From Epidemiology to Risk Factors

aka DDREF: Light and Shadows

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Outline

- DDREF Origins and Background
- DDREF in Practice
- Defining the DDREF
  - LSS low dose extrapolation factors (DDREF)
  - BEIR VII Bayesian analysis
  - Pooling epi studies
- Whither (wither) DDREF - personal views and random thoughts

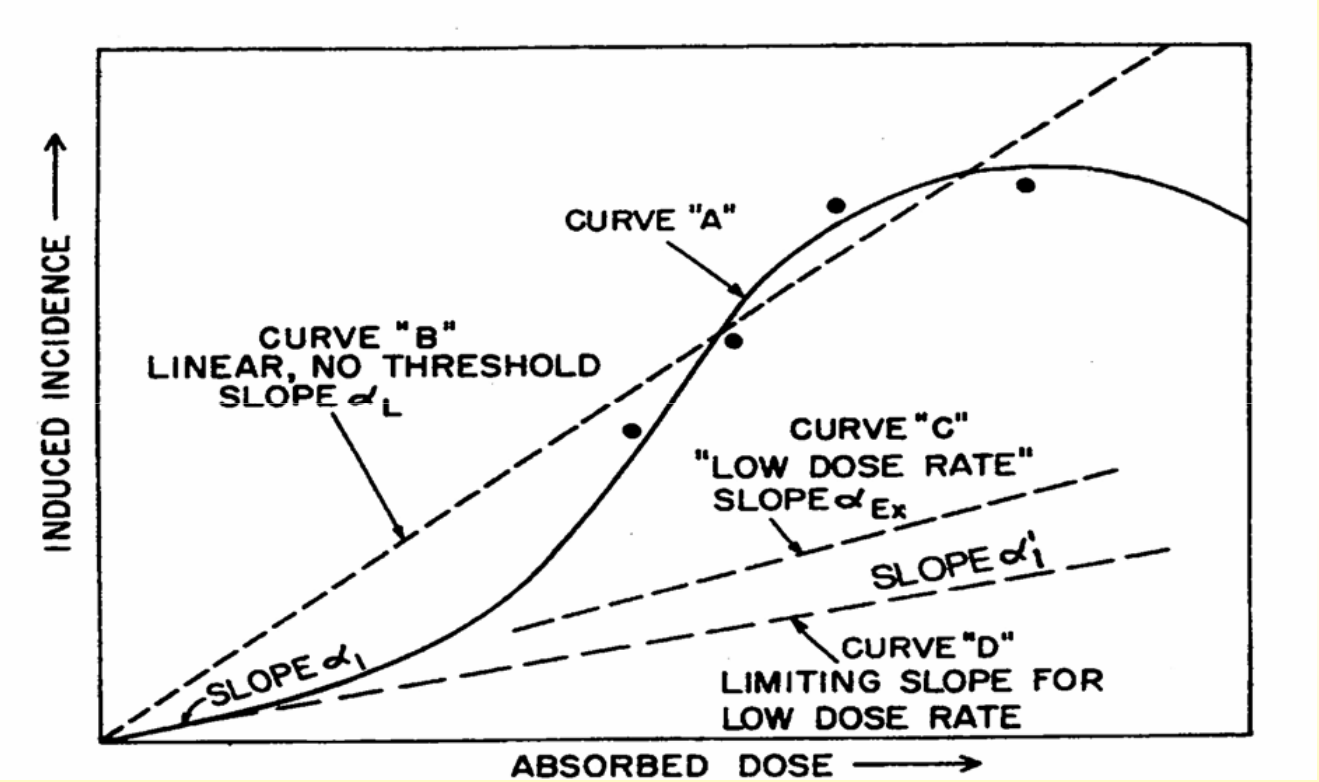
Radiation Protection

- Define limits for occupational and public radiation exposures to protect against unnecessary and unjustifiable risks
  - Primary focus on lifetime cancer risks
  - Some concern with hereditary and fetal risks
- Relatively low doses (e.g. 1 – 100 mGy)
- Fractionated or chronic low dose rate exposures (e.g. < 5 mGy per hour) are most common
- Low LET exposures (e.g. x-rays, gamma rays) most likely

State of Knowledge Circa 1980

- Atomic bomb survivor data indicated increased cancer rates
  - Acute exposures
  - Information largely from higher doses (0.2 to 4 Gy)
  - Little information on dose response shape or low dose effects
    - Dose response estimates not included in early LSS reports
- Chromosome aberration data suggest non-linear dose response for acute exposures
  - Upward curvature over low dose range
- Other experimental data suggested non-linear dose response and reduced effects at low dose rates

Dose and Dose-Rate Effects
View from 1980



- NCRP Report 64 1980

(Original) DDREF Justification

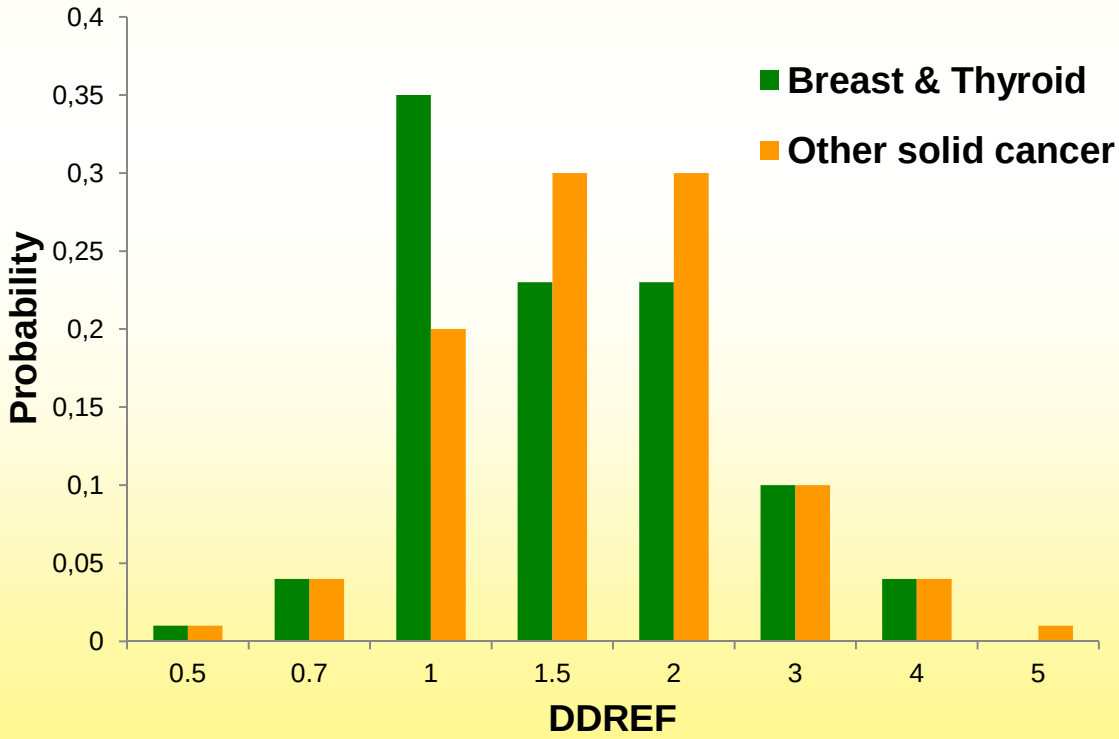
- Because
  - Linear extrapolation of survivor risks to low doses believed to over-estimate response
    - "True" dose response in survivors likely to be concave upward
  - Chromosome aberration data from human and experimental data concave upward at lower doses
  - Experimental data suggested risk per unit dose decreased with decreasing dose rate
- Therefore
  - A ***Dose / Dose Rate Effectiveness Factor*** **(DDREF)** should be used to reduce A-bomb survivor based risk estimates used to develop radiation protection standards

DDREF in Practice

- ICRP 1990 and 2007
  - Consensus value of 2 for solid cancers
  - Leukemia risk estimates based on LQ model with no adjustments
- BEIR V
  - DDREF not applied
- BEIR VII
  - Developed a posterior distribution based on A-bomb survivor incidence data and some animal data
    - Mean of 1.5 and a 95% credible interval of about 1 to 3
    - Used 1.5 for computation of solid cancer risks

DDREF in Practice

- Interactive Radio-Epidemiological Program (IREP) risk projections



Characterizing the DDREF Today

- More LSS data
  - Risk estimates are described with more detail and precision
  - More knowledge of effect modification
- Other epi studies provide relevant risk estimates
  - Mayak and Techa River
  - UK nuclear workers (NRRW), IARC 15-country worker study, …
  - Chernobyl liquidators
- Evolving efforts to more fully characterize uncertainty in risk estimates
  - Dose errors, model uncertainty, …
- “New” radiobiology
  - Adaptive response, bystander effects, genomic instability, …

Estimating a DDREF (LDEF) from acute exposure data

- Assess as a function of curvature in LQ dose response model

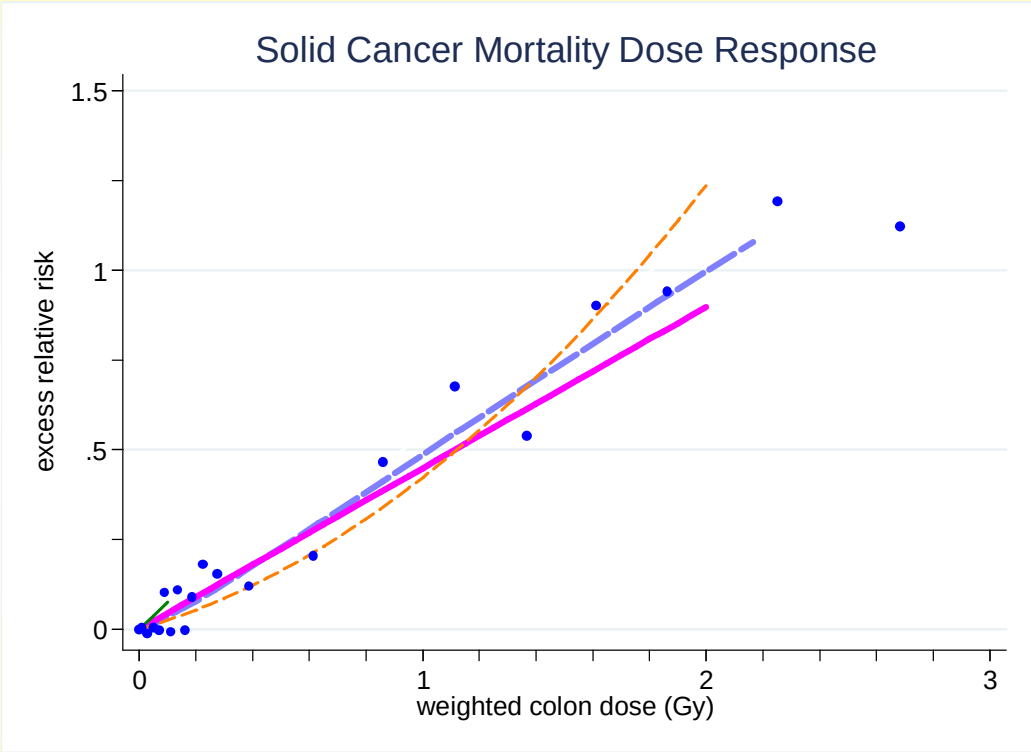
$$LDEF(d) = \frac{\alpha + \beta d^2}{\alpha d} = 1 + \frac{\beta}{\alpha} d = 1 + \theta d$$

- For the A-bomb survivor Life Span Study (LSS) data
  - Fit linear dose response model $\alpha_L d$
  - Fit linear quadratic model with curvature θ : $\alpha_{LQ}(d + \theta d^2)$
  - Define $\mathrm{LSS}_{\mathrm{LDEF}}(\theta)$ as $\frac{\alpha_{LQ}}{\alpha_L}$

    For LSS with data doses up to 1.5 or even 2 Gy $\mathrm{LSS}_{\mathrm{LDEF}}(\theta) \approx 1 + \theta$

LSS Solid Cancer Mortality Dose Response

- Linear ERR/Gy
  0 – 2 Gy 0.45
- Suggestion of non-linearity (LQ model on 0 – 2 Gy)
  P = 0.03
- Curvature 0.77
  LSS-LDEF 1.97
- LSS often described as a high dose study, but has as more information on risk at relatively low doses (<100 mGy) than many low dose studies

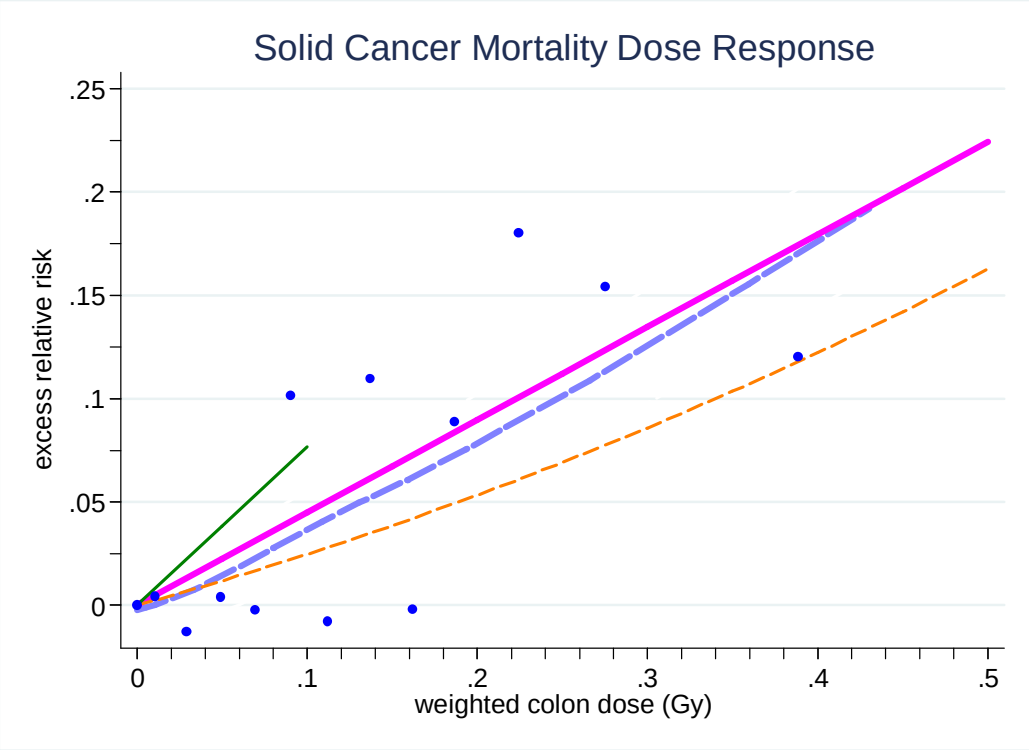


Using RERF public dataset DS02can.csv (www.rerf.or.jp)

Proximal zero dose baseline (adjusted for distal and NIC)

LSS Solid Cancer Mortality Dose Response 0 – 0.5 Gy

- Linear ERR/Gy
  - 0 – 2 Gy 0.45
  - 0 – 0.1 Gy 0.76
  - 0 – 0.15 Gy 0.71
- Test for trend
  - 0 – 0.1 Gy P = 0.04
  - 0 – 0.15 Gy P = 0.006

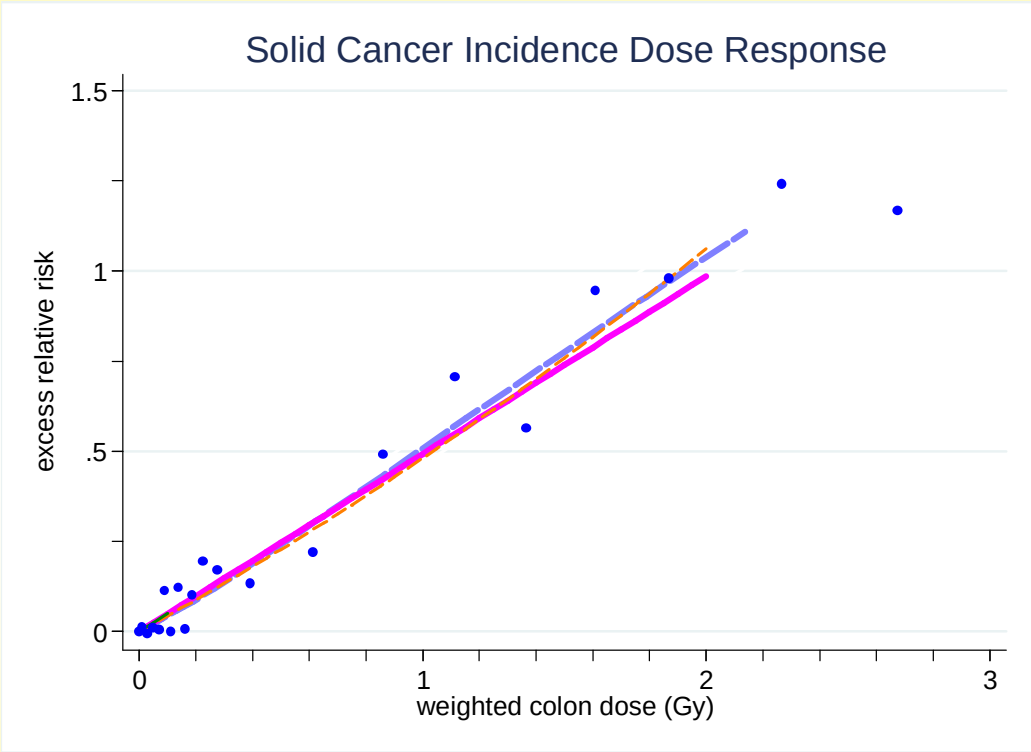


Using RERF public dataset DS02can.csv (www.rerf.or.jp)

Proximal zero dose baseline (adjusted for distal and NIC)

LSS Solid Cancer Incidence Dose Response

- Linear ERR/Gy
  0 – 2 Gy 0.49
- No evidence of non-linearity
  (LQ model on 0 – 2 Gy)
  P > 0.5
- Curvature 0.12
  LSS-LDEF 1.14

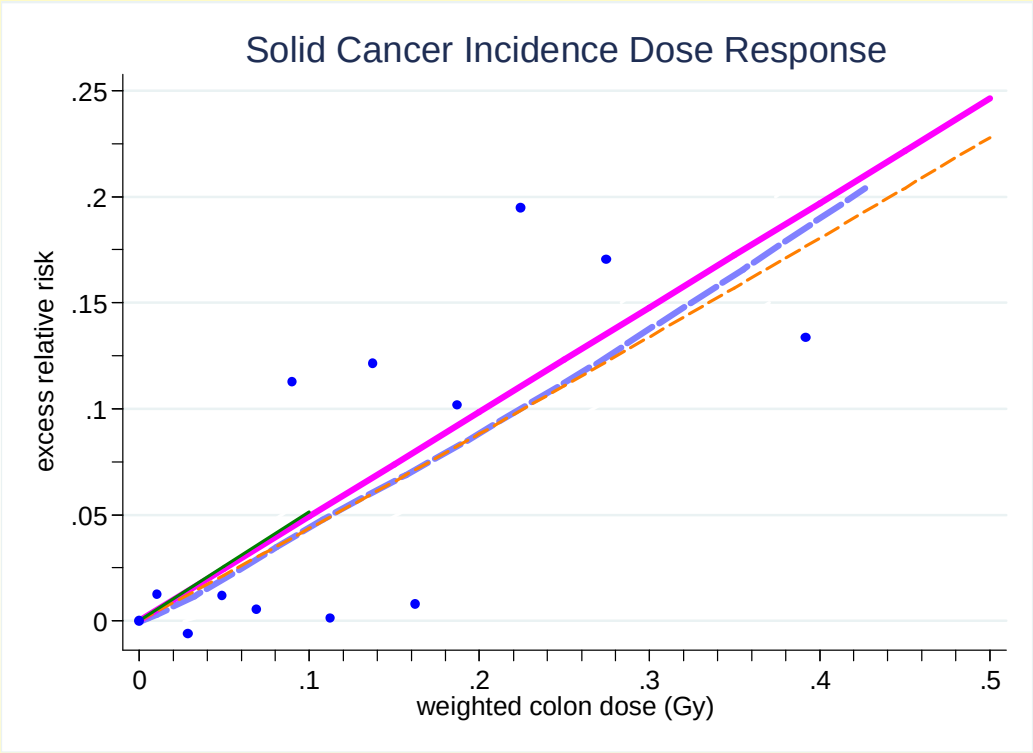


Using RERF public dataset DS02can.csv (www.rerf.or.jp)

Proximal zero dose baseline (adjusted for distal and NIC)

LSS Solid Cancer Mortality
Dose Response 0 – 0.5 Gy

- Linear ERR/Gy
  0 – 2 Gy 0.49
  0 – 0.1 Gy 0.51
  0 – 0.15 Gy 0.51
- Test for trend
  0 – 0.1 Gy P = 0.08
  0 – 0.15 Gy P = 0.01



Using RERF public dataset DS02can.csv (www.rerf.or.jp)

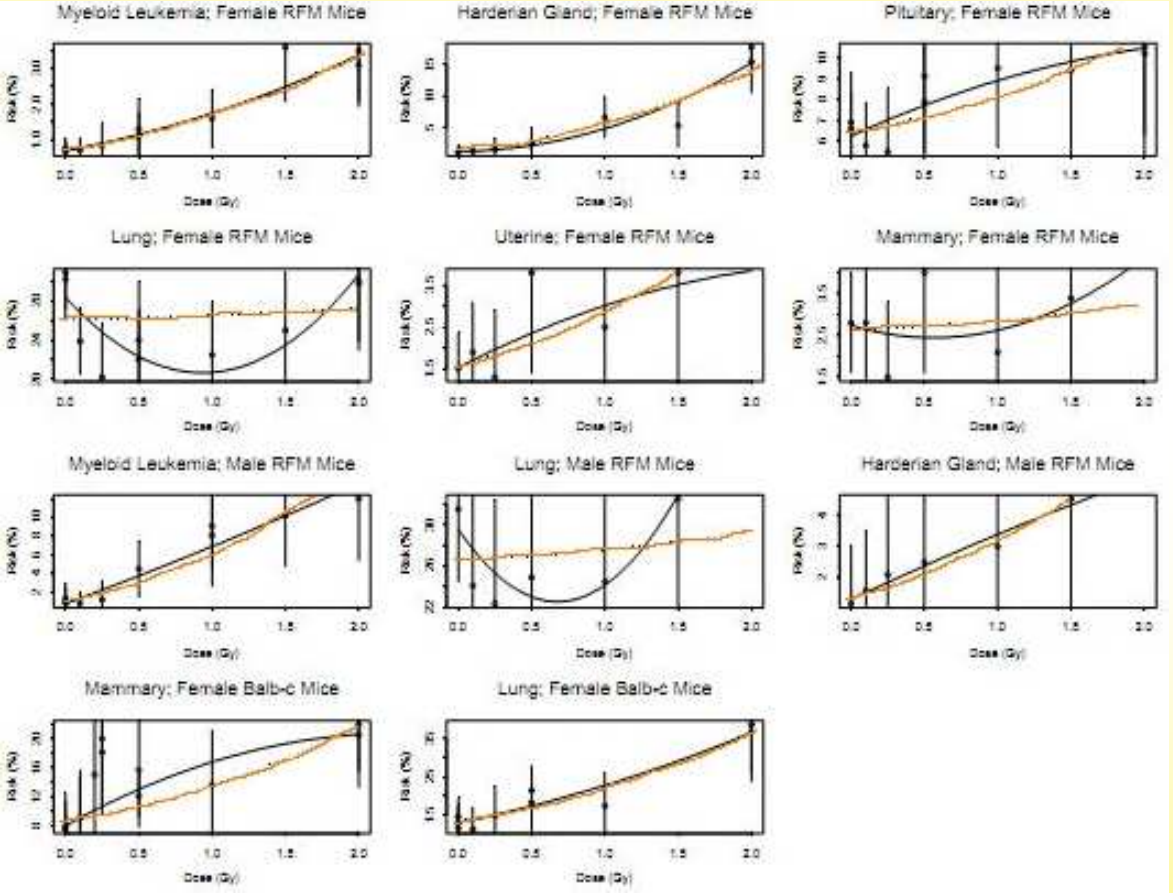
Proximal zero dose baseline (adjusted for distal and NIC)

BEIR VII Bayesian Analysis
Data Sources

- LSS cancer incidence data (Preston et al 2007)
- Selected mouse studies of radiation and cancer
  - Doses < 2 Gy
  - Adjusted for competing risks
  - 11 ORNL experiments in RFM or Balb-C mice (also used by NCRP In 1980)
    (Edwards, 1992 / Storer 1979)
    - Cancer risks
      - Lung (3); Hardrerian gland (2); Mammary (2); Uterine (1); Pituitary (1); Myeloid leukemia (2)
    - Life-Shortening
      - Acute and Chronic exposure experiments

BEIR VII Bayesian Analyses
Animal Cancer Data

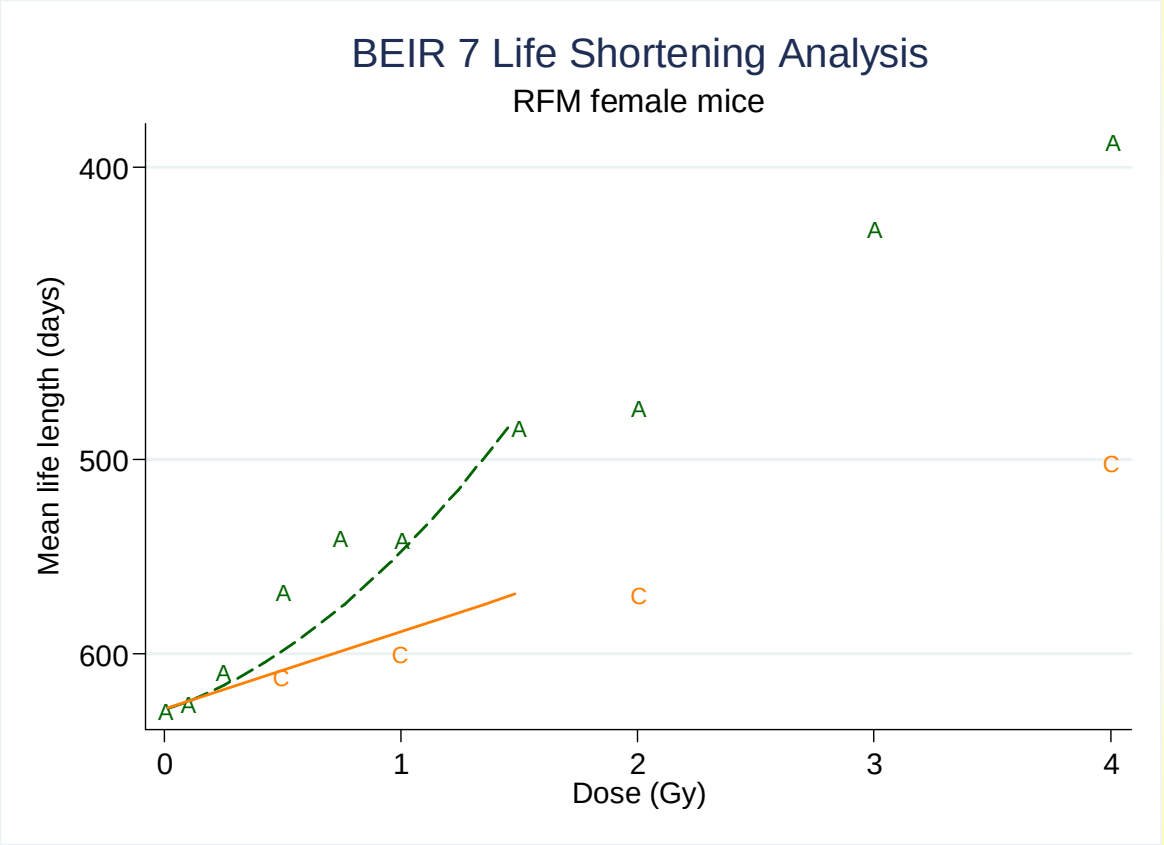
- Data from 11 cancer experiments with unconstrained (black) and constrained (orange) LQ fits
- Common curvature assumed for constrained fits



Data taken from experiments described by Edwards (1992)

BEIR VII Bayesian Analyses
Life Shortening Data

- Life Shortening in female RFM female following **acute** and **chronic** exposures to different total doses with dose response curve fitted to 0 – 1.5 Gy range



Data taken from Storer et al (1992)

BEIR VII Bayesian Analysis
Risk models

- LSS
  - Estimate curvature in LQ model fit to all solid cancer
- Mouse cancer data
  - Cancer dose response modeled assuming LQ models with common curvature across experiments
- Life Shortening data
  - Model dose response for inverse life expectancy with

$$\frac{1}{\overline{L}(d)} = \alpha d + \beta d^2$$ for acute exposures and

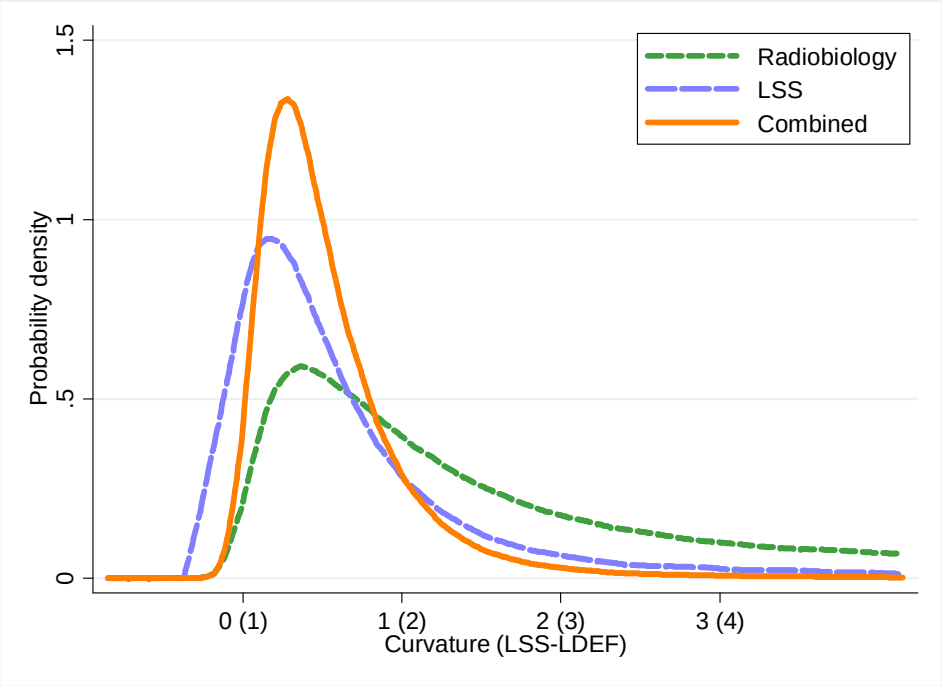
$$\frac{1}{\overline{L}(d)} = \alpha d$$ for chronic exposures

  - Estimate curvature as $\frac{\beta}{\alpha}$

BEIR VII Bayesian Analysis
Posterior Densities

- LSS
  - Define posterior density as normalized profile likelihood for curvature (θ)
- Animal data
  - Define posterior densities for cancer and life shortening data using normalized profile likelihoods for the curvature
  - Average these densities and renormalize to obtain "radiobiological" posterior
- Combined data
  - Define posterior density as the (normalized) product of the LSS and "radiobiological" posterior densities

BEIR VII Bayesian Analysis Results



	MLE	Mean	Median	90% Cred. Int.
Radiobiology	1.4	2.3	2.0	(1.1 to 4.5)
LSS	1.2	1.6	1.4	(0.9 to 3.2)
Combined	1.2	1.5	1.4	(1.0 to 2.4)

BEIR VII Bayesian analysis Criticisms

- Are the experiments used appropriate
  - Might certain tumor types distort the results (Harderian glands)
  - 8 of the experiments involved female mice whose ovaries are very sensitive to radiation which might distort hormonal balance and risks
  - Why include studies with leukemia as an outcome
- Why not use other animal studies
  - e.g. fractionation study discussed in BEIR VII
- Why not consider other epi studies
- What about other non-animal radio-biology experiments

DDREF Estimation From Epi Studies (Jacob et al 2009)

- Identified 12 analyses of 8 low-dose-rate moderate dose studies with solid cancer or all-cancer risk estimates
  - Techa River, Chernobyl Clean-up workers
  - Rocketdyne. ORNL, and Hanford workers
  - UK nuclear workers, French nuclear workers
  - IARC 15-country nuclear work study
  - Significant dose response in 7 of 12 analyses
- Compared published ERR/Gy estimates with analogous linear LSS risk estimate
  - Comparable LSS subset and dose (e.g. LSS skin dose : film badge dose)

DDREF Estimation From Epi Studies

- Computed ERR ratios $q_s = \frac{ERR_s}{ERR_{LSS(s)}}$ with a monte-carlo based variance estimate (V_s)
- Computed pooled risk ratio as

$$Q = \frac{\sum_s q_s / V_s}{\sum_s V_s^{-1}}$$

- DREF = 1/Q

DDREF Estimation From Epi Studies Results and Conclusions

- Individual mortality studies DREF = 0.8 (90% CI 0.5 to 2.0)
  - Rocketdyne, Chernobyl clean-up workers, Techa River, UK radiation workers, ORNL workers, French workers, Hanford workers
- Alternate grouping of mortality studies Q = 0.5 (90% CI 0.3 to 0.8)
  - Rocketdyne, 15-country worker study, Chernobyl clean-up workers, Techa River
- Incidence studies Q = 1.0 (90% CI 0.65 to 2.4)
- Conclusions
  - Low dose rate studies do not seem to have lower risks per unit dose than the LSS
  - Use of a DDREF of 2 may be inappropriate

Contrary Views
Is the Current DDREF Too Small?

- EPRI 2009
  "… there is a need to re-evaluate the magnitude of the dose and dose-rate effectiveness factors (DDREF) including **significant radiobiology data suggesting non-linear effects at low and very low doses, implying that health effects may be significantly less at low dose-rates than risk factors currently used. "** [Emphasis added]

  - Animal and experimental data
  - Recently discovered cellular processes (e.g. adaptive response, bystander effects, genomic instability, …)
  - High background radiation and other neglected epi studies

Contrary Views
Is the Current DDREF Too Small?

Table 6-1 Dose-Dose Rate Effectiveness and Dose Rate Reduction Factors (DDREF and DREF)

Subject of Study	Reference/Study Basis of Value	DDREF or DREF
DDREF derived with curve fitting of the human data		
	BEIR VII [1]	1.5
	ICRP [137]	2
DREF derived from animal and experimental data		
	Experimental Molecular/Cellular	4-???
	Chromosome Aberrations	4-6
	Mouse data	
	Lung Adenocarcinoma	3-7
	Ovarian Tumors	7-35
	Thymic lymphoma	10-30
	Mammary tumors	1-4
	Myeloid Leukemia	2-6
	Dog Data	
	Acute Bone Marrow Death	3-4
	Acute Lung Disease	10-30
	Dog Data (Cancer) [140]	10-35

From *Program on Technology Innovation: Evaluation of updated research on health effects and Risks Associated with low-dose ionizing radiation*. (EPRI 2009)

Whither DDREF
Personal Views

- DDREF concept developed around 1980 to allow for perceived inadequacies in low dose/.low dose-rate risk estimates based on the atomic bomb survivor data
  - Reflected a view that with more data dose response would be concave upward at low doses (cf the battle of BEIR III)
- Shorthand for real issues
  - What is shape of the radiation dose response in the low dose region
  - How does the dose response change with dose rate
- Cancer (and possible non-cancer) dose response is highly uncertain at low doses and low-dose rates
  - Likely to differ for different outcomes (cf solid cancer and leukemia in the LSS)
- Epi studies are extremely unlikely to resolve issue at doses / dose-rates of primary interest to radiation protection (e.g. < 10 mGy)
- Relevance of experimental radiobiology unclear (and will remain so)

Whither DDREF
Personal Views

- There is no compelling evidence against the LNT as a description of radiation effects on cancer risks
- Despite limitations the Epi data are the most relevant to radiation protection
- Little reason to use DDREF for radiation protection at this time
- Develop resources to facilitate better definition and estimation of DDREF
  - Database of relevant studies (with as much detailed data as possible)
  - More thought about how to combine these data to estimate the quantity (quantities) of interest

Whither DDREF
Challenges

- Develop better/ more complete methods to characterize uncertainty in the risk estimates from specific studies
- Take these uncertainties into account in developing the risk estimates that underlie standards and risk projections

Acknowledgments

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