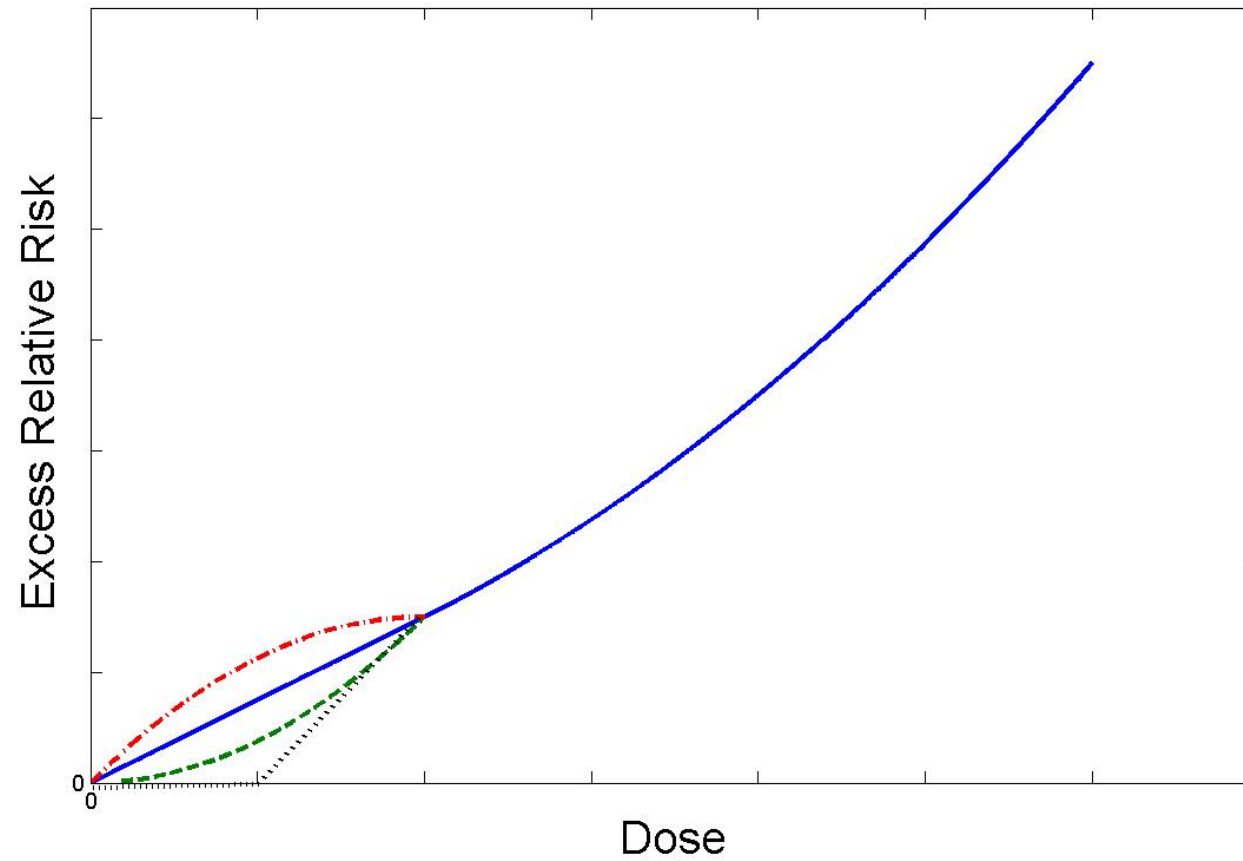
- 1) Large population (120,000 survivors)
- 2) All ages, both genders
- 3) All organs irradiated
- 4) Long, detailed medical follow-up
- 5) Wide range of doses (instantaneous, mostly γ -rays)
- 6) Good dose estimates

Solid Cancer among Atomic Bomb Survivors (1958-1998)



(LSS Report 13, Preston et al, 2003)

Low Dose Extrapolations

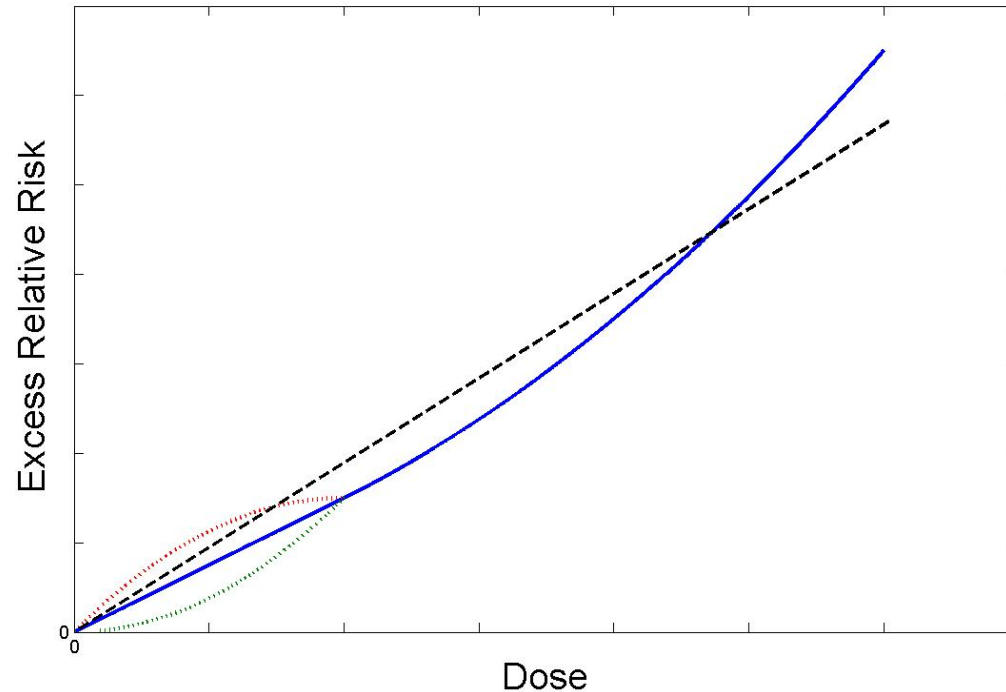


Dose & Dose Rate Effectiveness Factor (DDREF)

- A factor to account for a decrease in the effectiveness of low-LET radiation in causing a biological end-point, e.g., cancer, at low doses and dose rates compared with observations made at high, acutely delivered doses.
- If the dose response for acute exposures is LQ, then the effect per unit dose at low doses (and presumably at low dose rates) will be equal to the slope of the linear component of the dose response.

DDREF (2)

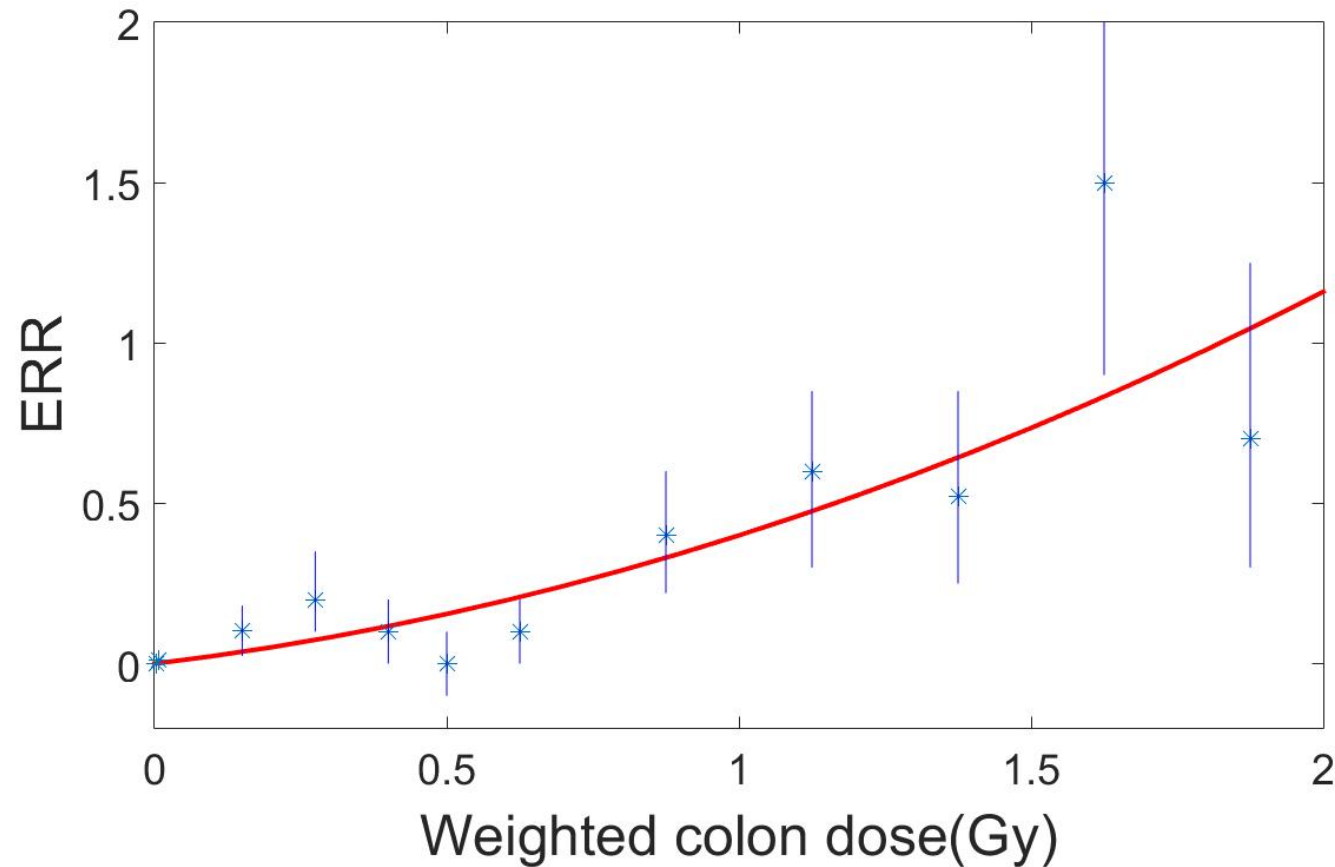
The slope of the dotted line represents ERR per unit dose at a large acute dose. Low Dose Effectiveness Factor (**LDEF**) is the ratio of this slope to the linear component of the LQ dose response (blue).



BEIR VII DDREF Estimate

- DDREF = 1.5 < 2 (recommended by ICRP, NCRP)
- Based on analyses of LSS and radiobiological animal experiments
 - LSS Data: DDREF = 1.3
 - Animal experiments: DDREF = 1.5
- Hoel (2015): “changing the DDREF from 2 to 1.5 is not justified”
 - Their use of animal data was inappropriate
 - Should have compared dose response for acute vs. prolonged exposures
 - Criticized selection of tumor sites
 - Estimated curvature depends on [subjective] decisions, e.g. range of data analyzed and dose categories used.
 - The shape of the dose response depends on the cancers that are included
 - Without thyroid and breast cancer, much more curvature.

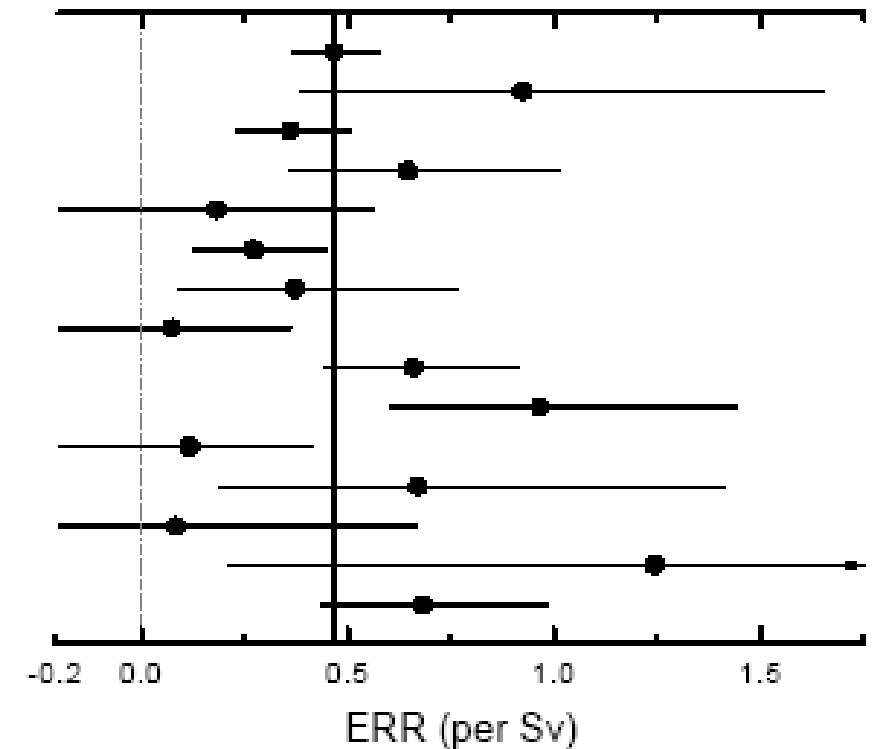
Atomic Bomb Survivor Solid Cancer Mortality (1950-2003)



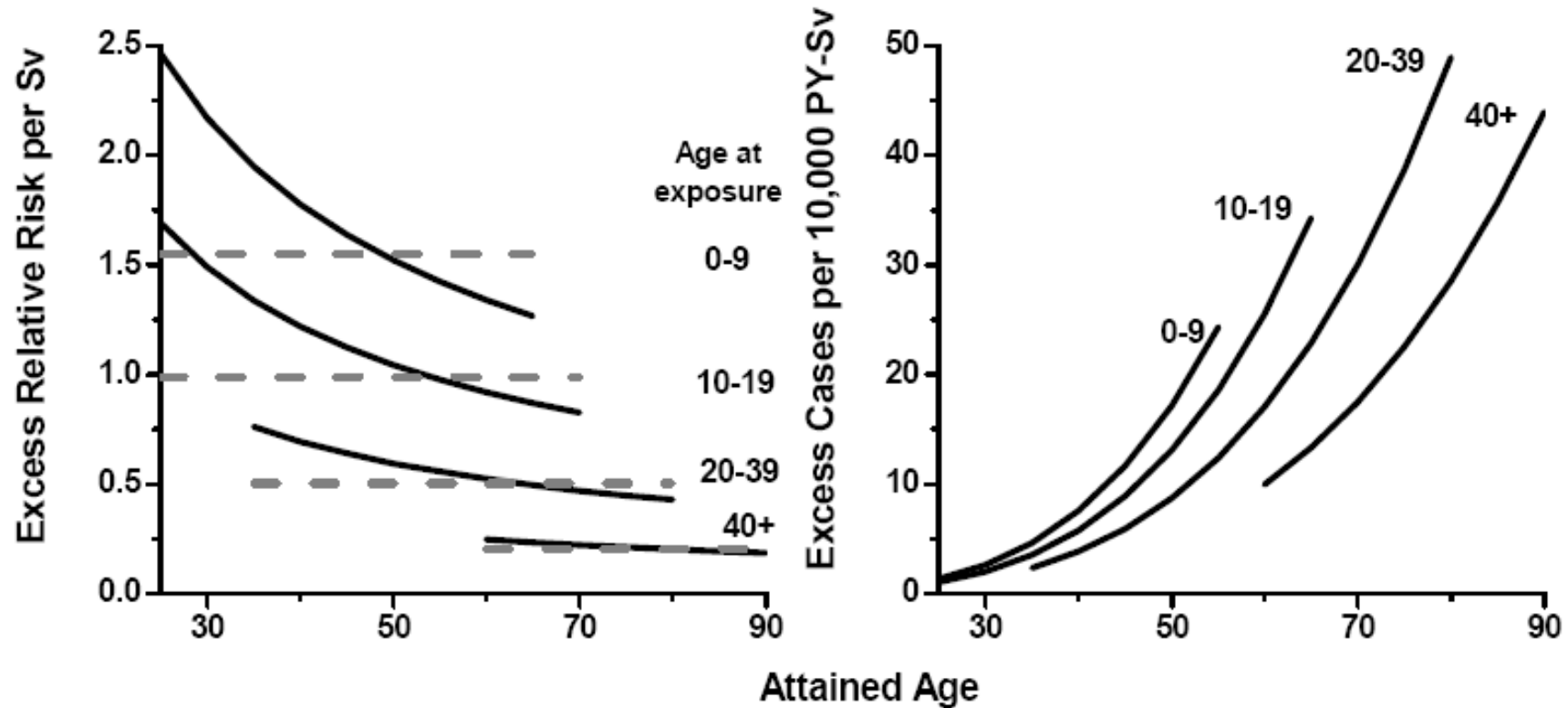
Wish It Could be so Simple!

- ERR/Sv depends on cancer site
- Estimates subject to uncertainty from sampling variation
- Risks also depend on sex, age, temporal factors and ...

--	Deaths	P-values
All solid cancers	9335	P<0.001
Esophagus	291	P<0.001
Stomach	2867	P<0.001
Colon	478	P<0.001
Rectum	370	P=0.14
Liver	1236	P<0.001
Gall bladder	328	P=0.007
Pancreas	407	P=0.29
Lung	1264	P<0.001
Breast	275	P<0.001
Uterus	518	P=0.20
Ovary	136	P=0.004
Prostate	104	P=0.42
Bladder	150	P=0.02
Other solid	911	P<0.001



Age and Temporal Patterns in Radiation Risk



(LSS Report 13, Preston et al, 2003)

New Information from LSS: Specific Cancer Sites

- **LUNG CANCER** (Furukawa et al 2010; Egawa et al 2012)
 - More in-depth analyses of radiation and smoking effects on lung cancer
 - Could it have a substantial impact on risk estimates for inhalation of radionuclides and childhood exposures?
- Bone cancer (Samartzis et al. 2011)
 - Evidence for risks at lower doses than some had previously thought possible
 - 95% CI for threshold dose: (0.12 to 1.85 Gy)
 - See Crump (Critical Review in Toxicology, 2011) on threshold models
 - But **very small sample size!** (4 bone cancers at doses > 1 Gy)
- Soft Tissue Sarcomas (Samartzis et al 2013)
 - ERR: 1.01 per Gy, 95% CI: 0.13-2.46), 104 cases

New Information from LSS: Specific Cancer Sites (2)

- **Thyroid** cancer (Furukawa et al. 2013)
 - Follow-up to 2005 (371 cancers), excluded papillary microcarcinomas
 - **Excess risk persists > 50 y past exposure**
 - ERR = 1.28, 95% CI = (0.59, 2.7) for e = 10, a = 60
 - ERR decreases with age-at-exposure* and attained age (ns)
 - **Risks might be especially high at pediatric ages.**
 - No excess risk found for age-at-exposure > 30 y
 - EAR* and ERR (ns) greater for females

New Information from LSS: Specific Cancer Sites (3)

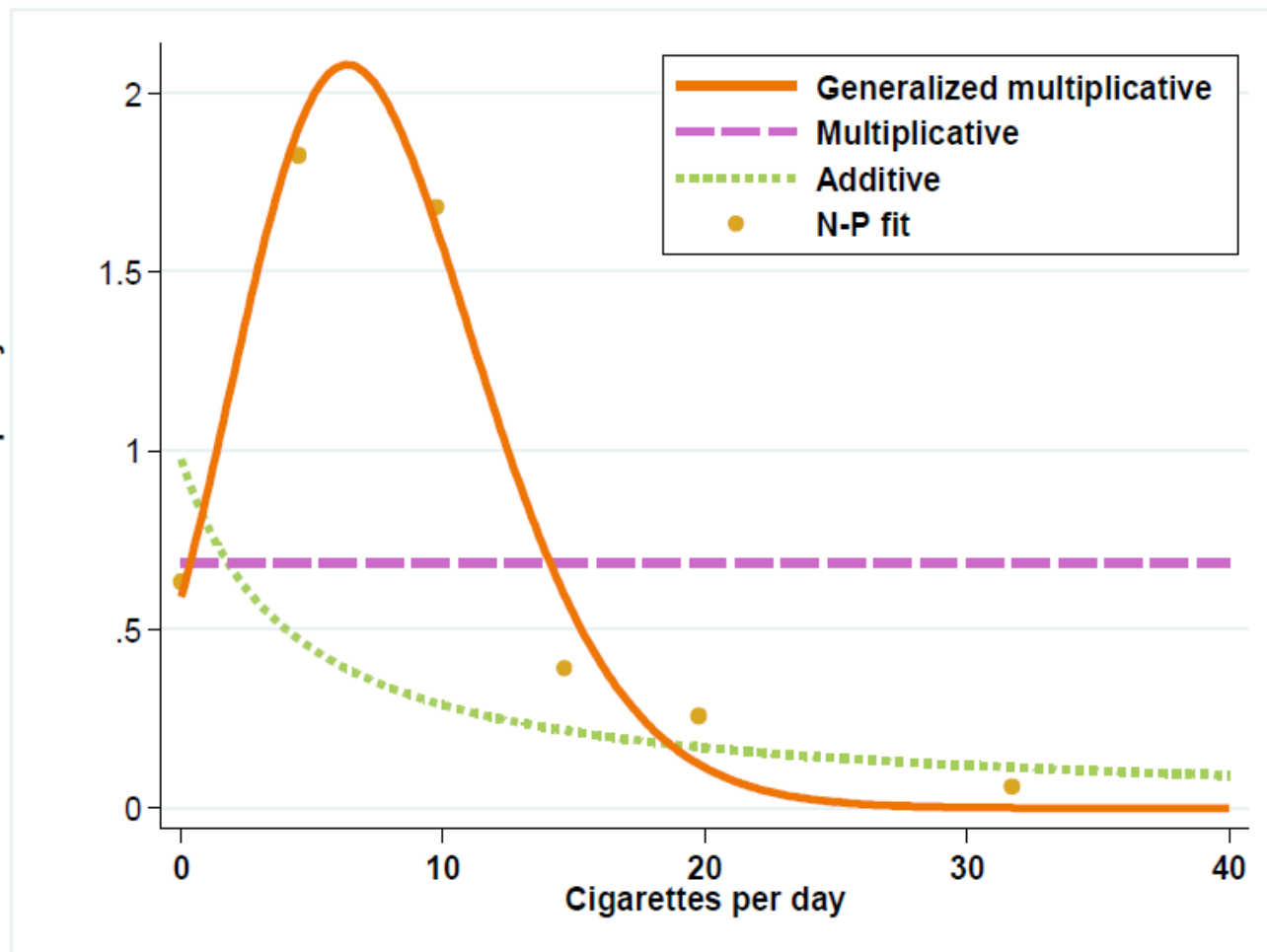
- Leukemia, Lymphoma, and Multiple Myeloma (Hsu et al. 2013)
 - Follow-up 1950-2001, Eligible cases: Leukemia (371), lymphoma (437), MM (136)
 - **40% diagnosed during last 14 y of followup**
 - Pooled analysis of leukemia types other than ATL and CLL
 - **Risk persists (elevated risk seen in last 12 of follow-up).**
 - Complicated! Clear that age/temporal patterns in risk depend on leukemia subtype
 - **Predicted risks consistent with estimates from other studies**
 - **Techa River and British Fuel**
 - CLL: Significant linear dose response detected BUT
 - Only 12 eligible cases
 - Japanese CLL genetically and biologically different from CLL seen in Western populations
 - No clear evidence of an excess risk for lymphomas, MM

Dependence on Age at Exposure

- BEIR VII model: ERR falls by about 25% for every decade increase in exposure age up to age 30 and then levels off.
 - For most solid cancer sites – ***including LUNG cancer.***
- The dependence on age-at-exposure depends on the cancer site
 - Risks greater for childhood exposures for thyroid cancer
 - ***No evidence of decrease with age-at-exposure for lung and colon cancers !!!***
 - ***BUT difficult to estimate age/time patterns for individual cancer sites !!!***
 - For lung cancer: ***NEED to account for effects of smoking !!!***
 - ***BEIR VII did NOT !!!***

Smoking-Radiation Interaction (ERR/Gy by Smoking Intensity)

It is very
COMPLICATED!
Plausible?



* Relative to unexposed with same smoking history

Observed vs. Future LSS Cancer Deaths

(Ozasa et al. 2012; Furukawa et al. 2009)

- 1950-2003: 10,929 Cancer Deaths, Estimated Excess = 527
- 2003-2010: About 250 cancer deaths per year
- 2010-2025: Cancer deaths decline steadily to about 190 per year
- For 0-9 ATB:
 - Increase roughly ten-fold from 1980 (5) -2000 (50)
 - Projected to peak at about 110 around 2020
- For 10-19 ATB:
 - Roughly twice the number for 0-9 ATB in 2000.
 - Peaks earlier around 2010 and declines to about 50 per year in 2020.

DDREF Controversy

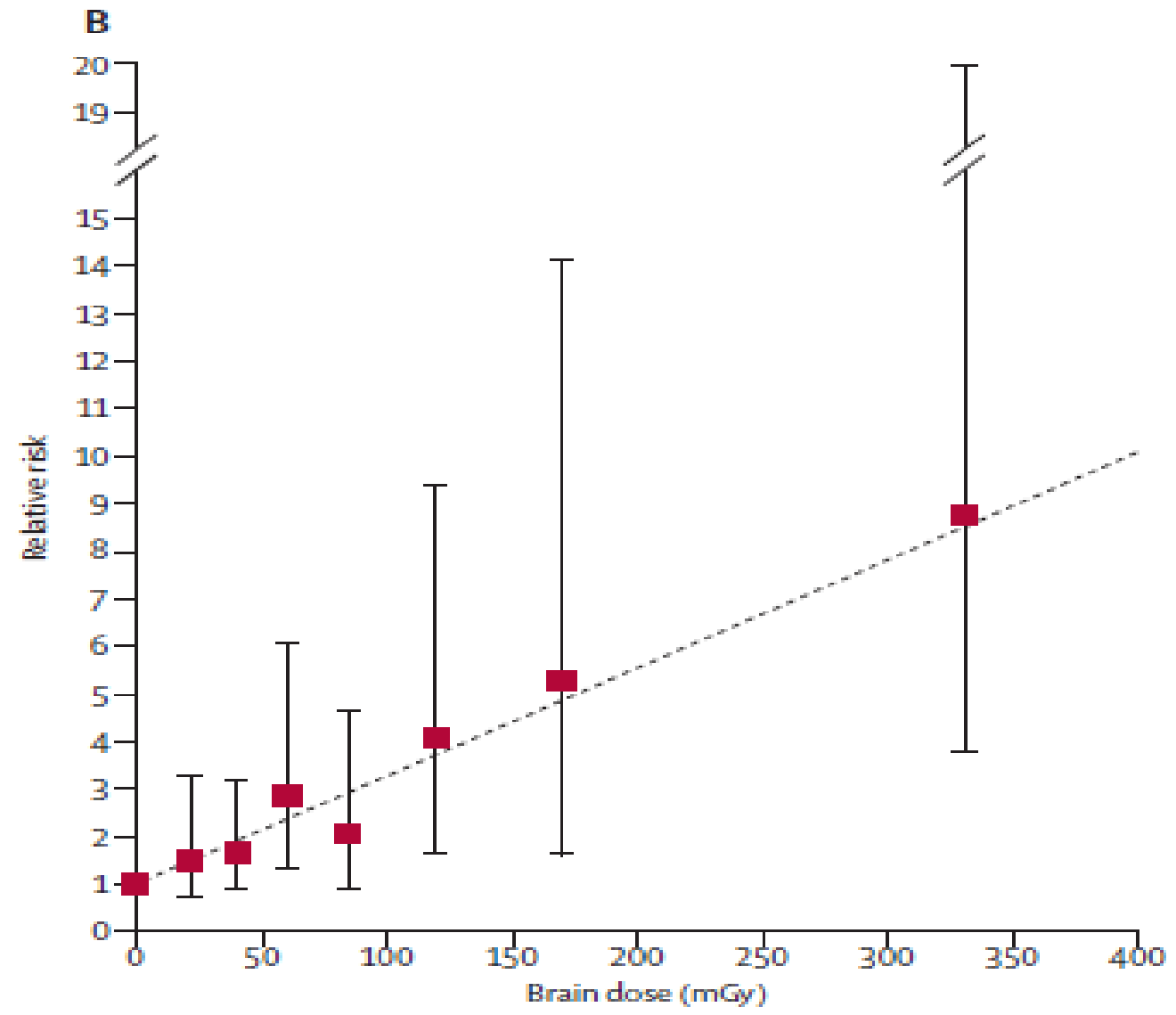
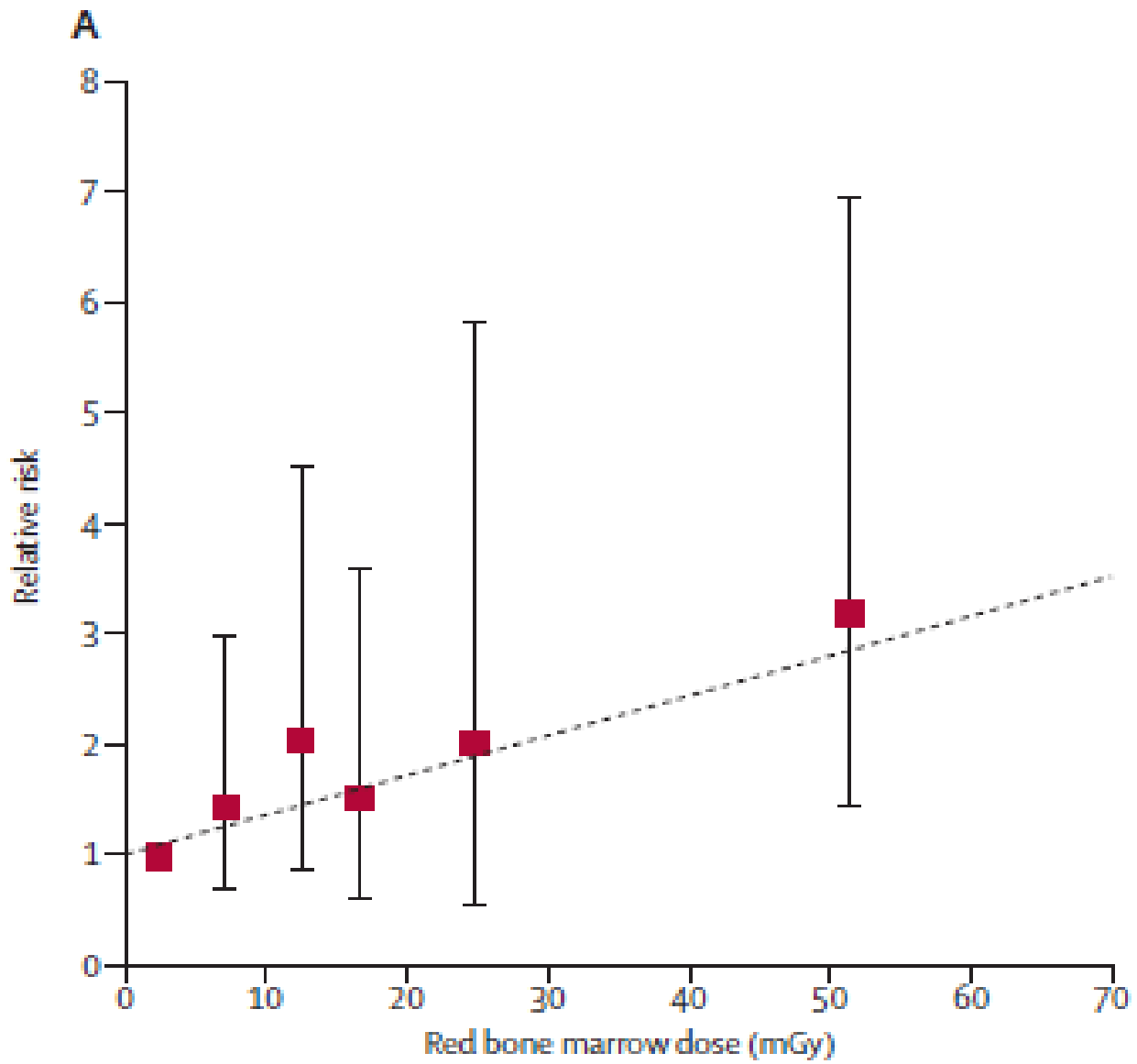
- Dedicated Workshop on Use of DDREF for Radiation Protection (May, 2015; Kyoto, Japan)
 - Key assumption is that the linear component of the dose response does not depend on dose rate, but there is radiobiological data that indicates this might not be the case.
 - Criticism of BEIR VII's Use and Choice of Animal Data
 - German Commission on Radiological Protection concluded (as summarized by Rühm et al (2015): “that various scientific criteria indicate that the DDREF would not be introduced if not already in place. Based on current scientific findings, the SSK no longer considers justifications for the use of the DDREF in radiological protection as being sufficient.”

Epidemiological Studies other than the LSS

Low Dose/Dose Rate (LDDR) Issue

- Most important to “us”!
- Evaluate data from epidemiological studies of *chronic exposures* (nuclear workers, Techa R. cohort, Taiwanese building residents, natural background exposures, etc.) and *low dose acute exposures* (CT), along with radiobiological data to more reliably characterize low dose/dose rate risks
- Quantify LDDR cancer risk estimates and uncertainties, taking into account the entire body of information from epidemiology and radiobiology

Cancer Risks from Childhood CT (Pearce et al, *Lancet* 2012)



What Can (Very Large) Studies Tell Us About Risks from Risks from CT Scans?

- Walsh et al. (2014) JRP Editorial: Large (11 M) Australian study of (solid) cancer risks illustrates limitations of CT scan studies
- Who Gets CT Scans and Why?
 - Reverse causation: Are they performed due to suspected cancer?
 - Some other reason why CT patients would be at higher risk?
- Journy et al. (2015): Adjusted preliminary risk estimates to account for predisposing factors (genetic effects and immune deficiencies) for CNS, leukemia, lymphoma
 - Pattern of CT scans depends on whether a patient has PFs
 - Risk estimates smaller after adjustment.

CT Scan Studies: Stay Tuned!

	Size of exposed cohort	Age at exposure (years)	Start date of accrual	Estimated report date
Belgium	30 000	0-15	2002	2016
Denmark	30 000	0-18	2000	2016
France	90 000	0-5*	2000	2016
Germany	140 000	0-15	1985	2016
Netherlands	40 000	0-18	1998	2016
Norway	20 000	0-20	2005	2016
Spain	200 000	0-20	2005	2016
Sweden	95 000	0-18	1984	2016
UK	400 000†	0-21	1985	2012‡
EPI-CT (pooled European)	1 045 000§	0-21	1984-2005	2016
Australia	660 000	0-19	1985	2012-13
Ontario, Canada	370 000	0-17	1985	2013
Ontario, Canada	4 105 000	≥18	1991	2013
Israel	42 000	0-22	1985	2013
Israel	18 000	0-22	1999	2013

Data for European studies adapted from reference 7. Additional data provided by G Chodick (Maccabi Healthcare Services), A Kesminiene (International Agency for Research on Cancer), V Kirsh (Cancer Care Ontario), J Mathews (University of Melbourne), and I Thierry-Chef (International Agency for Research on Cancer). *0-10 years from 2007. †Including the extended cohort. ‡Pearce and colleagues' study. §Estimated size.

Table: Cohort studies of CT exposure and cancer incidence

From A. Einstein (2012)

New Information from Occupational Cohorts

Chronic or episodic exposures, usually good dosimetry

- **Nuclear workers (N. American & European) – leukemia, solid cancers**
- Radiologists and radiological technicians – *leukemia, breast*
- Mayak workers (α, γ) – *lung, liver, bone, leukemia*
- Chernobyl clean-up workers – *leukemia*

Confounding in Occupational Studies

- Other occupational exposures --- chemicals
- Lifestyle factors
 - Smoking, alcohol
 - Presumably, less an issue for leukemia than for lung, esophagus, etc.

Cancer in US, UK, & French Nuclear Workers (INWORKS)

(Richardson et al, British Medical Journal 2015)

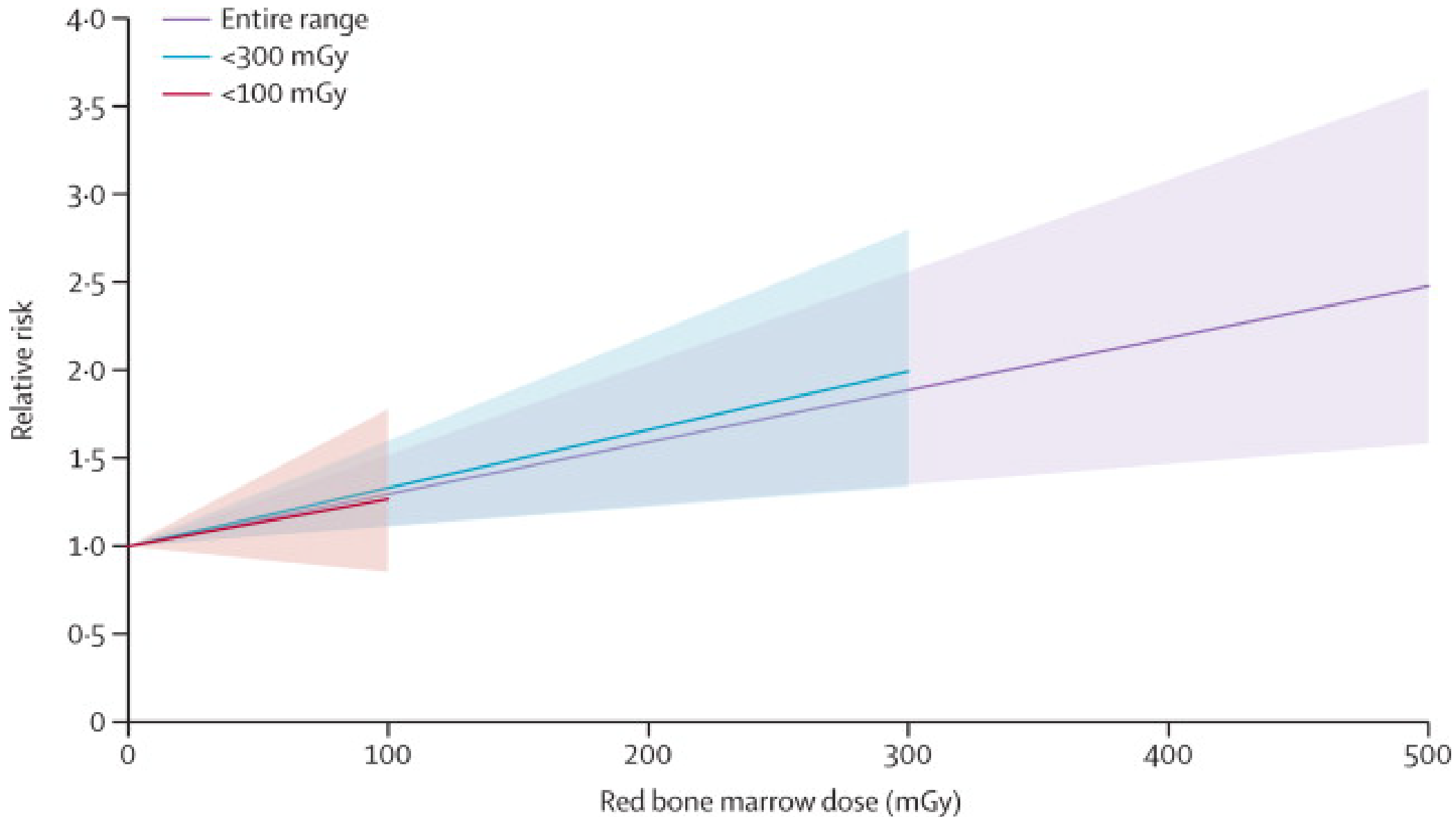
- 308K with follow-up from 1944-after 2000, 20K cancers,
- Avg. colon dose = 21 mGy, 211 with doses above 300 mGy.
- Lacks information on lifestyle factors (smoking), occupational exposures (benzene, asbestos)

Cancer in Nuclear Workers (INWORKS)

Results

- Suggest linear increase in cancer rate with radiation exposure
- ERR per Gy with 90% CI:
 - All cancers: 0.51 (0.23 to 0.82)
 - Solid cancers: 0.47 (0.18 to 0.79)
 - As compared to 0.32 (0.01 to 0.50) from LSS (20-60 y ATB)
 - Solid other than lung: 0.46 (0.11 to 0.85)
 - Solid other than smoking-related cancers: 0.37 (-0.14 to 0.95)
- Risks were not driven by results by any one country, whether workers flagged for incorporating internal radionuclides were excluded, etc.
- At 300 mGy, the estimated ERR is about 0.1 to 0.15.

Leukemia in US, UK, & French Nuclear Workers (INWORKS) (Leuraud et al, *Lancet Haematol* 2015)

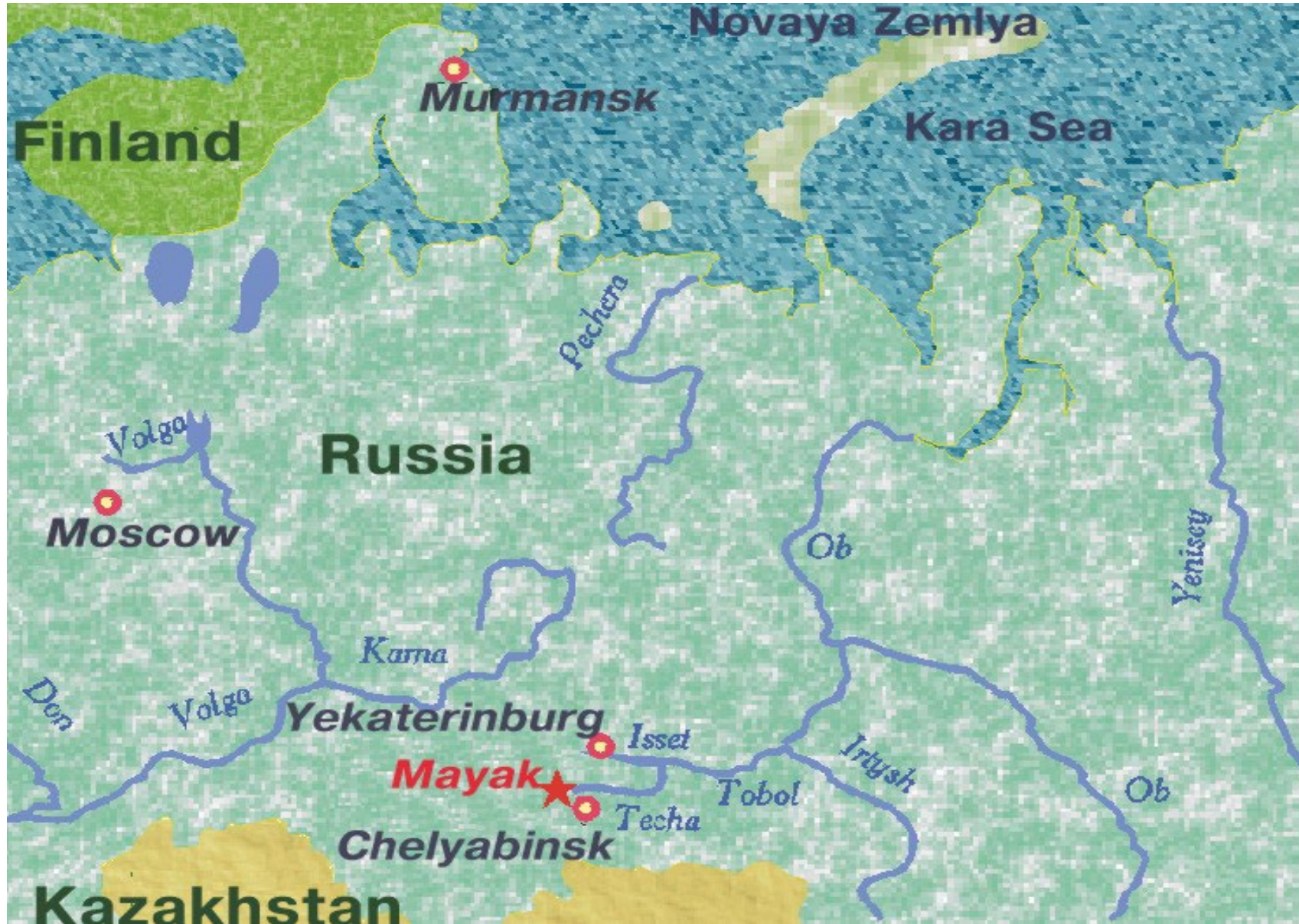


Environmentally Exposed Cohorts

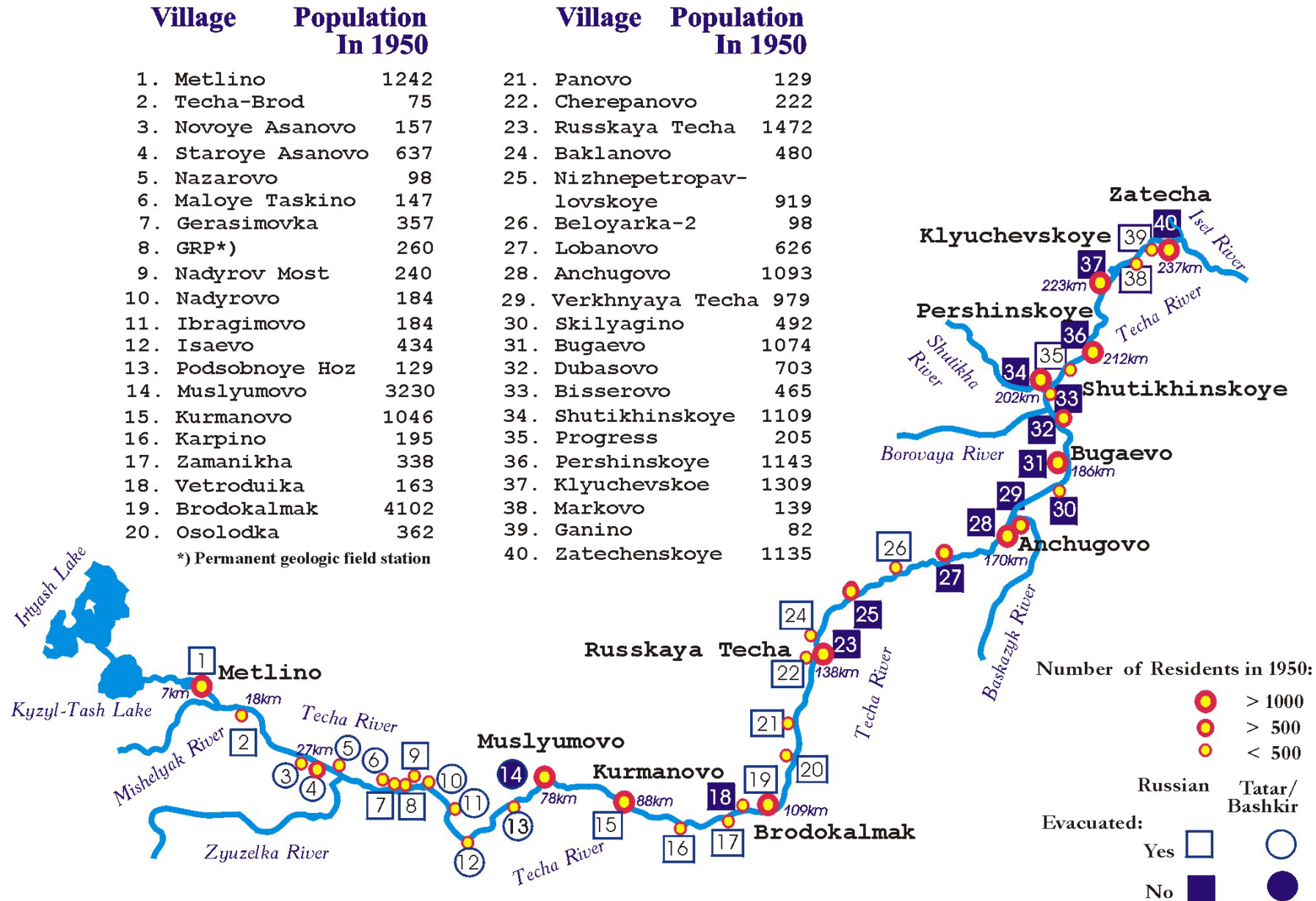
Chronic exposures, require dose reconstruction

- Techa River cohort – *leukemia, solid cancers; risks about as high as in LSS*
- Taiwanese residents of apartments built with ^{60}Co -contaminated steel – *leukemia, breast*
- Natural background exposures

Mayak Area



Techa River Contamination



Techa River Cohort Dosimetry¹

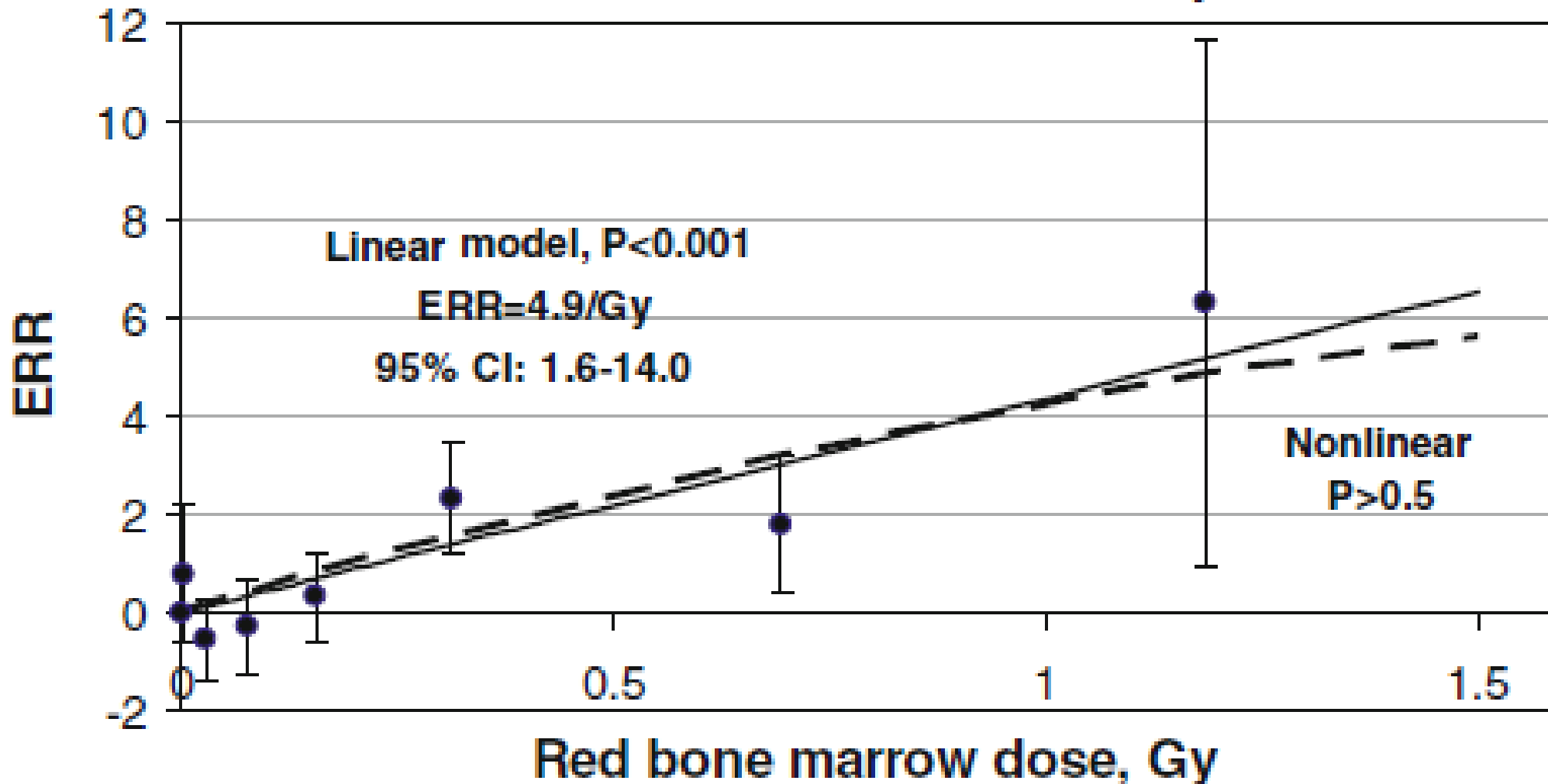
- Main pathways
 - External: Cs-137
 - Ingestion: Cs-137, Sr-90
- Dosimetry based on environmental measurements and whole-body counting (Sr-90)
- External dose relatively more important upstream
- Currently, average location used for each village, but this will be improved

¹ Degteva, Napier, Anspaugh

Leukemia in Techa River Cohort

(Krestinina et al, *Radiat Environ Biophys* 2010)

Non-CLL incidence dose response



Preliminary Findings on Techa River Cohort

- Leukemia: ERR/Gy = 4.9 (1.6-14)¹
- All solid cancers: ERR/Gy = 0.77 (0.13-1.5)²
- Reasonable agreement with LSS estimates
- Individual sites: significant for esophagus, uterus, but information on individual sites limited and somewhat hard to interpret

¹Krestinina et al, *Radiat Environ Biophys* 2010

²Davis et al, *Radiat Res* 2015

Studies of Natural Background Low-LET Radiation

- Ecological studies in China and India (Kerala) show no evidence of excess risk
- Cohort study in Kerala underway
- British case-control study found association between NBR (~ 1 mGy/y) and childhood leukemia, in reasonable agreement with LSS (Kendall et al, *Leukemia* 2013)
- Swiss cohort study found significant association between NBR dose and childhood CNS cancers and leukemia (Spycher et al, *EHP* 2015)

Variations in cancer rates due to other causes may swamp out those due to IR exposure — confounding

Protracted Exposures: Leukemia

- Meta-analysis (Daniels & Schubauer-Berigan, *Occup Environ Med* 2011)
 - 21 of 23 studies “positive”
 - Techa, NRRW (UK), Taiwan, Mayak, et al. statistically significant
 - Combined estimate of ERR/100 mGy = 0.19 (0.07, 0.32)
 - Central estimate of linear component of LQ from LSS data: 0.15 (-0.11, 0.53)
- More recent studies (INWORKS, Ukrainian Chornobyl cleanup workers, British & Swiss studies of NBR) support results of meta-analysis

Protracted Exposures: Solid Cancers

- Incidence in Techa R. Cohort found to increase with dose:
 - $ERR/Gy = 0.77$ (95% CI: 0.13 – 1.5)
 - Comparable to LSS
- Solid cancers also increased in worker cohorts:
 - Mayak: $ERR/Gy = 0.16$ (0.08-0.24) [excluding lung, liver, bone]
 - NRRW: $ERR/Gy = 0.32$ (0.02-0.67) [“]
 - Russian Chernobyl cleanup workers: $ERR/Gy = 0.47$ (0.03-0.96)
- CNS cancer increase with natural background exposure

Time for BEIR VIII?

- Are justifications for the use of the DDREF in radiological protection sufficient?
- Update of LSS and analysis of radiobiological and animal data to improve estimate of DDREF
- More integration of information from diverse epidemiological studies to obtain improved estimates of risk for specific cancer sites?
 - Age and time patterns in radiological risk?
 - Consider synergism between radiation and other risk factors (smoking)
 - Special concerns, e.g., thyroid cancer in Fukushima