Childhood leukaemia in the Japanese atomic bomb survivors and in radiotherapeutically exposed groups

ICNIRP/WHO/BfS International workshop on "Risk factors for childhood leukaemia" Berlin, 5-7 May 2008

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Outline of talk

- Background
- What data is available?
  - A-bomb data (*in utero* exposed, exposed in childhood)
  - Childhood radiation-therapy data
- Methods of analysis
- Discrepancy in risks between these datasets: can they be explained by cell sterilisation effects?
- Problems with analysis
- Conclusions

Background

- Ionizing radiation known to induce most major leukaemia subtypes (all except chronic lymphocytic)
- A-bomb and other data exhibit significant upward curvature in ionising radiation dose response
- Modifications to leukaemia radiation risk also reasonably well known: excess relative risk per unit dose in A-bomb survivors decreases with increasing age, age at exposure
- Calculations using latest (BEIR VII, UNSCEAR 2006) models indicate that ~20% of childhood leukaemias in UK caused by natural background radiation (mainly gamma) (Little *et al.* 2008)

What data is available in atomic bomb survivors (1)?

- Delongchamp *et al.* (*Radiat. Res.* 1997 **147** 385-95) 3289 *in utero*, 14,312 exposed under age 6, followed for mortality (DS86 dose): 2 *in utero* exposed leukaemias, 24 childhood-exposed + 4 control leukaemias
- Preston *et al.* (*Radiat. Res.* 2004 **162** 377-89) 26,744 exposed under age 15, followed for mortality (DS02 dose): 65 leukaemias
- Preston *et al.* (*Radiat. Res.* 1994 **137** S68-S97) 26,789 exposed under age 15, followed for incidence (DS86 dose): 38 radiogenic leukaemias (AML, ALL, CML)

What data is available in atomic bomb survivors (2)?

- Retrospectively assembled cohorts: dosimetry based on responses to questionnaire (mostly 1950s)
- Follow-up for most starts in October 1950, 5.2 years after bomb – missing radiation-induced leukaemia cases? Almost certainly
- Variable end of follow-up
  - Delongchamp *et al.* (*Radiat. Res.* 1997 **147** 385-95) 12/1992
  - Preston *et al.* (*Radiat. Res.* 1994 **134** S68-S97) 12/1987
  - Preston *et al.* (*Radiat. Res.* 2004 **162** 377-89) 12/2000
- Does this matter? Most radiation-induced leukaemias within first 20 years
- Mixed radiation field, 1-2% high energy (>1 MeV) neutrons, rest high energy (>1 MeV) gamma
- Doses in range 0-4 Sv (some higher in Delongchamp *et al.*)
- Average dose ~0.1 Sv (~0.02 Sv in Delongchamp *et al. in utero*)

What data is available in childhood radiotherapy studies? (1)

- Second cancer studies (Tucker *et al.* (*J. Natl Cancer Inst.* 1987 **78** 459-464), Hawkins *et al.*(*Br. Med. J.* 1992 **304** 951-958), Kleinerman *et al.* (*J. Clin. Oncol.* 2005 **23**, 2272-2279), Haddy *et al.* (*Eur. J. Cancer* 2006 **42** 2757-2764))
- Haemangioma studies (Lindberg *et al.* (*Acta Oncol.* 1995 **34** 735-740), Lundell & Holm (*Radiat. Res.* 1996 **145** 595-601))
- Tinea capitis studies (Ron *et al.* (*Am. J. Epidemiol.*, 1988 **127** 713-725), Shore *et al.* (*Health Phys.* 2003 **85** 404-408)
- Nasopharyngeal radium study (Ronckers *et al.* (*J. Natl Cancer Inst.* 2001 **93** 1021-1027))

What data is available in childhood radiotherapy studies? (2)

- Doses obtained via retrospective evaluation based on treatment notes, phantom measurements etc
- In many studies doses are heterogeneous: not taken into account in published reports
- Mean dose in most studies (except haemangioma studies) tends to be much higher (>1 Gy) than A-bomb survivors (~0.1 Sv)
- Dose to parts of organs in or near beam tend to be very high (>10 Gy), particularly in second cancer studies
- In second cancer studies (Tucker *et al. J. Natl Cancer Inst.* 1987 **78** 459-464, Hawkins *et al. Br. Med. J.* 1992 **304** 951-958, Haddy *et al. Eur. J. Cancer* 2006 **42** 2757-2764) chemotherapy (CT) also given - CT (alkylating agents, epipodophyllotoxins) generally leukaemogenic – potential for confounding with radiation

What data is available in other radiotherapy studies (including some childhood)?

- Second cancer studies (Kaldor *et al.* (*New Engl. J. Med.* 1990 **322** 7-13), Boivin *et al.* (*J. Natl Cancer Inst.* 1995 **87** 732-741))
- Benign locomotor lesion study (Damber *et al.* (*Acta Oncol.* 1995 **34** 713-719))
- Diagnostic and therapeutic ^{131}I study (Hall *et al.* (*Lancet* 1992 **340** 1-4))
- Thorotrast study (Andersson and Storm (*J. Natl Cancer Inst.* 1992 **84** 1318-1325))
- Ankylosing spondylitis study (Weiss *et al.* (*Radiat. Res.* 1995 **142** 1-11))
- **Will not say more: separate risk estimates for childhood exposure impossible to extract from published reports**

Methods of analysis (1)

- No significant ($p>0.10$) (linear-quadratic) dose-response curvature for exposure in childhood in atomic bomb survivors
- Significant ($p<0.05$) variation of excess relative risk per unit dose by age at exposure, attained age in childhood-exposed A-bomb data
- However, from published radiotherapy data impossible to analyse controlling for age at exposure, attained age

Methods of analysis (2)

- Simple linear excess relative risk models fitted to all data (in A-bomb stratified by sex, city, age at exposure, attained age etc), unadjusted for anything else
- For RT studies analysis using open-literature published summary data (except Haddy *et al.* (*Eur. J. Cancer* 2006 **42** 2757-2764) for which trend estimate given)

Japanese A-bomb excess relative risks (ERR) Sv^{-1}

Cohort	ERR (Sv^{-1}) (+95% CI)
Delongchamp *et al* (*Radiat. Res.* 1997 **147** 385-95) *in utero*, mortality	-0.40 (<-0.40, 29.2)
Delongchamp *et al* (*Radiat. Res.* 1997 **147** 385-95) childhood (0-5), mortality	51.28 (19.0, 176.2)
Preston *et al.* (*Radiat. Res.* 2004 **162** 377-89) childhood (0-14), mortality	9.89 (5.24, 18.53)
Preston *et al.* (*Radiat. Res.* 1994 **137** S68-S97) childhood (0-14), incidence	17.69 (7.95, 41.59)

Japanese A-bomb *in utero*: lack of power compared with Preston *et al.* (*Radiat. Res.* 2004 **162** 377-89)

Dose group (Sv)	Deaths	Expected deaths assuming Preston *et al.* (2004) risks
0	4	4.000
0.01-0.025	1	0.053
0.025-0.05	1	0.057
0.05-0.1	0	0.090
0.1-0.25	0	0.202
0.25-0.5	0	0.233
0.5-1.0	0	0.273
1.0-2.0	0	0.217
>2.0	0	0.147

Cell sterilisation

- High doses of ionising radiation cause cell sterilisation (inactivation/death of cells)
- Well understood in biological systems (UNSCEAR 1993)
- Potential for reducing excess leukaemia risk at high doses (counteracting mutagenic initiation effect)
- Some analyses of leukaemia in RT patients have taken this into account (Boice *et al. J. Natl Cancer Inst.* 1987 **79** 1295–1311, Thomas *et al. Biometrics* 1992 **48** 781–94, Little *et al. Radiat. Res.* 1999 **152** 280-92)

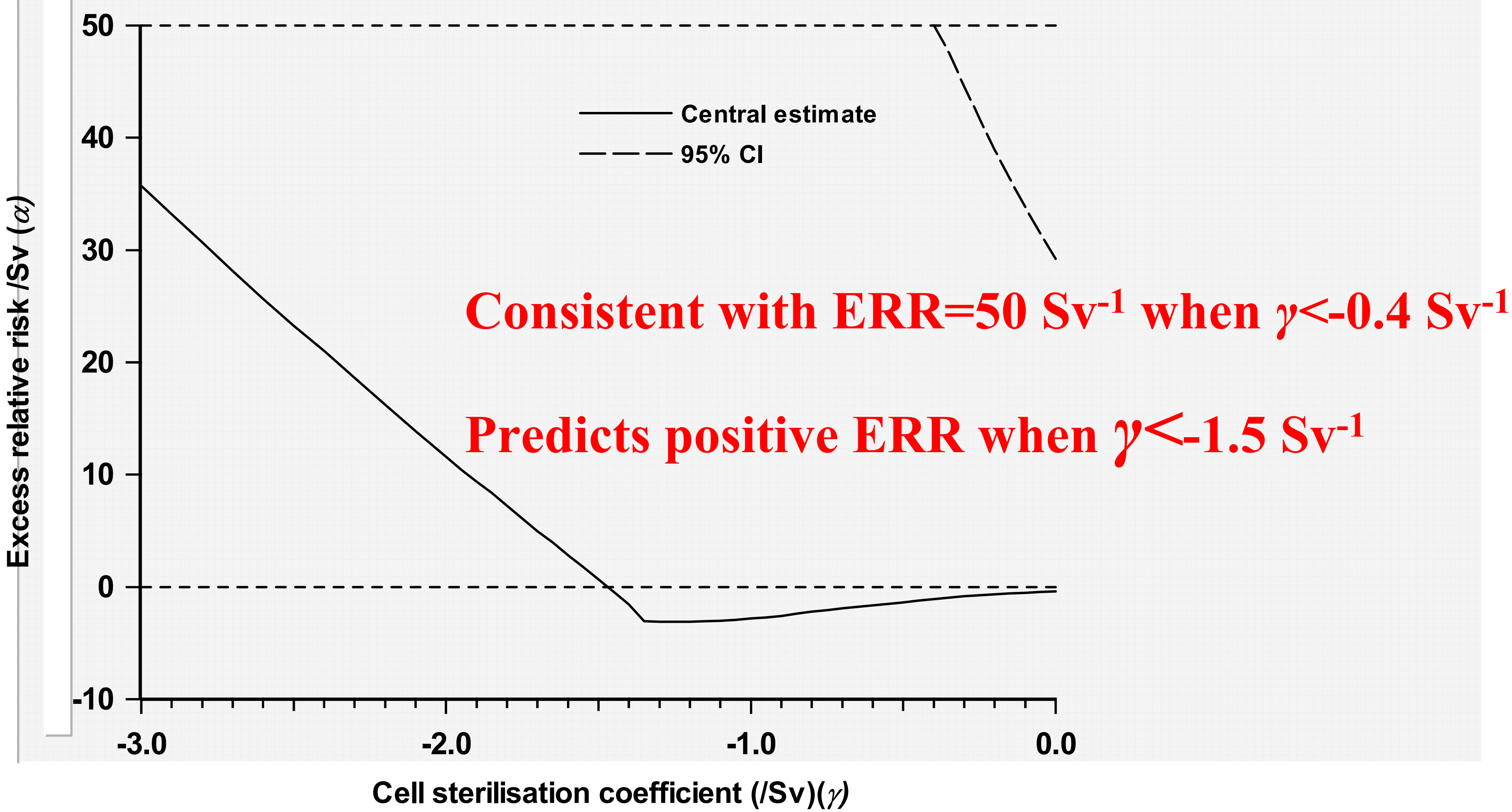
Could cell sterilisation explain lack of *in utero* risk in LSS?

- Fit linear-exponential relative risk model to Delongchamp *et al.* (*Radiat. Res.* 1997 **147** 385-95) *in utero* LSS data, using range of cell-sterilisation coefficients

$$\text{ERR} = \alpha \cdot D \cdot \exp(\gamma \cdot D)$$

- Cell sterilisation coefficients in biological data range - 1.72 – -0.30 Gy^{-1} (review of Deschavanne & Fertil (*Int. J. Radiat. Oncol. Biol. Phys.* 1996 **34** 251-66))
- Compute best estimate of linear ERR Sv^{-1} (α) and (upper) 95% CI for cell sterilisation coefficients (γ) fixed at various values in this range

Could cell sterilisation explain lack of *in utero* risk in LSS? Linear ERR (α) vs cell sterilisation coefficient (γ) (Delongchamp *et al. Radiat. Res.* 1997 **147** 385-95)



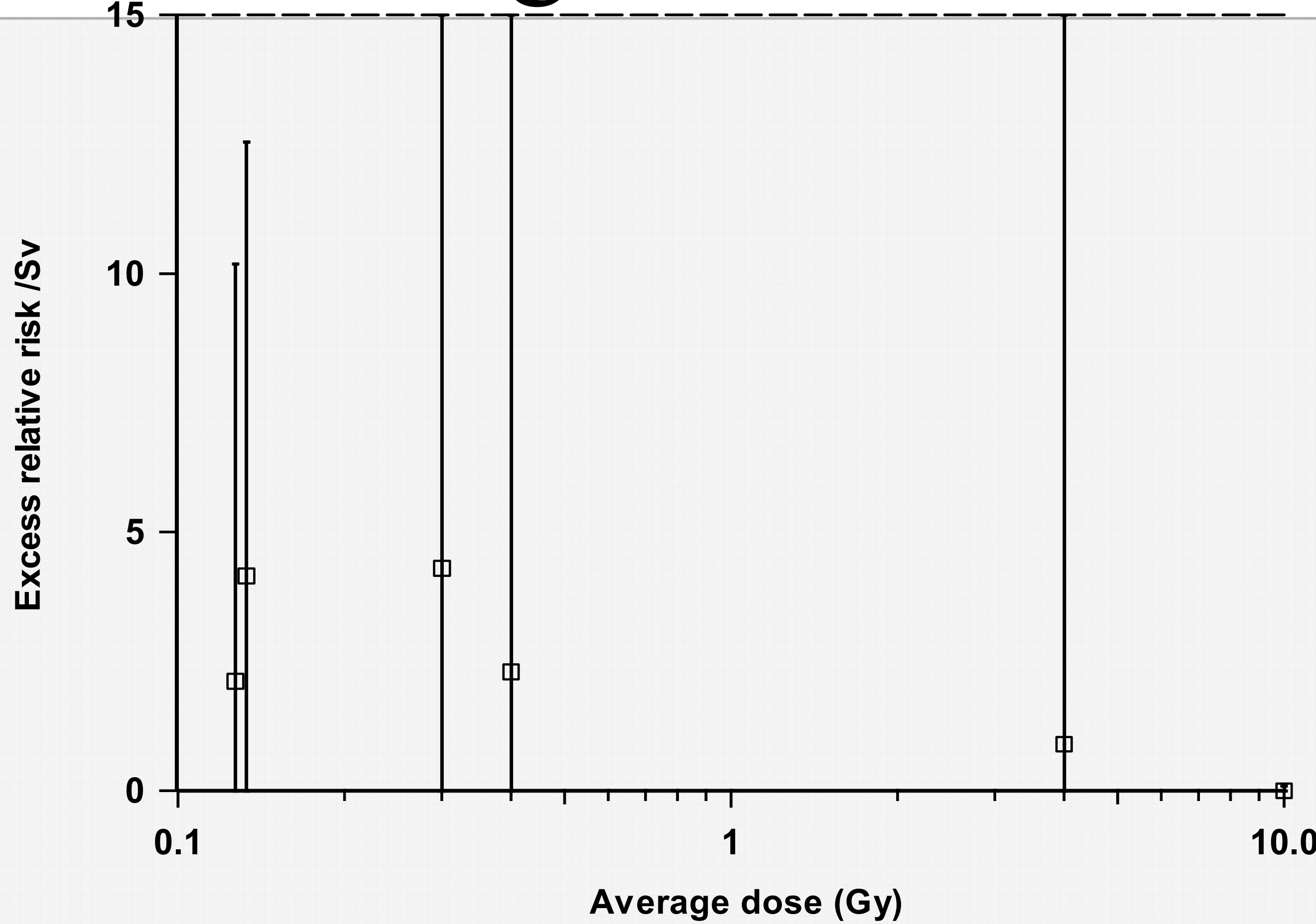
Childhood RT excess relative risks (ERR)

Cohort	ERR (Sv^{-1}) (+95% CI)
Tucker *et al.* (1987)	-0.00 (-0.03, 0.09) [###]
Ron *et al.* (1988)	4.3 (0.0, 15.3)
Hawkins *et al.* (1992)	0.24 (0.01, 1.28) [###]
Lindberg *et al.* (1995)	4.15 (-1.38, 12.54) [#]
Lundell & Holm (1996)	2.12 (-0.70, 10.18)
Ronckers *et al.* (2001)	2.3 (-1.0, 15.5) [###]
Shore *et al.* (2003)	0.9 (-0.1, 26.5) [###]
Kleinerman *et al.* (2005)	-0.76 (<-0.76, 2.86) [###]
Haddy *et al.* (2006)	0.31 (-0.32, 0.94) [###]

ERR much lower than A-bomb, statistically significantly lower in many cases

[#] p<0.05, [##] p<0.01, [###] p<0.001 2-sided incompatibility with A-bomb data

Childhood RT: excess relative risk Sv^{-1} vs average dose



Decreasing trend of ERR Sv^{-1} with average dose

Could discrepancy be due to cell sterilisation?

Could discrepancy between LSS and RT be due to cell sterilisation?

- Known cell sterilisation coefficient (-0.65 Sv^{-1}) (median from review of Deschavanne & Fertil (*Int. J. Radiat. Oncol. Biol. Phys.* 1996 **34** 251-266))
- Fit linear-quadratic-exponential (LQE) relative risk model to A-bomb data (mortality, incidence), using this cell-sterilisation coefficient

$$\mathrm{ERR} = (\alpha \cdot D + \beta \cdot D^2) \cdot \exp(\gamma \cdot D)$$

- Obtain average ERR: weight LQE dose response to dose distribution in RT cohort, taking account of fractionation

$$Avg[\mathrm{ERR}] = \sum_i w_i^{0.5} \cdot [(\alpha \cdot D_i + (\beta / n) \cdot D_i^2) \cdot \exp(\gamma \cdot D_i / n)] / \sum_i w_i^{0.5} \cdot D_i$$

Childhood RT relative risks adjusted for cell killing

Cohort	ERR (Sv^{-1}) (+95% CI) from study	Adjusted ERR (Sv^{-1}) from A-bomb
Ron *et al.* (1988)	4.3 (0.0, 15.3)	1.55
Lindberg *et al.* (1995)	4.15 (-1.38, 12.54)	9.71
Lundell and Holm (1996)	2.12 (-0.70, 10.18)	4.17
Ronckers *et al.* (2001)	2.3 (-1.0, 15.5)	5.81
Shore *et al.* (2003)	0.9 (-0.1, 26.5)	14.81
Kleinerman *et al.* (2005)	-0.76 (<-0.76, 2.86)	2.02

NB: requires dose distribution, average number of fractions, so can only do for these 6 (out of 9) studies

Problems with analysis (1)

- Analysis based on summary, collapsed RT data
- Assume linear relative risk models, unadjusted for age at exposure, sex, time since exposure, dose-response curvature
- These variables, e.g., age at exposure, attained age, known from A-bomb data to be important modifiers of leukaemia radiation risk

Problems with analysis (2)

- Assuming relative risk /dose invariant between cohorts: might not be true - UNSCEAR (1994) suggests that in different circumstances relative or absolute excess might be invariant – or combination of two (Little *et al. Stat Med* 1999 **18** 17-33)
- No account taken of chemotherapy (CT) in second cancer studies (Tucker *et al. J. Natl Cancer Inst.* 1987 **78** 459-464, Hawkins *et al. Br. Med. J.* 1992 **304** 951-958, Haddy *et al. Eur. J. Cancer* 2006 **42** 2757-2764) - CT (alkylating agents, epipodophyllotoxins) generally leukaemogenic
- No account taken of heterogeneity of dose, dose timing

Problems with analysis (3)

- Cell repopulation within and between bone arrow compartments known to be important in leukaemia (Shuryak *et al. J. Natl Cancer Inst.* 2006 **98** 1794-1806, Little *J. Theoret. Biol.* 2007 **245** 83-97)
- Not properly taken into account here, and might invalidate approximate cell sterilisation calculations

Conclusions (1)

- Very substantial leukaemia risks associated with radiation exposure in childhood in A-bomb data: ERR of ~10 - 50 Sv^{-1}
- No *in utero* risk in A-bomb data: lack of statistical power, possibly due to cell sterilisation?
- Preliminary analysis indicates that risks in A-bomb data are much greater than in childhood radiotherapy (RT) studies
- If account taken of cell sterilisation then risks in A-bomb data much more compatible with childhood RT studies

Conclusions (2)

- Problems with radiotherapy (RT) data: all analysis based on summary published data, taking no account of chemotherapy (known leukaemogens): potential confounder
- No account of distribution of dose in bone marrow, dose timing, repopulation etc in RT studies - might well invalidate argument based on cell sterilisation
- No account taken of age at exposure, attained age, known to be important modifiers of leukaemia risk