Childhood Leukaemia Following Antenatal or Postnatal Exposure to X-rays for Diagnostic Purposes

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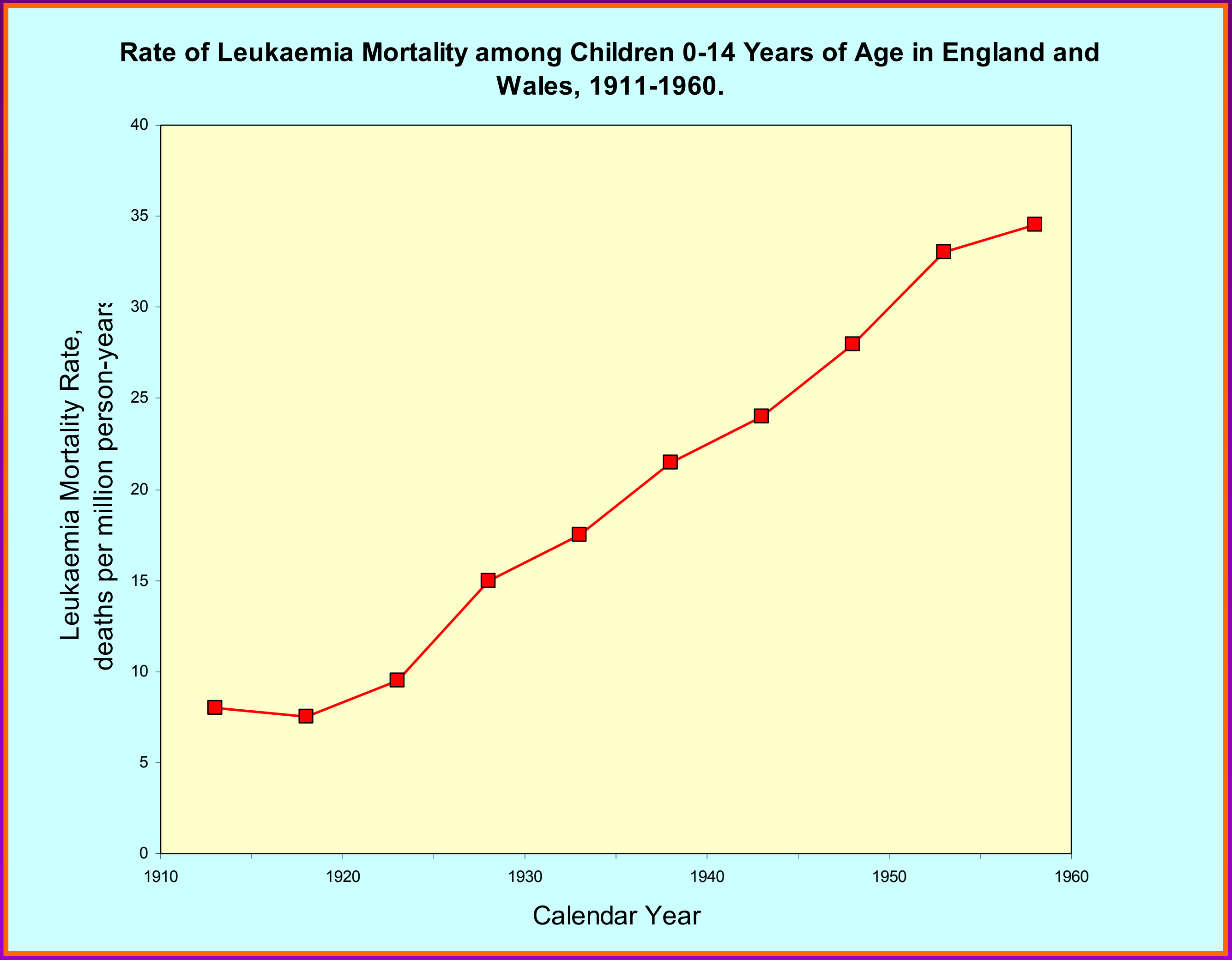
Childhood Leukaemia Trend

(R. Doll, *J R Statist Soc* A 1989; **152**: 341-351)



Oxford Survey of Childhood Cancers (OSCC)

- In the early-1950s a nationwide case-control study of mortality from leukaemia and other cancers among children in Great Britain was initiated by Dr Alice Stewart and her colleagues. This became the Oxford Survey of Childhood Cancers (OSCC).
- First results reported in *The Lancet* in 1956.

Diagnostic Intrauterine Irradiation

(A. Stewart *et al.*, *Lancet* 1956; **ii**: 447)

Deaths from Childhood Cancer during 1953-1955						
Maternal irradiation during relevant pregnancy	**Leukaemia***			**Other Cancers***		
	Cases	**Controls**	**Relative Risk (95% confidence interval)**	**Cases**	**Controls**	**Relative Risk (95% confidence interval)**
Abdomen	42	24	1.92 (1.12, 3.28)	43	21	2.28 (1.31, 3.97)
Other	25	23	1.19 (0.65, 2.16)	33	32	1.15 (0.68, 1.94)
None	202	222	1 (reference)	202	225	1 (reference)

* Death under 10 years of age

Initial Reaction to Association

- The preliminary findings of Stewart *et al.* (1956) were received with scepticism.
  - Information on X-ray exposure was obtained from maternal interviews − possible recall bias.
  - It was not believed that low dose X-rays could induce cancer, especially solid tumours − possible confounding (e.g. maternal ill health).

Further Findings

- Preliminary findings confirmed by extended OSCC study results reported in *BMJ* in 1958.
- Concerns over maternal recall bias met by study of MacMahon (1962) in the North-East USA based on contemporary hospital records of antenatal X-rays.
- Maternal recall in OSCC largely confirmed by medical records of X-ray exposures.

Childhood Leukaemia

- The most recent result from the OSCC for childhood leukaemia as a separate category was reported by Bithell and Stewart (1975):

Relative Risk (RR) = 1.49 (95% CI: 1.33, 1.67)

- Results have now been reported from many independent case-control studies from around the world:

Case-control Study	Study Details	Cases (Exposed/Total)	Information	RR (unadjusted)	95% CI
Bithell and Stewart (1975)	GB (OSCC); deaths, 1953-67	569/4052	297	**1.49**	**(1.33, 1.67)**
Monson and MacMahon (1984)	NE USA; deaths, 1947-60	94/704	76	**1.48**	**(1.18, 1.85)**
Robinette and Jablon (1976)	USA military hospitals; deaths, 1960-69	64/429	44	**1.08**	**(0.80, 1.46)**
Naumburg *et al.* (2001)	Sweden; incident cases, 1973-89	68/624	29	**1.13**	**(0.78, 1.63)**
Roman *et al.* (2005)	England & Wales (UKCCS); incident cases, 1992-96	37/1196	28	**1.05**	**(0.73, 1.52)**
Shu *et al.* (2002)	North America (CCG); ALL incident cases, 1989-93	55/1809	26	**1.16**	**(0.79, 1.71)**
Polhemus and Koch (1959)	Los Angeles; incident cases, 1950-57	66/251	23	**1.23**	**(0.82, 1.85)**
Infante-Rivard (2003)	Quebec; ALL incident cases, 1980-98	42/701	21	**0.85**	**(0.56, 1.30)**
Hopton *et al.* (1985)	N England; leukaemia and lymphoma incident cases, 1980-83	37/245	19	**1.35**	**(0.86, 2.11)**
Kaplan (1958)	California; acute leukaemia deaths, 1955-56	40/150	17	**1.60**	**(1.00, 2.57)**
Graham *et al.* (1966)	USA "tri-state"; incident cases, 1959-62	27/313	17	**1.40**	**(0.87, 2.27)**
van Steensel-Moll *et al.* (1985)	Netherlands; ALL incident cases, 1973-79	41/517	12	**2.22**	**(1.27, 3.88)**
Ford *et al.* (1959)	Louisiana; deaths, 1951-55	21/78	11	**1.71**	**(0.96, 3.06)**
Stewart (1973); Mole (1974)	GB (OSCC) **twins**; deaths, 1953-64	51/70	11	**2.17**	**(1.19, 3.95)**
Salonen (1976)	Finland; incident cases, 1959-68	15/300	10	**1.01**	**(0.54, 1.90)**
Ager *et al.* (1965)	Minnesota; deaths, 1953-57	20/107	10	**1.27**	**(0.68, 2.37)**
Roman *et al.* (1997)	S England; incident cases, 1962-92	16/143	10	**0.72**	**(0.39, 1.34)**
Golding *et al.* (1992)	SW England; incident cases, 1971-91	14/63	9	**2.03**	**(1.06, 3.88)**
Magnani *et al.* (1990)	N Italy; AL incident cases, 1981-84	10/164	6	**1.09**	**(0.49, 2.44)**
Rodvall *et al.* (1990)	Swedish **twins**; incident cases, 1952-83	10/27	5	**1.83**	**(0.77, 1.47)**
Gunz and Atkinson (1964)	New Zealand; incident cases, 1958-61	14/102	5	**1.11**	**(0.47, 2.61)**
Shu *et al.* (1988)	Shanghai; incident cases, 1974-86	8/309	4	**1.86**	**(0.71, 4.87)**
Roman *et al.* (1993)	S England; leukaemia plus NHL incident cases, 1972-89	5/37	4	**1.12**	**(0.40, 3.15)**
Shu *et al.* (1994)	North America (CCG); infant AL incident cases, 1983-88	7/291	4	**1.10**	**(0.43, 2.83)**
Harvey *et al.* (1985)	Connecticut **twins**; incident cases, 1935-81	5/13	3	**1.81**	**(0.55, 5.99)**
Wells and Steer (1961)	New York; incident cases	4/77	3	**0.72**	**(0.22, 2.34)**
Kjeldsberg (1957)	Norway; incident cases, 1946-56	5/55	3	**0.59**	**(0.18, 1.93)**
McKinney *et al.* (1999)	Scotland (UKCCS), incident cases, 1991-94	6/144	3	**2.31**	**(0.69, 7.70)**
van Duijn *et al.* (1994)	Netherlands; ANLL incident cases, 1973-79	6/80	3	**2.35**	**(0.78, 6.99)**
Murray *et al.* (1959)	New York; deaths, 1940-57	3/65	2	**0.92**	**(0.25, 3.36)**
Gardner *et al.* (1990)	NW England; incident cases, 1950-85	3/20	2	**1.19**	**(0.31, 4.55)**

Childhood Leukaemia OSCC *vs.* The Rest

Case-control Study	Cases (Exposed/Total)	Statistical Information	Relative Risk	95% Confidence Interval
OSCC	620/4122	308	**1.51**	**(1.35, 1.69)**
All Except OSCC	746/9764	411	**1.26**	**(1.14, 1.39)**

Statistical Association

- It is now generally accepted that a statistical association exists between childhood leukaemia and fetal exposure to diagnostic X-rays.

- However, a statistical association does not necessarily reflect a direct cause-and-effect relationship – chance, bias and confounding are alternative explanations.

Possible Confounding

- Extensive searches for a confounding factor that might explain the association have failed to identify one.

- Case-control studies of twins, with a materially higher rate of obstetric radiography than singletons, find a similar level of association with an antenatal X-ray examination as that for singleton births.

Grounds for Controversy

(J. D. Boice Jr and R. W. Miller, *Teratology* 1999; **59**: 227-33)

1) Apparent discrepancy with findings of cohort studies, especially the Japanese A-bomb survivors irradiated *in utero.*

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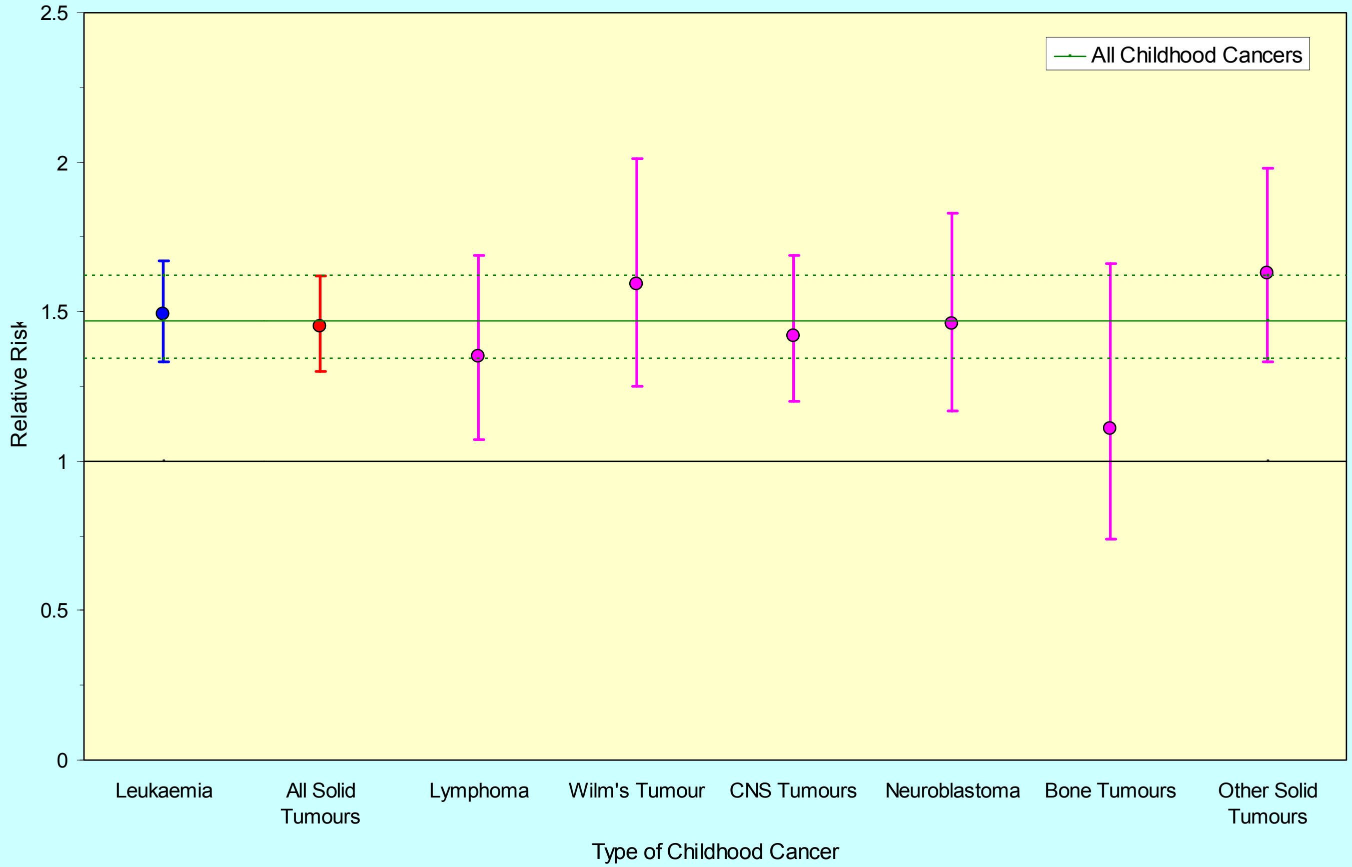
2) Apparent discrepancy with findings of studies of postnatal irradiation.
3) Twins appear to have the same, or a lower, risk of childhood cancer when compared with singletons, despite more radiography.
4) All types of childhood cancer seem to be elevated to a similar degree.

Type of Childhood Cancer

(J. F. Bithell and A. M. Stewart, *Br J Cancer* 1975; **31**: 271-87)



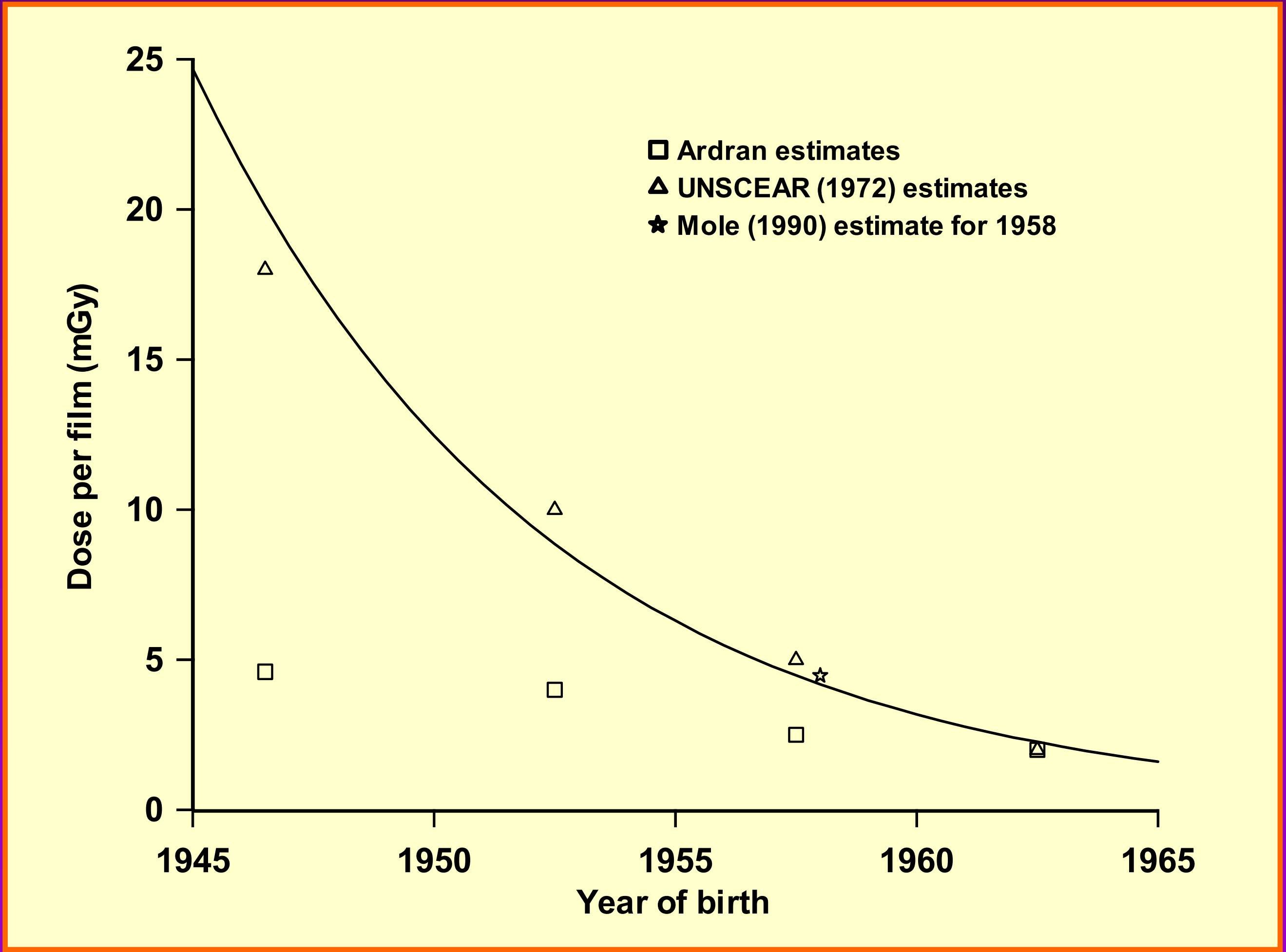
Risk Coefficient

- To derive a risk coefficient (risk per unit dose received by the fetus) for childhood cancer estimates of fetal doses are required.

- Detailed fetal doses have only been derived for the OSCC, and this study is the only one large enough to provide risk estimates having reasonable precision.

Average Fetal Dose per X-ray Film Exposed

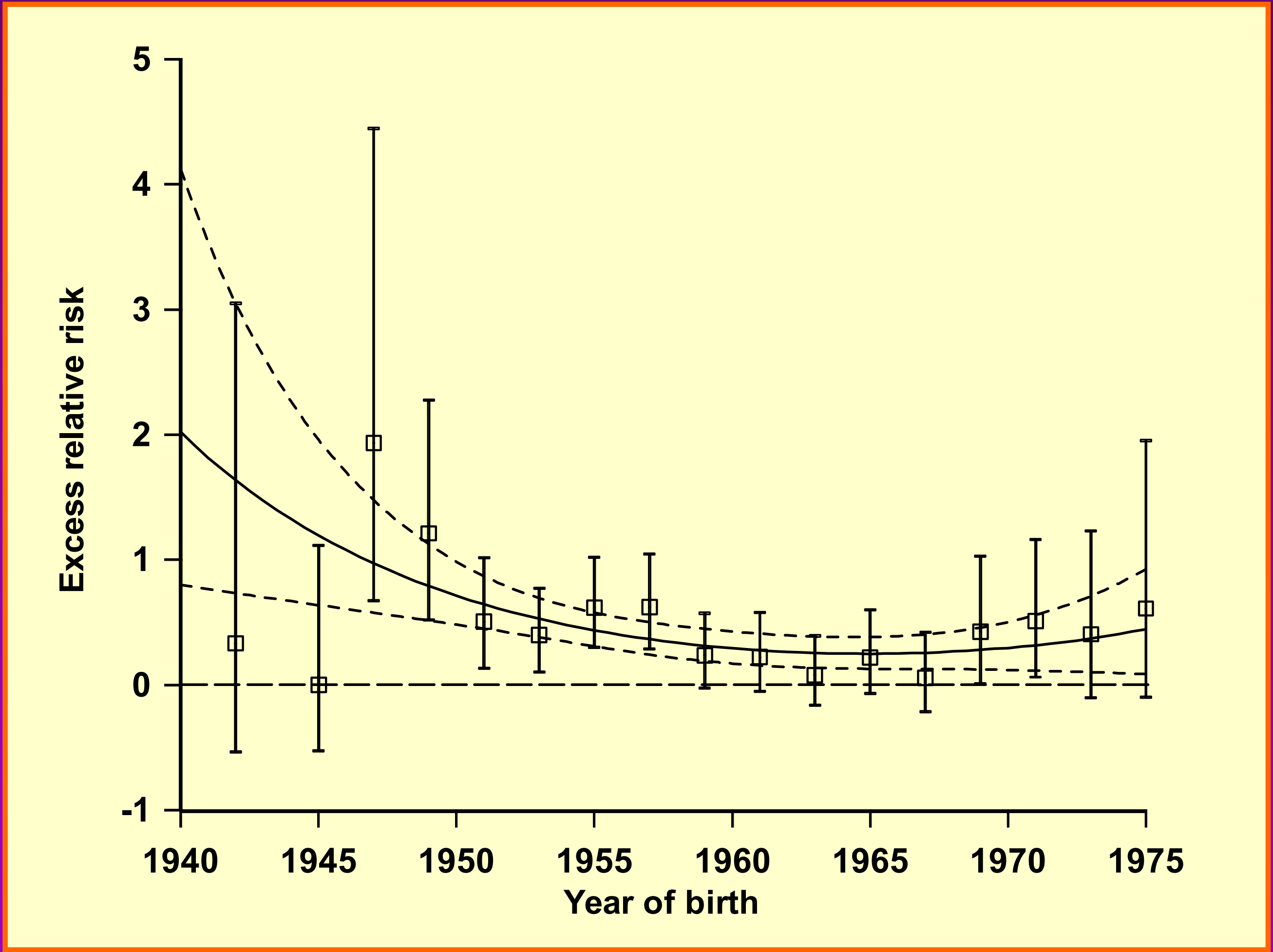
(Four periods: 1943-49, 1950-54, 1955-59, 1960-65)



ERR of Childhood Cancer by Birth Cohort

(OSCC data for births during 1940-76 and deaths during 1953-79)

(Error bars and band show 95% confidence intervals.)



Risk Coefficients from OSCC

- Using the Excess Relative Risk (ERR) model obtained from the OSCC birth cohort data, an ERR for a birth in 1959 may be obtained.
- Use the Adrian Committee average fetal dose estimate for 1958 of 6.1 mGy.
- Derive an ERR coefficient of

$$51 \text{ (95\% CI: 28, 76) Gy}^{-1}$$

R. Wakeford and M. P. Little, *Int J Radiat Biol* 2003; **79**: 293-309

Risk Coefficients from OSCC

- Apply the ERR coefficient obtained from the OSCC to a baseline absolute risk of childhood (<15 years of age) cancer incidence in Great Britain of 1577 cases per million live births.
- Derive an Excess Absolute Risk (EAR) coefficient of

$$8.0 \text{ (95\% CI: 4.4, 12.0)} \times 10^{-2}\ Gy^{-1}$$

R. Wakeford and M. P. Little, *Int J Radiat Biol* 2003; **79**: 293-309

Risk Coefficients from OSCC

- ERR coefficient is the same for childhood leukaemia and childhood solid tumours.
- Derive EAR coefficients for
  - childhood leukaemia incidence

    3.0 (95% CI: 1.7, 4.6) x 10^{-2} Gy^{-1}
  - childhood solid tumour incidence

    5.0 (95% CI: 2.8, 7.6) x 10^{-2} Gy^{-1}

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Risk Coefficients from OSCC

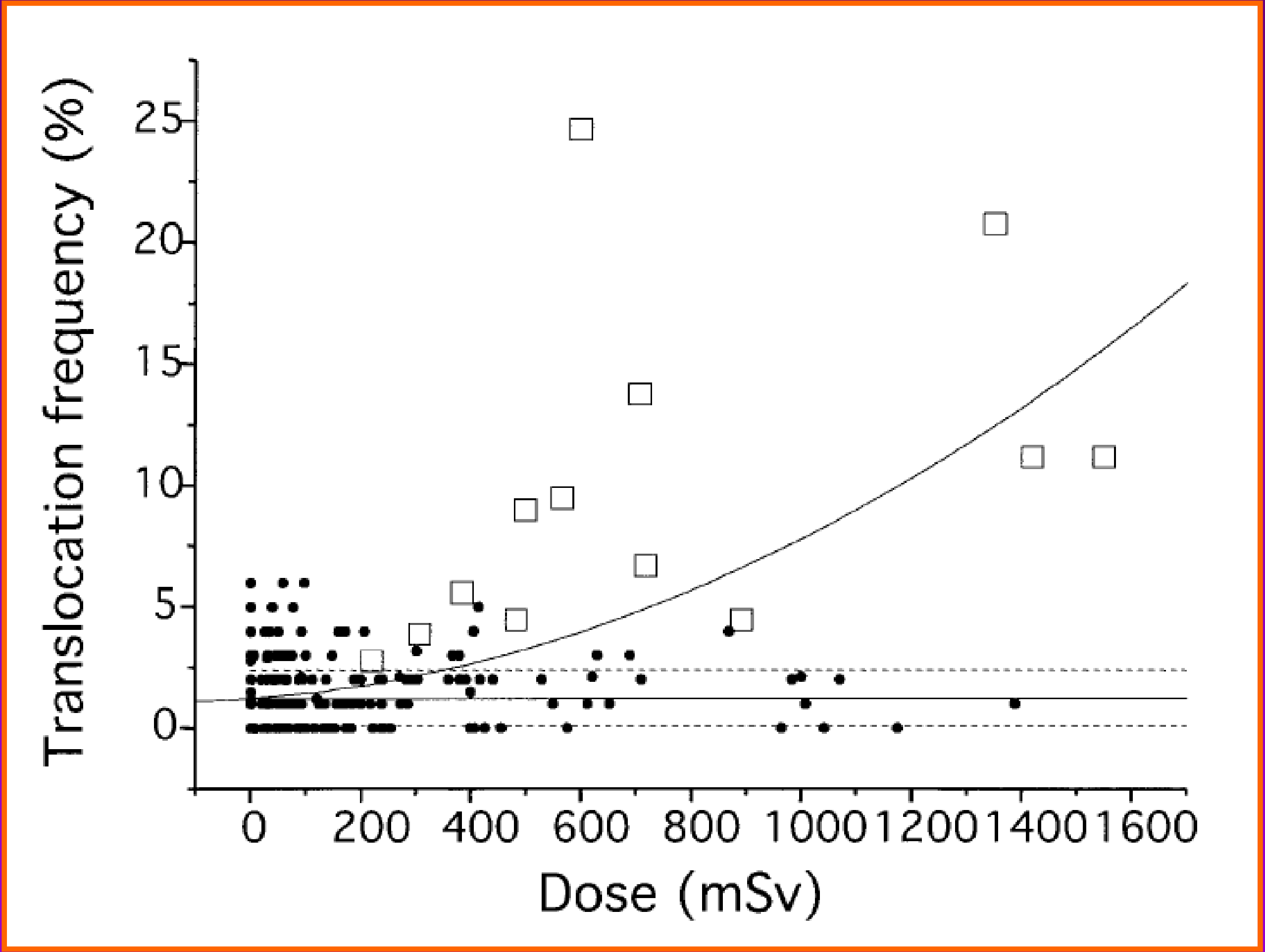
- Note that the confidence intervals associated with these risk estimates address statistical errors *only*. They do *not* incorporate uncertainties due to dosimetry, modelling and other sources.
- The upturn in ERR associated with births after 1967 may be artificial, implying that these risk coefficients could be overestimates by a factor of up to four.

R. Wakeford and M. P. Little, *Int J Radiat Biol* 2003; **79**: 293-309

Childhood Leukaemia OSCC *vs.* Bomb Survivors

- The level of risk of childhood leukaemia associated with antenatal diagnostic radiography is compatible with that found among Japanese atomic bomb survivors irradiated postnatally.
- The absence of childhood leukaemia among survivors irradiated *in utero* may be due to small numbers, missing cases or some other factor (e.g. cell killing).

Chromosome Translocation Frequencies in Atomic Bomb Survivors Exposed *in utero* (●), and in some of their Mothers (□). (Ohtaki *et al.*, *Radiat Res* 2004; **161**: 373-9)



Interpretation

"We conclude that there is strong evidence that low dose irradiation of the fetus *in utero*, particularly in the last trimester, causes an increased risk of cancer in childhood."

R. Doll & R. Wakeford, *Br J Radiol* 1997; **70**: 130-9

Postnatal X-ray Exposure

- The influence of diagnostic X-ray exposure after birth upon the risk of childhood leukaemia has also been studied.
- However, the studies have been less extensive than those considering antenatal exposure.

Postnatal X-ray Exposure

Case-control Study	Study Details	Cases (Exposed/Total)	Statistical Information	Relative Risk (unadjusted)	95% Confidence Interval
Meinert *et al.* (1999)	Germany; incident cases, 1980-94	328/1184	166	**0.80**	**(0.69, 0.93)**
Infante-Rivard (2003)	Quebec; ALL incident cases, 1980-98	301/701	83	**1.29**	**(1.04, 1.60)**
Stewart *et al.* (1958)	GB (OSCC); deaths, 1953-55	90/619	51	**1.09**	**(0.83, 1.43)**
Graham *et al.* (1966)	USA “tri-state”; incident cases, 1959-62	93/319	50	**0.73**	**(0.55, 0.96)**
Magnani *et al.* (1990)	N Italy; AL incident cases, 1981-84	58/164	25	**0.64**	**(0.43, 0.95)**
Polhemus and Koch (1959)	Los Angeles; incident cases, 1950-57	80/251	23	**1.84**	**(1.23, 2.76)**
Ager *et al.* (1965)	Minnesota; deaths, 1953-57	22/109	11	**1.20**	**(0.67, 2.16)**
Nishi and Miyake (1989)	N Japan; ALL incident cases, 1986-87	49/63	5	**0.30**	**(0.12, 0.72)**
All Studies		**1021/3410**	**414**	**0.98**	**(0.89, 1.08)**

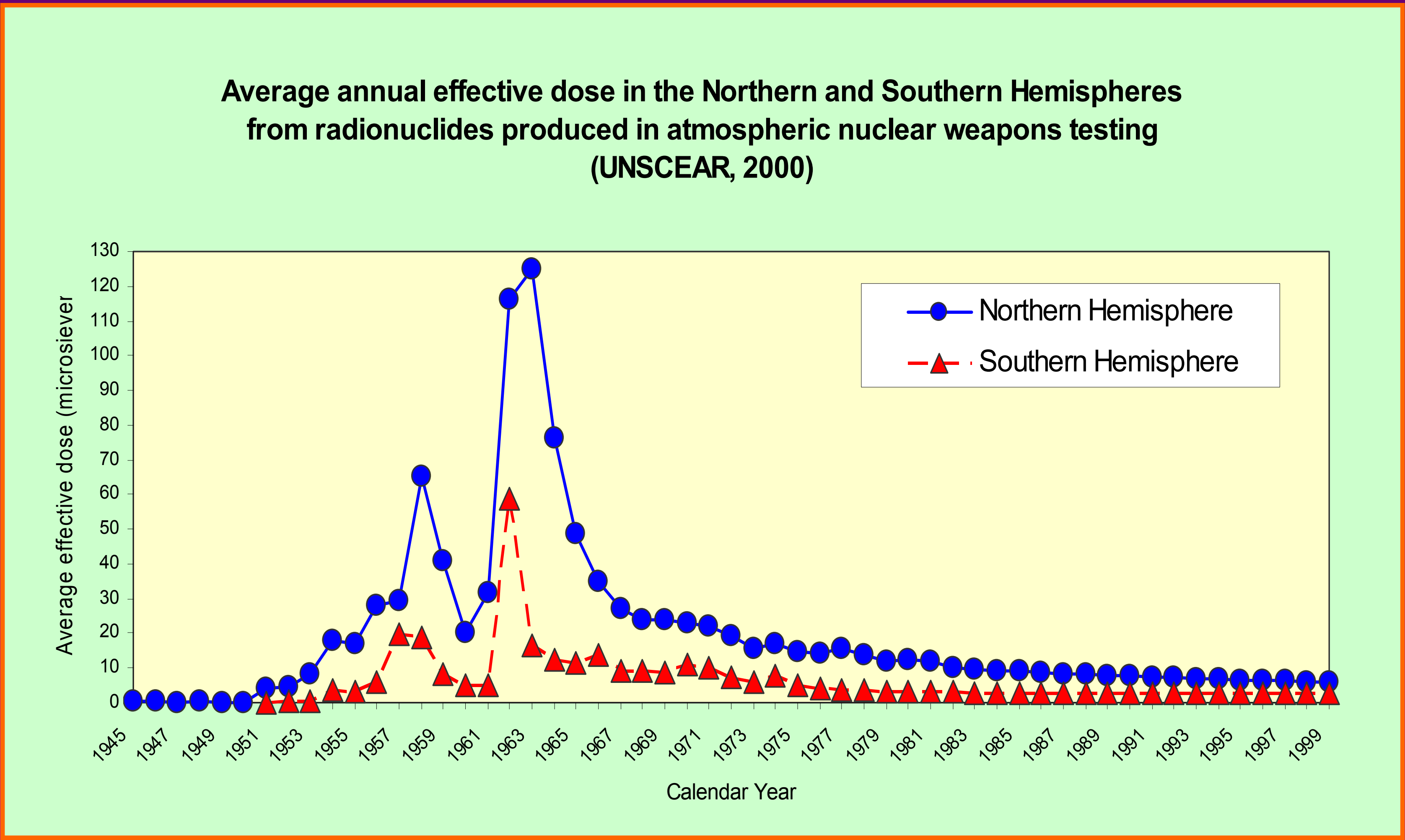
Issues

- X-ray exposures close to diagnosis
  - Investigation of children already ill
- Age matching of controls
  - Older children will have had more opportunity of being X-rayed
- Recall bias
  - Parents erroneously recalling the X-ray exposures of their children
- Types of X-ray exposures
  - Chest, extremities, dental, etc.

Postnatal X-ray Exposure

- Although standard risk models predict a risk of childhood leukaemia resulting from postnatal exposure to diagnostic X-rays that should be capable of detection, findings of studies conducted to date are, collectively, unpersuasive.
- This lack of clarity is particularly regrettable given the development of relatively high dose diagnostic procedures (such as paediatric CT scans).

Weapons Testing Fallout



Childhood Leukaemia Incidence