Evidence from epidemiology and dose curvature analyses

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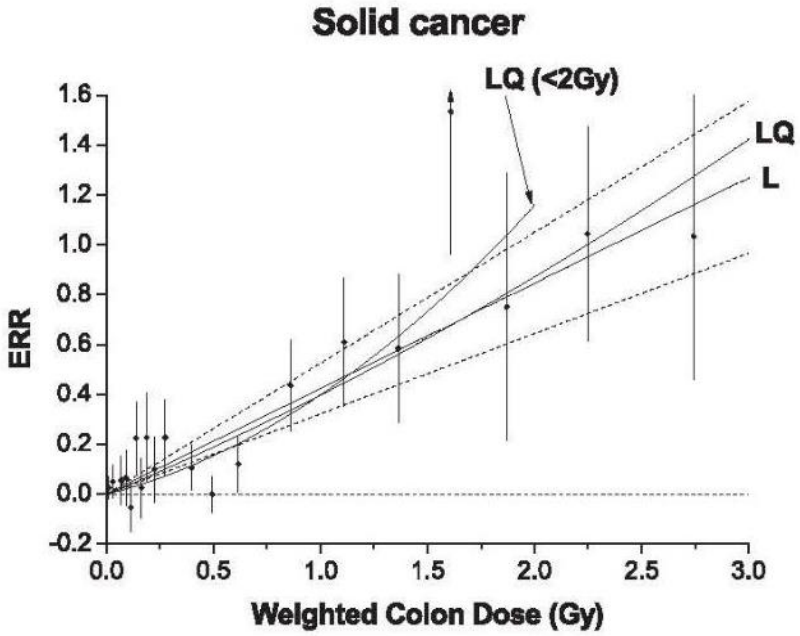
Outline of talk

- Introduction
- LSS data analysed and method of analysis
- Results
- Conclusions

LSS 14 mortality data A-bomb survivors

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



Highly significant dose response

- **Threshold of >0.15 Gy can be excluded**
- **Weak indications of upward curvature, particularly over 0-2 Gy (p=0.02)**

Aims and method of analysis (1)

- In LSS (and other high dose rate data) could get handle on DDREF by assessing curvature in dose response
- Can estimate low dose extrapolation factor (LDEF) via:

  = linear dose response coefficient /

  linear coefficient from linear-quadratic model

Aims and method of analysis (2)

- To assess curvature in dose response by assessing LDEF (ratio of linear coefficients in linear-quadratic models to linear)
- Analysis of LSS14 mortality data of Ozasa *et al* 2012, also LSS incidence data of Grant *et al* 2017, 2021, Cahoon *et al*/2017
- Analyze using linear-quadratic models, adjusting for age, *a*, age at exposure, *e*, sex, *s*, with semi-parametric adjustment for background

$$PY_i\lambda_i\left[1+(\alpha D+\beta D^2)\exp[\gamma_1(e-e_{av})+\gamma_2\ln(a/a_{av})+\gamma_3 1_{sex=female}]\right]$$

Aims and method of analysis (3)

(Little *et al Radiat Res* 2020 194 259-276)

- **Assessment of curvature in dose response in Life Span Study (LSS) using solid cancer mortality data** (Ozasa *et al Radiat Res* 2012 177 229-43) **and updated (DS02R1) dosimetry via linear-quadratic relative risk and absolute models for**
  - Solid cancer
  - Lung cancer
  - Stomach cancer
  - Breast cancer
  - All other solid cancer
- **Fitting of generalized ERR, EAR models**
- **Assess population risks at various test doses, using ERR, EAR models**
- **Use of two-step Bayesian Markov Chain approach to model classical dose errors in LSS similar to that used b y UNSCEAR (2006) and Little *et al*** (*Radiat Res* 2008 169 660-76)

Results of analysis of mortality data of Ozasa *et al*/2012 (0-4 Gy vs 0-2 Gy)

	0-4 Gy			0-2 Gy		
	Linear term (/Gy)(95% CI)	Quadratic/linear term (/Gy) (95% CI)	p-value lin-quad vs lin	Linear term (/Gy) (95% CI)	Quadratic/linear term (/Gy) (95% CI)	p-value lin-quad vs lin
All solid	0.233 (0.121, 0.380)	0.105 (-0.087, 0.544)	0.362	0.159 (0.025, 0.332)	0.809 (0.080, 8.571)	0.017
Female breast	1.155 (0.355, 2.425)	-0.102 (-0.256, 0.200)	0.330	0.584 (-0.285, 2.150)	0.760 (-0.220, 3.040)	0.261
Colon	0.055 (-0.254, 0.364)	1.787 (-10.536, 14.107)	0.024	0.009 (-0.083, 0.100)	2.594 (-28.705, 33.893)	0.237
Liver	0.380 (-0.066, 0.987)	-0.093 (-0.462 , 0.275)	0.721	0.067 (-0.519, 0.825)	4.109 (-37.580, 0.736)	0.246
Lung	0.474 (0.155, 0.941)	-0.099 (-0.312, 0.376)	0.480	0.324 (-0.034, 0.829)	0.330 (-0.242, 1.553)	0.430
Stomach	0.121 (-0.064, 0.374)	0.081 (-0.223, 3.957)	0.749	0.207 (-0.115, 0.614)	-0.251 (-0.684, 3.027)	0.483

- Indications of curvature for some cancer sites (e.g. colon) over full dose range 0-4 Gy
- Stronger indications of curvature over lower dose range 0-2 Gy

LDEF predicted by mortality data of Ozasa *et al*/2012 (0-3 Gy) (Little & Hamada *Radiat Res* 2022 198 582-9)

Endpoint	Linear model	Linear-quadratic model			LDEF (+95% CI)
	ERR / Gy (+ 95% CI)	ERR / Gy (+ 95% CI)	ERR / Gy^2 (+ 95% CI)	p-value lin-quad vs lin	
All solid cancer	0.608 (0.395, 0.864)	0.477 (0.247, 0.792)	0.084 (-0.042, 0.224)	0.186	1.273 (0.913, 2.182
Lung	0.614 (0.158, 1.507)	0.761 (0.180, 2.006)	-0.084 (-0.433, 0.172)	0.459	0.806 (0.313, 1.760
Stomach	0.536 (0.280, 0.856)	0.497 (0.019, 1.047)	0.024 (-0.236, 0.309)	0.859	1.077 (0.526, >100
Female breast	2.818 (1.382, 4.843)	2.964 (1.142, 5.553)	-0.096 (-0.889, 0.930)	0.826	0.951 (0.578, 2.369
All solid excluding lung, stomach, breast	0.790 (0.459, 1.214)	0.362 (-0.024, 0.882)	0.282 (0.031, 0.613)	0.027	2.183 (1.090, >100

- Indications of curvature for some cancer sites over 0-3 Gy dose range – LDEF mostly < 2.5

LDEF predicted by LSS incidence data (0-3 Gy) (Little & Hamada *Radiat Res* 2022 198 582-9)

Endpoint	Linear model	Linear-quadratic model			LDEF (+95% CI)
	ERR / Gy (+ 95% CI)	ERR / Gy (+ 95% CI)	ERR / Gy^2 (+ 95% CI)	p-value lin-quad vs lin	
All solid cancer	0.553 (0.421, 0.698)	0.466 (0.313, 0.652)	0.069 (-0.026, 0.169)	0.155	1.186 (0.942, 1.626)
All solid cancer, excluding autopsy only cases	0.585 (0.449, 0.734)	0.509 (0.346, 0.704)	0.060 (-0.040, 0.163)	0.237	1.150 (0.920, 1.554)
Lung cancer	0.429 (0.109, 0.867)	0.510 (0.122, 1.165)	-0.063 (-0.335, 0.177)	0.558	0.842 (0.344, >100)
Urinary tract cancer	0.618 (0.080, 1.444)	0.476 (0.003, 1.545)	0.114 (-0.364, 0.703)	0.570	1.298 (<0, 7.723)

- Indications of curvature for some cancer sites over 0-3 Gy dose range – LDEF generally < 1.3

England & Wales population risk using Bayesian MCMC models fit to LSS14 data

(Little *et al Radiat Res* 2020 194 259-276)

		Relative risk model	Absolute risk model
Cancer mortality endpoint	Test dose (Gy)	Radiation exposure-induced deaths / Gy (× 10^2) (95% BCI)	Radiation exposure-induced deaths / Gy (× 10^2) (95% BCI)
All solid cancer	0.01	3.57 (0.70, 6.81)	3.11 (-0.13, 6.51)
	0.1	3.88 (1.17, 6.97)	3.56 (0.54, 6.78)
	1	6.59 (4.82, 8.46)	7.51 (5.61, 9.50)
Lung cancer	0.01	2.57 (0.40, 5.09)	1.58 (-0.36, 4.07)
	0.1	2.61 (0.55, 5.02)	1.65 (-0.17, 4.03)
	1	2.99 (1.66, 4.53)	2.25 (0.86, 4.14)
Stomach cancer	0.01	0.09 (-0.02, 0.26)	0.54 (-0.33, 1.47)
	0.1	0.09 (-0.01, 0.26)	0.58 (-0.23, 1.45)
	1	0.11 (0.03, 0.26)	0.90 (0.38, 1.58)
Breast cancer	0.01	2.03 (0.49, 4.94)	0.91 (0.30, 1.76)
	0.1	2.01 (0.53, 4.80)	0.90 (0.32, 1.73)
	1	1.87 (0.72, 3.82)	0.87 (0.46, 1.50)
All solid cancer excluding lung, stomach, breast	0.01	0.22 (-1.56, 2.23)	-0.52 (-2.75, 1.94)
	0.1	0.48 (-1.17, 2.38)	-0.13 (-2.21, 2.21)
	1	2.93 (1.76, 4.38)	3.57 (2.15, 5.22)

- Population risks at test dose of 0.01 Gy in aggregate about half of these using test dose of 1 Gy
- Some cancer sites show greater reduction than this, some (e.g. breast, stomach) less
- This is NOT the same as LDEF – but does nevertheless give an indication of curvature

Conclusions

- Stronger indications of curvature over lower dose range (0-2 Gy, 0-3 Gy)
- Some indications of curvature in mortality data as indicated by LDEF < 2.5 overall
- Slightly weaker indications of curvature in incidence data as indicated by LDEF of 1.2-1.3 overall
- Reductions in population risk from models fitted to LSS14 data by factors of about 2 in going from test dose of 1 Gy to 0.01 Gy

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