National Cancer Institute

Second primary cancers in adults after radiotherapy – an epidemiological review

Article 31 Group meeting

Radiation induced long-term health effects after medical exposure

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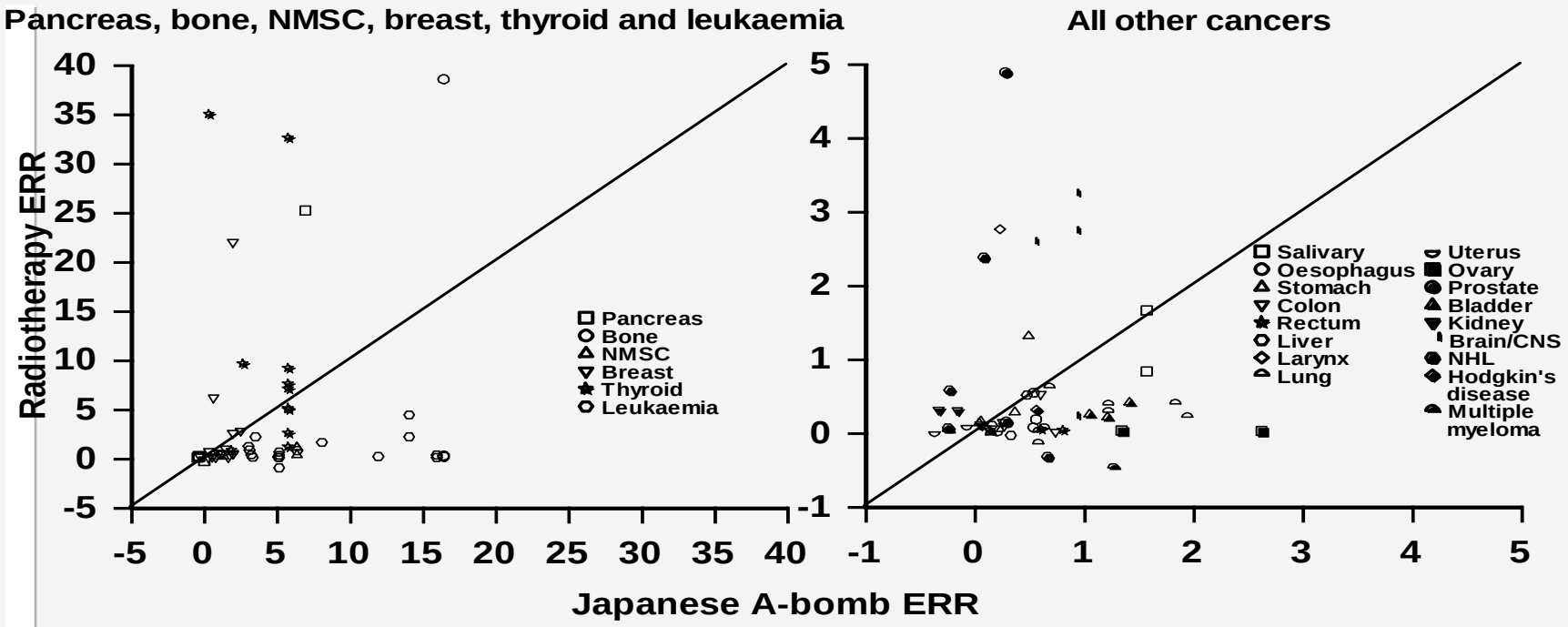
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Structure of talk

- Comparison of risks in radiotherapeutic populations with those in A-bomb survivors
- Accounting for risks using various models of cell mutation, cell sterilization and repopulation (and for leukaemia redistribution of cells between bone compartments)
- Taking account of bone marrow dose distribution for leukaemia
- Other considerations
- Conclusions

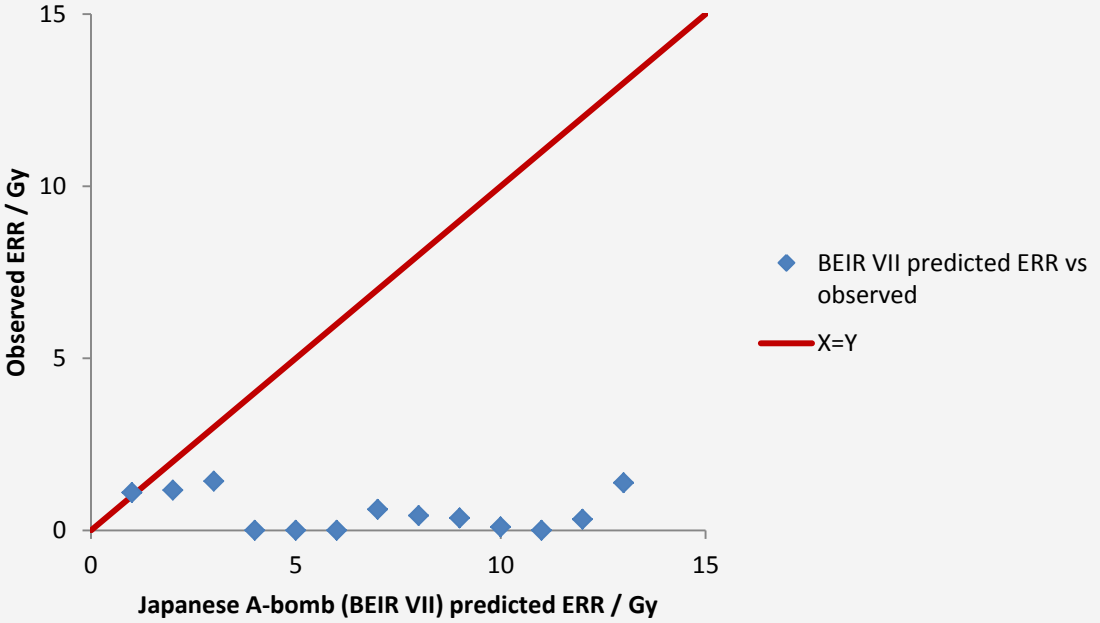
Comparison of A-bomb risks with radiotherapy risks (Little *Int J Radiat Biol* **77**:431-64;2001, *Lancet Oncol* **2**:212-20;2001)



Excess relative risks/Sv in radiotherapy datasets tend to be lower than in comparable (age-, sex-matched) subsets of A-bomb data

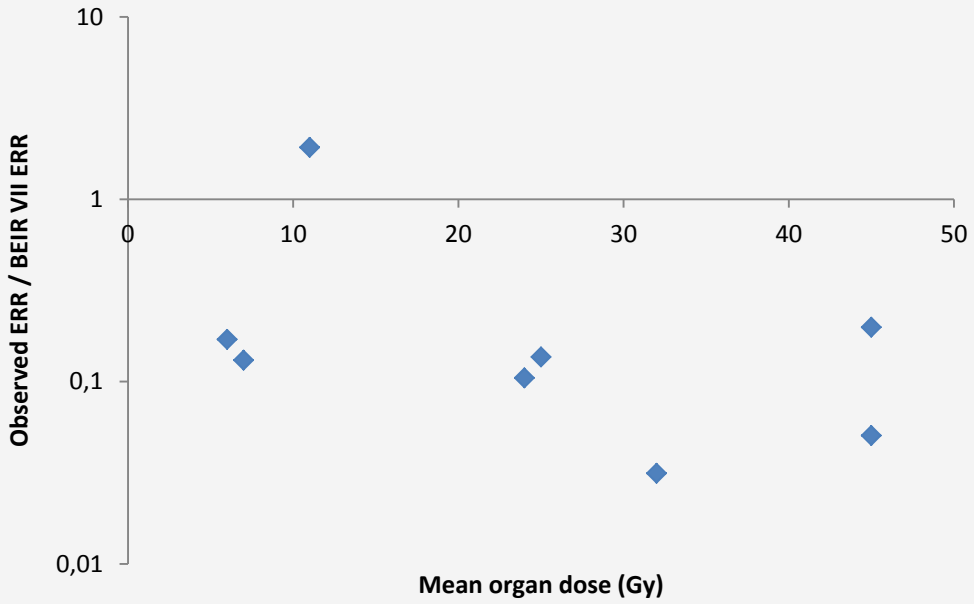
Note: This includes some data for childhood irradiation

Comparison of BEIR VII predicted A-bomb risks with high dose (> 5 Gy) radiotherapy risks: exposure in adulthood (Berrington de Gonzalez *et al IJROBP* **86**:224-33;2013)



Excess relative risks/Sv in radiotherapy datasets tend to be lower than for BEIR VII predicted (as function of age-, sex- etc) risks from A-bomb data

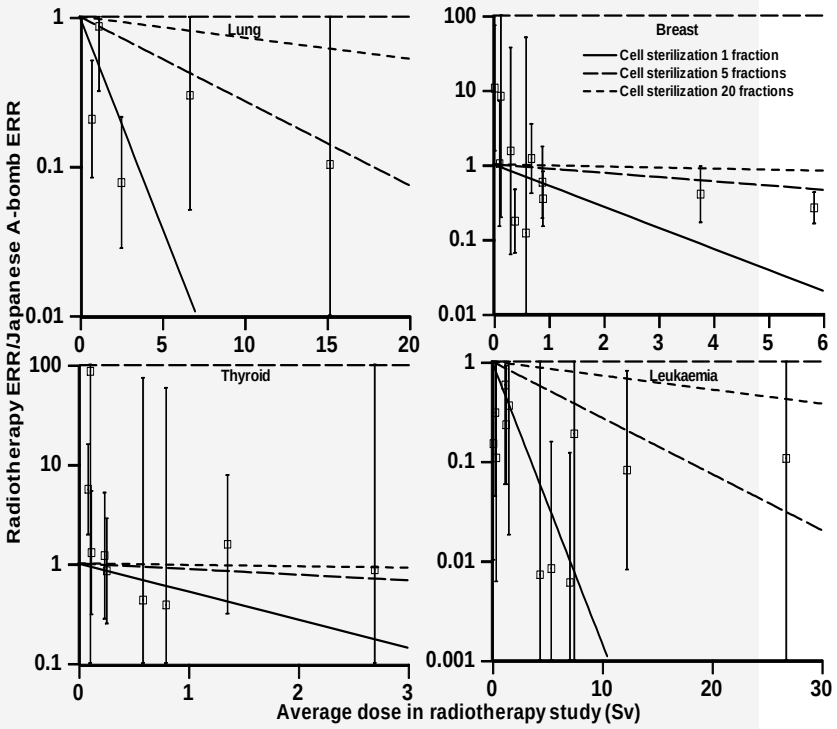
Ratio of high dose (> 5 Gy) radiotherapy risks to A-bomb (via BEIR VII) risks vs mean dose: exposure in adulthood (Berrington de Gonzalez *et al IJROBP* **86**:224-33;2013)



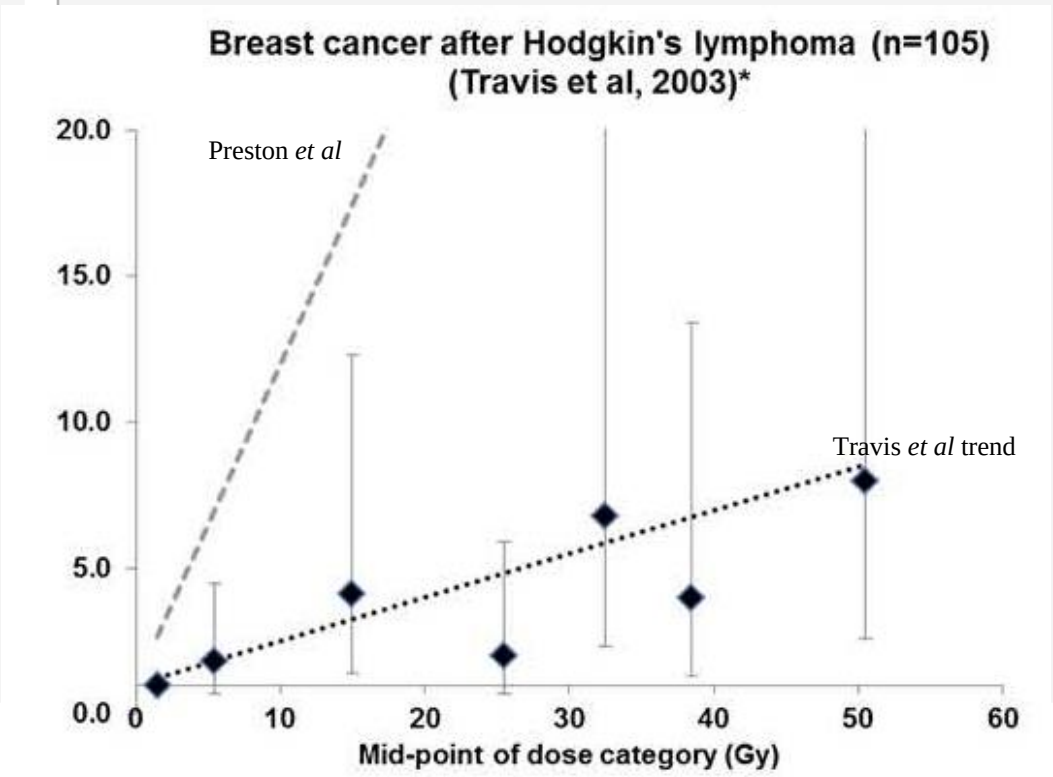
Ratio of excess relative risks/Sv in radiotherapy:A-bomb datasets tends to decrease with mean dose, suggestive of cell sterilization effect

Variations by cancer site and mean dose in ratio of risks [excess observed in RT:excess in A-bomb]

- For many cancer sites ratio of [excess risks /Sv in RT] to [excess risks /Sv in Japanese A-bomb] generally <1 and decreases with increasing dose, suggestive of cell sterilization effect (Little *IJRB* 2001 **77** 431-64)
- This is particularly marked for leukaemia and lung, but much less for certain other sites, e.g., thyroid, breast (Little *IJRB* 2001 **77** 431-64)



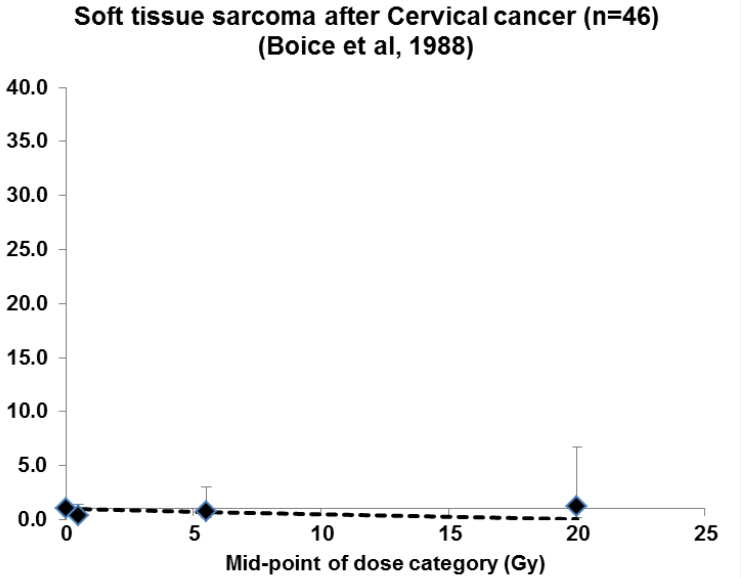
Breast cancer relative risk in group of women treated for Hodgkin's disease (Travis *et al. JAMA* 2003 **290** 465-475) and predicted risk from pooled breast cancer data (Preston *et al Radiat Res* 2002 **158** 220-35) (taken from Berrington de Gonzalez *et al IJROBP* **86**:224-33;2013)

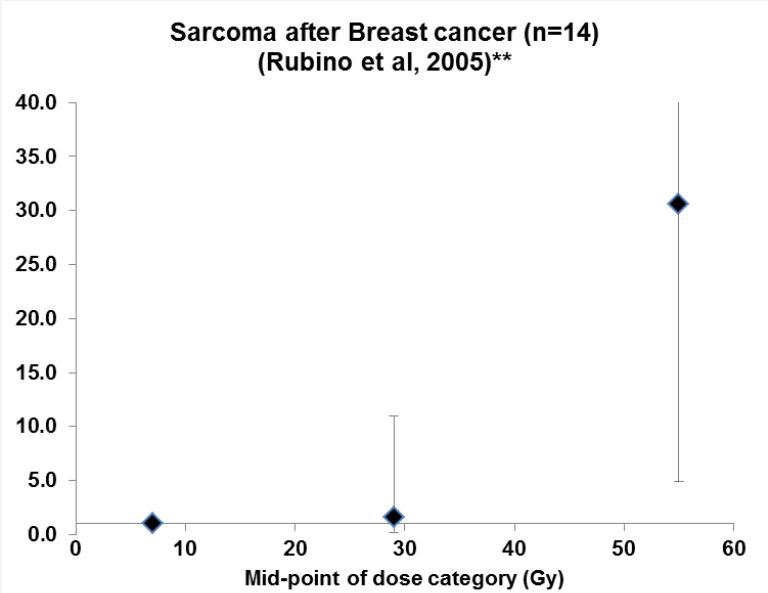


Risk increases linearly with dose in radiotherapy dataset – no suggestion of cell sterilization effect

Risk much lower than predicted by pooled analysis (Preston *et al Radiat Res* 2002 **158** 220-35)

Sarcoma relative risk in two groups of women treated for cancer (Boice *et al Radiat Res* 1988 **116** 3-55; Rubino *et al Breast Cancer Res Treat* 2005 **89** 277-88) (taken from Berrington de Gonzalez *et al IJROBP* **86**:224-33;2013)

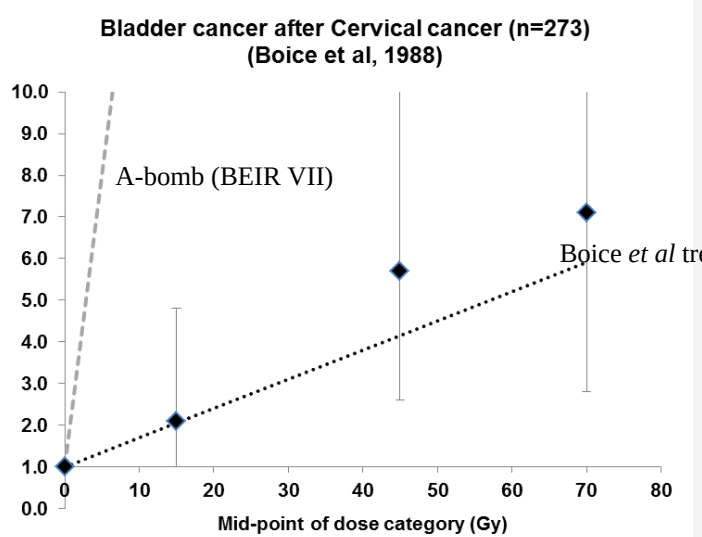


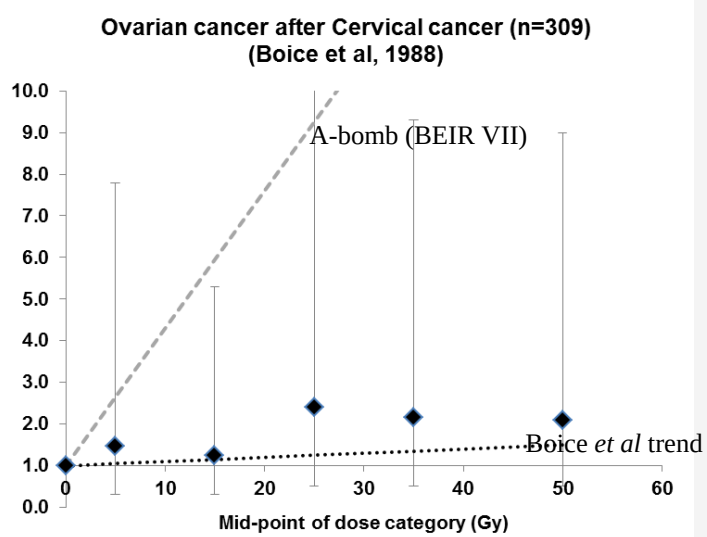


Sarcoma risk flat in Boice *et al.* cervical cancer data

Sarcoma risk increases with dose in Rubino *et al.* breast cancer data – but no suggestion of cell sterilization effect

Bladder and ovarian cancer relative risk in women treated for cervical cancer (Boice *et al Radiat Res* 1988 **116** 3-55) (taken from Berrington de Gonzalez *et al IJROBP* **86**:224-33;2013)



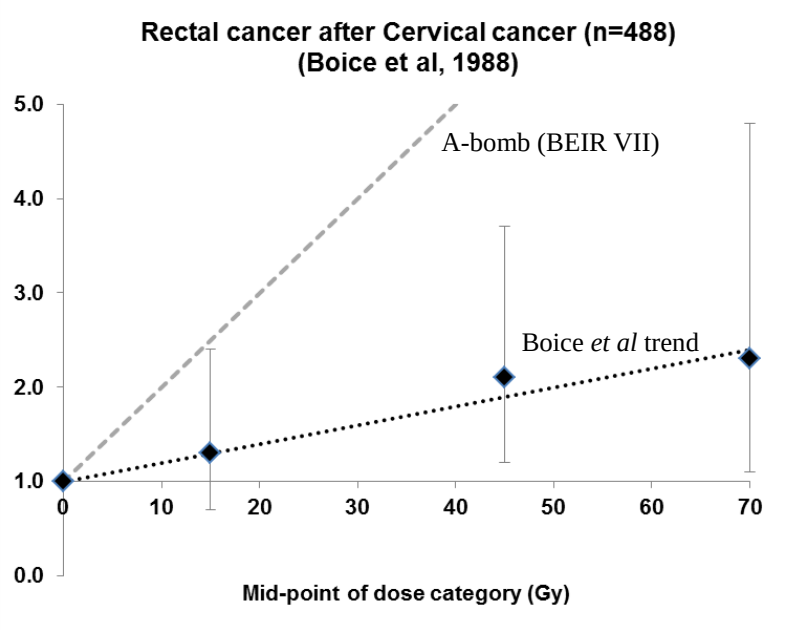


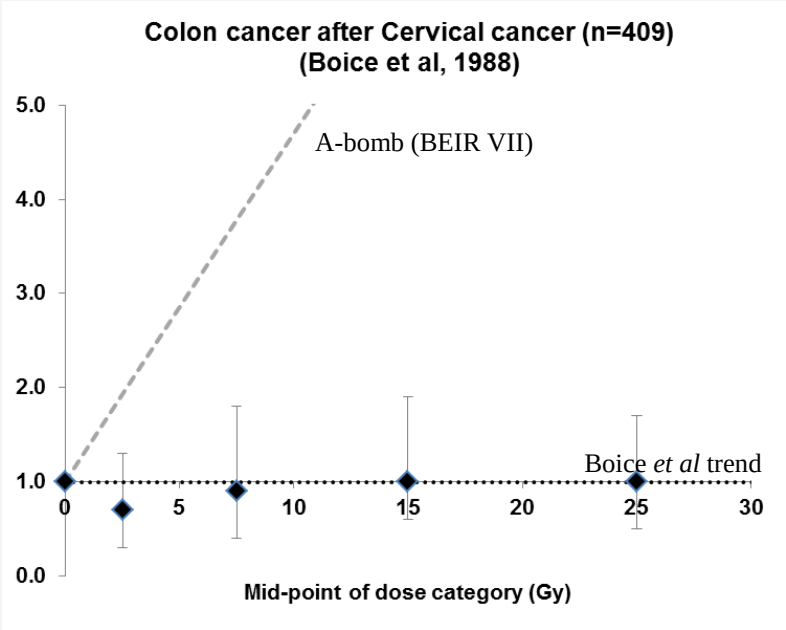
Risk increases with dose for bladder cancer – no suggestion of cell sterilization effect

Risk increases only weakly with dose for ovarian cancer – not (much) suggestion of cell sterilization effect

But risk is much lower than predicted by A-bomb (BEIR VII)

Rectal and colon cancer relative risk in women treated for cervical cancer (Boice *et al Radiat Res* 1988 **116** 3-55) (taken from Berrington de Gonzalez *et al IJROBP* **86**:224-33;2013)





Rectal cancer risk increases with dose – but no suggestion of cell sterilization effect

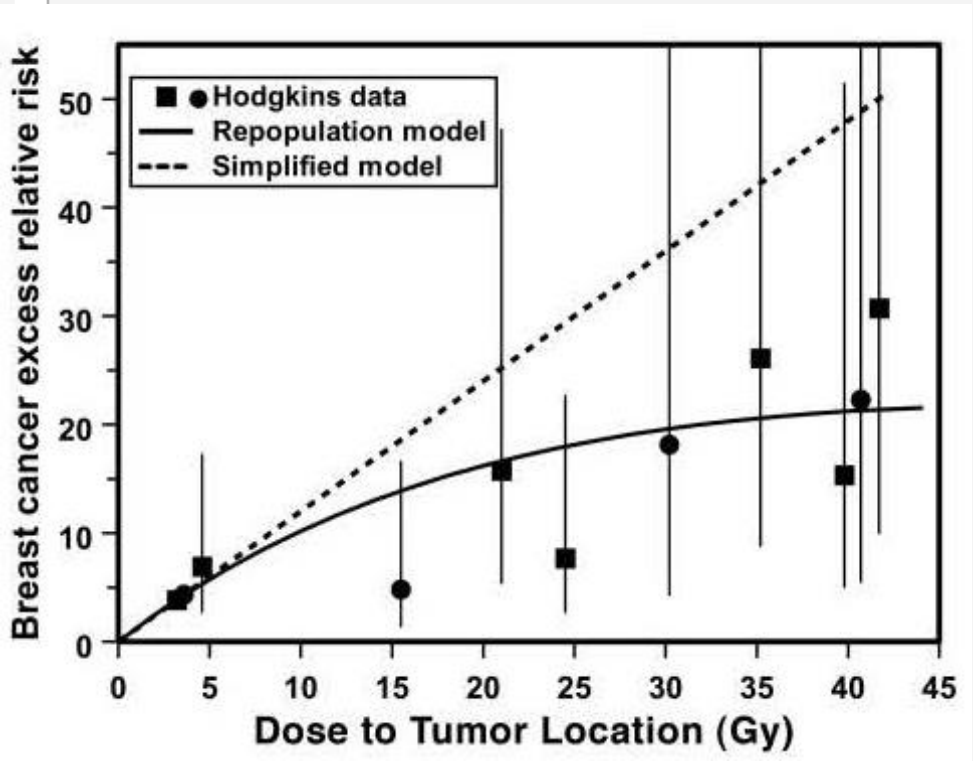
Nothing going on for colon cancer

Risk much less than for A-bomb (BEIR VII)

Evidence for stem cell repopulation

- Repopulation model of Sachs & Brenner (*PNAS* 2005 **102** 13040-5) modeled killing, transformation and repopulation of stem cells
- Mutant (transformed) cells are allowed to repopulate at different rate to normal (untransformed) cells
- When repopulation complete and mutant cells repopulate at same speed for normal cells, Sachs & Brenner model predicts that risks after high dose radiotherapy (RT) are same as without cell killing (so good model for certain cancers, e.g., breast cancer, thyroid)
- Known not to be case for leukaemia, lung (and many other sites): risks (per Sv) are less in most RT cohorts than in Japanese atomic bomb survivors (Little *IJRB* 2001 **77** 431-64)

Breast cancer excess relative risk in group of women treated for Hodgkin's disease (Travis *et al. JAMA* 2003 **290** 465-475) as modelled by Sachs & Brenner model (*PNAS* 2005 **102** 13040-5)



Simplified model (with repopulation of stem cells at same rate as transformed stem cells)(dashed line) slightly over-predicts risk

More complicated Sachs & Brenner repopulation model, with different repopulation rates for normal and transformed cells (solid line), fits well.

Evidence for haemopoietic stem cell repopulation (1)

- Bone marrow repopulation known to be rapid after radiotherapy (RT) (Sheridan *et al Lancet* 1992 **339** 640-4, Bensinger *et al Blood* 1993 **81** 3158-63), faster after treatment with granulocyte colony stimulating factor (gCSF)
- However, Sachs & Brenner model (*PNAS* 2005 **102** 13040-5) does not take account of certain additional features
  - Dosimetric heterogeneity (very important for leukaemia: bone marrow spread around body and most compartments get little dose from most RT)
  - Haemopoietic stem cells (HSC) recruited to and cleared from blood (Wright *et al Science* 2001 **294** 1933-6, Abkowitz *et al Blood* 2003 **102** 1249-53)

Evidence for haemopoietic stem cell repopulation (2)

- Haemopoetic stem cell (HSC) recruitment to/from blood

  in part response to cytokine exposure (Wright *et al Science* 2001 **294** 1933-6, Abkowitz *et al Blood* 2003 **102** 1249-53, Lapidot *et al Blood* 2005 **106** 1901-10)

- Speed of HSC recruitment is days to weeks (Wright *et al Science* 2001 **294** 1933-6, Abkowitz *et al Blood* 2003 **102** 1249-53), similar to *in situ* doubling speed (Mobest *et al Stem Cell* 1999 **17** 152-61, Flores-Guzman *et al Arch Med Res* 2002 **33** 107-14, Iwama *et al Immunity* 2004 **21** 843-51)

- Although much known about repopulation and HSC recruitment, much still not clear, e.g., whether it is globally or locally controlled

Stochastic or deterministic model? (Little *J Theoret Biol* 2007 **245** 83-97)

- Small number of haemopoietic stem cells (HSC) in bone marrow ~20,000 cells (Fliedner *Stem Cells* 1998 **16** 361-74) and very small number (~100) in circulating blood (Wright *et al Science* 2001 **294** 1933-6)
- Real possibility of extinction in certain bone marrow compartments (because of small numbers of HSCs) so important to use stochastic rather than deterministic model
- However, deterministic model (Shuryak *et al JNCI* 2006 **98** 1794-1806) generally more tractable

Ratio of average eventual numbers (at 200 days) of mutated HSCs per unit dose under various scenarios compared with predicted mutant HSC number in A-bomb data (single dose 0.1 Gy). (Little *J Theoret Biol* 2007 **245** 83-97)

Parameters	2 compartments (10^4 cells) receiving 10 x 0.1, 10 x 1.9 Gy, repopulating separately, no migration	2 compartments (10^4 cells) receiving 10 x 0.1, 10 x 1.9 Gy, repopulating jointly, no migration	2 compartments (10^4 cells) receiving 10 x 0.1, 10 x 1.9 Gy, repopulating jointly, with migration		3 compartments (2 x bone marrow: 9975 cells, 1 x blood: 50 cells) receiving 10 x 0.1, 10 x 1.9, 10 x 1.0 Gy, repopulating separately, with migration bone marrow ↔ blood)	
			Migration rate =0.07/day	Migration rate =7.0/day	Migration rate =0.07/day	Migration rate =7.0/day
Main	0.054	0.134	0.133	1.055	0.123	0.132
Alternate (mutant/normal repopulation rates <1 and higher linear-quadratic mutation initation rates)	0.030	0.041	0.040	0.030	0.034	0.037

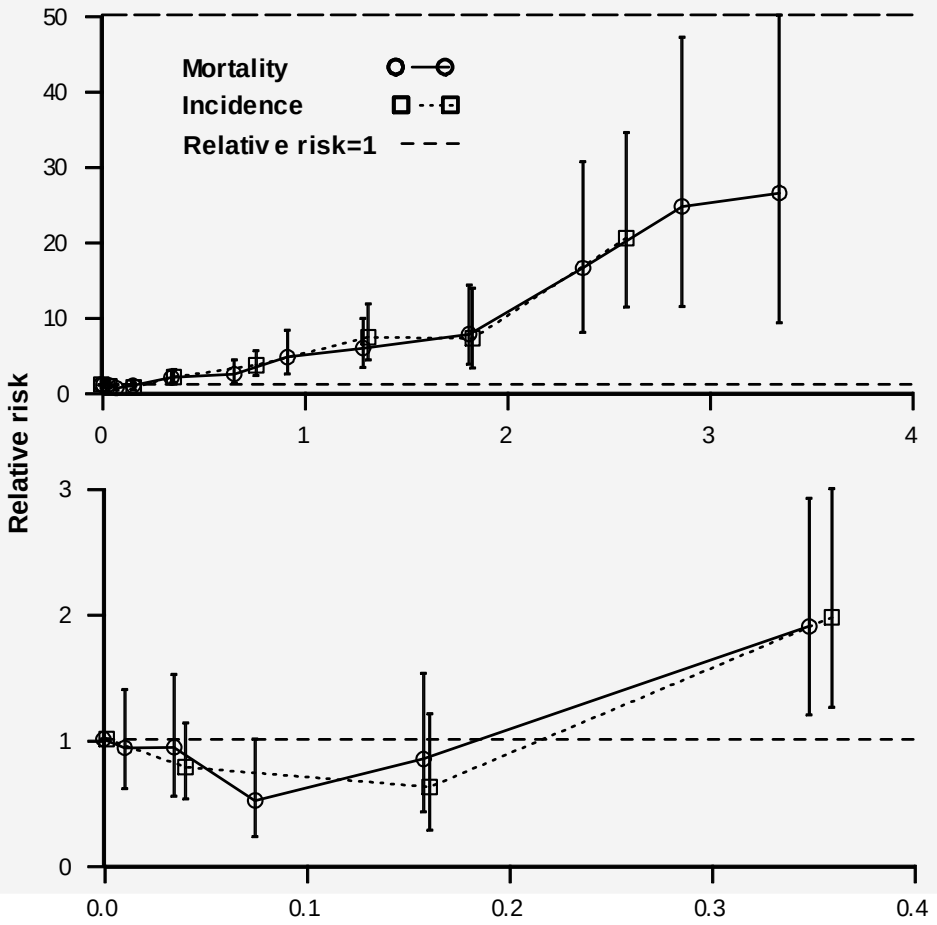
In general risks per unit dose much less than under A-bomb – only with joint (global) repopulation and rapid recruitment of HSCs to/from blood do risks approach those in A-bomb

Problem of dose heterogeneity in relation to radiation-induced leukaemia (1)

- Ionizing radiation induces all main leukaemia subtypes - acute myeloid leukaemia (AML), chronic myeloid leukaemia (CML), acute lymphocytic leukaemia (ALL) - with the exception of chronic lymphocytic leukaemia (CLL)(although there are some indications of this being in excess in latest LSS incidence data (Hsu *et al Radiat Res* 2013 **179** 361-82)
- There is significant upward curvature in the dose response for leukaemia in the A-bomb survivors (BEIR VII 2006, UNSCEAR 2006, Hsu *et al Radiat Res* 2013 **179** 361-82)
- Possibility of turnover in dose-response at higher doses (due to cell sterilization)?

Dose-response for radiation-induced leukaemia in A-bomb data

(Little and Muirhead *Int J Radiat Biol* 1998 **74** 471-480)



Problem of dose heterogeneity in relation to radiation-induced leukaemia (2)

- In many RT datasets there is substantial variation (by factors of at least 100) in dose to red bone marrow (RBM) compartments
- Taken together with curvature in dose response, it is critical that this taken into account in analysis

3-cohort leukaemia analysis (Little *et al.* *Radiat Res* 1999 **152** 280-92)

- Japanese atomic bomb survivors leukaemia incidence data (AML+CML+ALL) (Preston *et al* *Radiat Res* 1994 **137** (suppl) S68-S97)
- International Radiation Study of Cervical Cancer Patients leukaemia incidence study (Boice *et al J Natl Cancer Inst* 1987 **79** 1295-311)
- UK ankylosing spondylitis patients leukaemia mortality study (Weiss *et al Radiat Res* 1995 **142** 1-11)

Ankylosing spondylitis + International Radiation Study of Cervical Cancer Patients (IRSCCP)

- UK ankylosing spondylitis study
  - Study of cancer mortality in cohort of people treated for ankylosing spondylitis in UK between 1935-1957 (Weiss *et al Radiat Res* 1995 **142** 1-11)
  - Highly non-uniform doses to bone-marrow (mostly near the spine) from orthovoltage X-ray
  - Radiation delivered in high dose fractions (2 Gy/day) over periods up to 2 weeks, and with a number of treatment periods (in this cohort only treatments given within a year)
- IRSCCP
  - Study of second primary cancer incidence in cohort of 182,040 women treated for cervical cancer between 1920-1970 in 16 clinics and 17 cancer registries, followed up through early 1980s (Boice *et al. JNCI* 1987 **79** 1295-311)
  - Highly non-uniform doses to bone-marrow from intracavitary radium implants, orthovoltage X-ray, betatrons, van de Graaff generators and Linacs
  - Radiation delivered continuously over 2 days (radium implants) and in high dose fractions (2 Gy/day) over periods up to 6 weeks

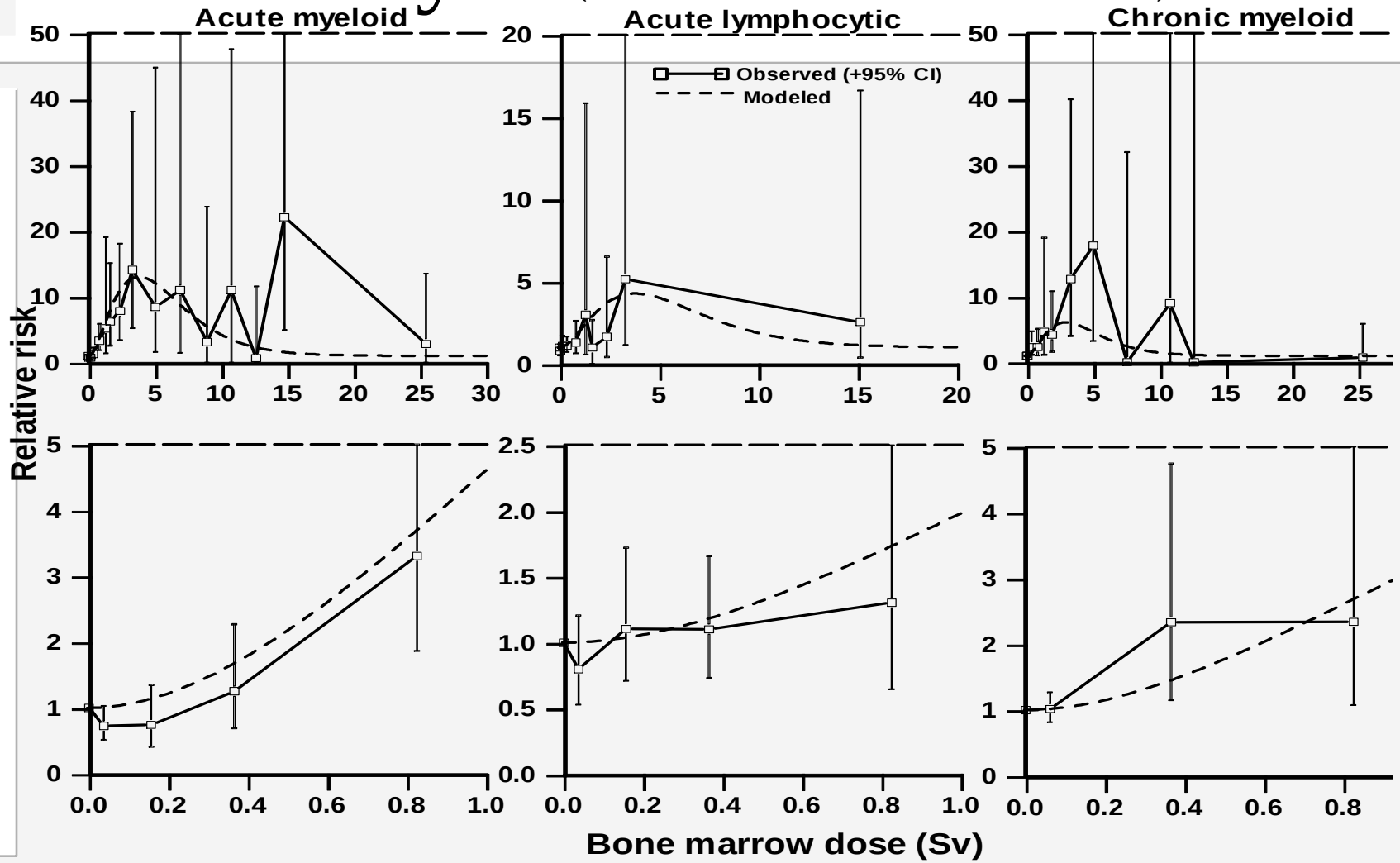
Characteristics of cohorts in 3-cohort analysis (Little *et al. Radiat Res* 1999 **152** 280-92)

	Japanese A-bomb	IRSCC	UK spondylitics
Persons	86,332	182,040	14,767
Person-years	2,242,928	1,278,951	267,234
Leukaemias	192	133	58
Dose range (Sv)	0.0->5.2 (mean 0.3)	0.5-25.2 (mean 7.1)	0.0-14.3 (mean 4.4)
Radiation dose rate/mode	Acute/ uniform whole body	Fractionated/ partial body Continuous/ partial body	Fractionated/ partial body

Main results from 3-cohort leukaemia analysis (Little *et al. Radiat Res* 1999 **152** 280-92)

- Significant trend with dose ($p<0.001$) for all three leukaemia subtypes in datasets analysed together
- Highly statistically significant heterogeneity ($p<0.00001$) between 3 datasets in optimal models fitted to all radiogenic leukaemias (AML+ALL+CML) combined
- When three leukaemia subtypes (AML, ALL, CML) are considered separately, there are no statistically significant differences between 3 datasets ($p>0.1$)

Leukaemia dose-response in 3-cohort analysis (Little *et al. Radiat Res* 1999 **152** 280-92)



Other considerations

- In all analysis I have emphasised comparison of excess relative risk per unit organ dose
- Background cancer rates in many radiotherapeutically treated populations (particularly if treated for cancer) is much higher than general population, probably because of selection
- It is known more generally that high background cancer rates tend to be offset by lower radiation-associated relative risks
- Possibly excess absolute risk or some other measure ought to be compared
- Adjuvant chemotherapy also needs to be taken into account, e.g., many chemotherapy regimes are highly leukaemogenic)

Conclusions

- RT risks generally less (per unit dose) than in Japanese A-bomb survivors, particularly for leukaemia
- However, for some endpoints (thyroid, breast) there is little or no evidence of reduction of risk, and for few endpoints does one see turnover characteristic of cell sterilization – possible explanation provided by Sachs & Brenner repopulation model
- For leukaemia, with disseminated target (RBM) may be important to take account of repopulation and redistribution of haemopoietic stem cells, and stochasticity (because of possibility of extinction of small cell populations) may also be important
- For endpoints such as leukaemia (with highly curved dose response) it is essential to take into account detailed RBM dose distribution