Intrauterine Irradiation – Historical Context and Epidemiological Studies

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Intrauterine Irradiation

- Irradiation of the conceptus, embryo and fetus (i.e., exposure of the developing organism *in utero*) requires the consideration of specific effects.

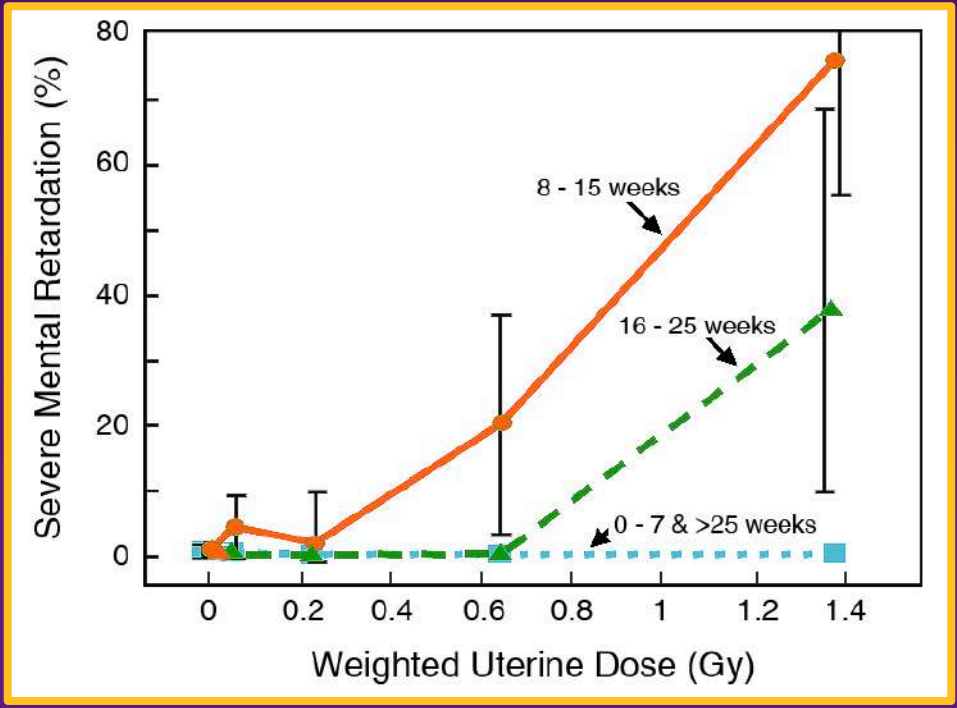
- These are teratogenic (developmental) effects, such as congenital malformations and mental retardation.

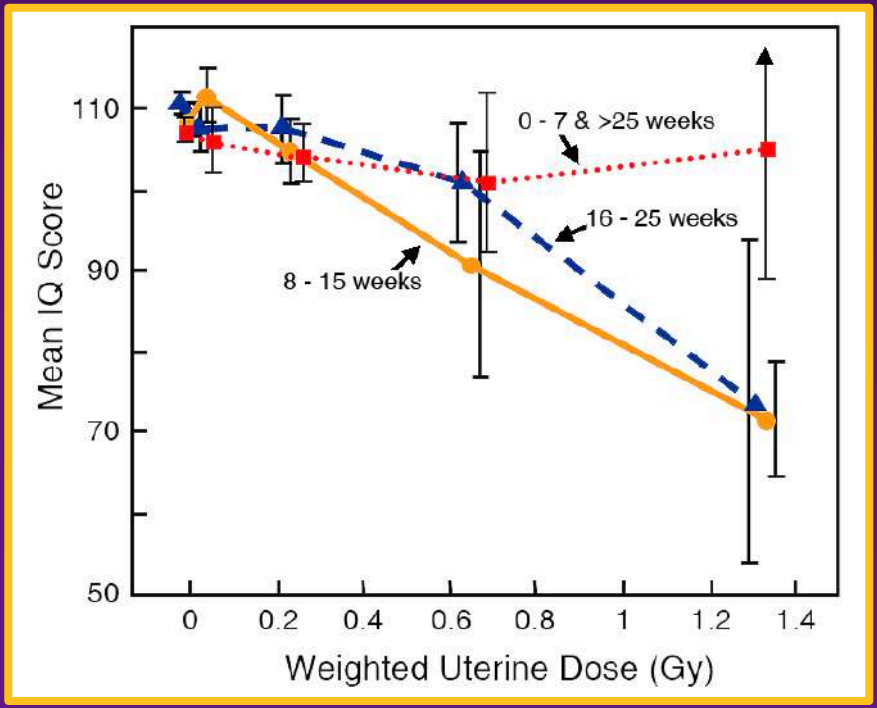
Severe Mental Retardation and Reduction in IQ

(Otake & Schull, *Int J Radiat Biol* 1998; **74**: 159-71
ICRP Publication 90, 2003
NCRP Report No. 174, 2013)

Japanese atomic-bomb survivors exposed *in utero*

(weeks since conception; DS86 uterine doses)

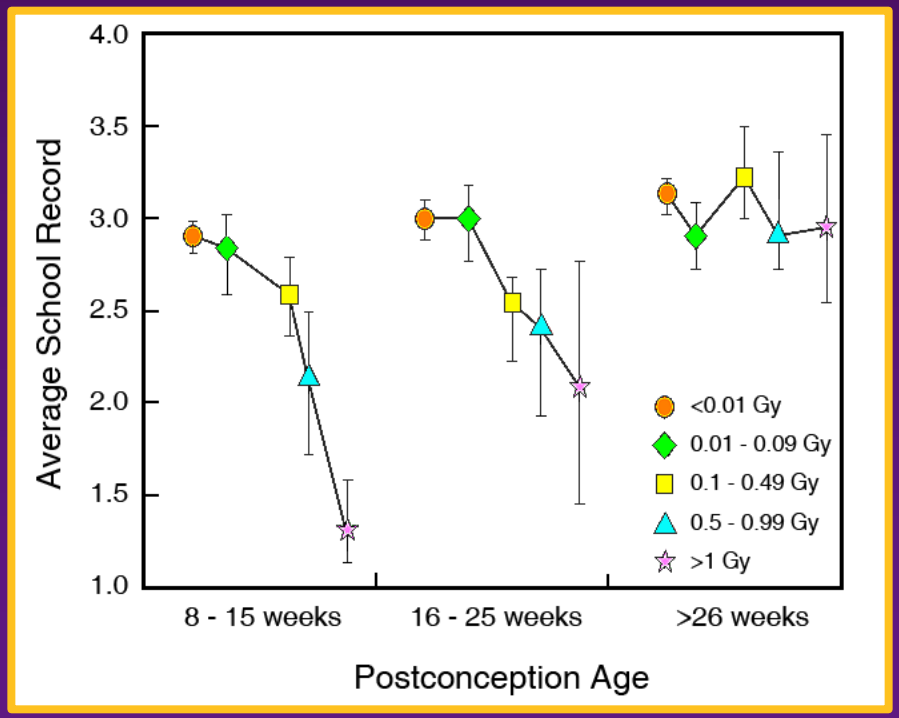


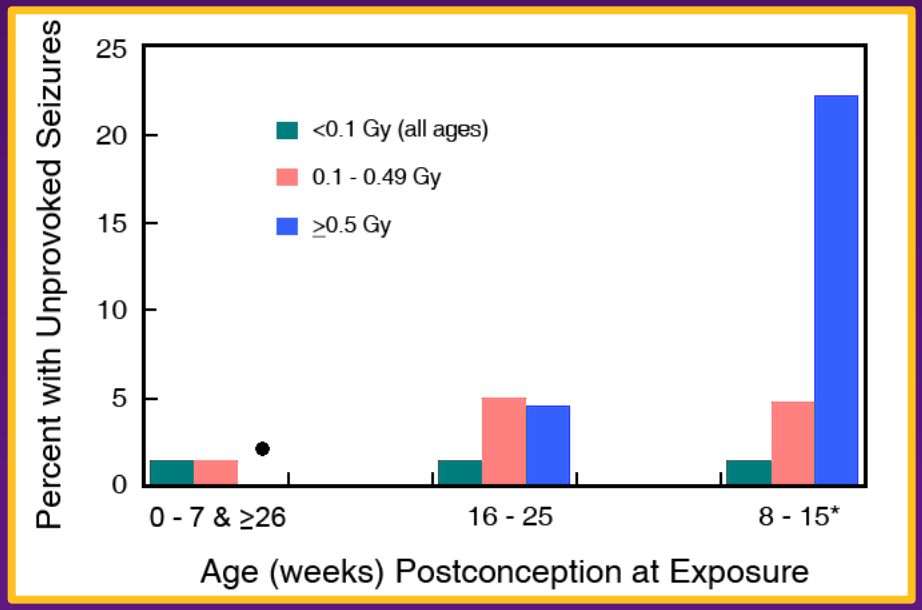


School Performance and Seizures

(Otake & Schull, *Int J Radiat Biol* 1998; **74**: 159-71
ICRP Publication 90, 2003
NCRP Report No. 174, 2013)

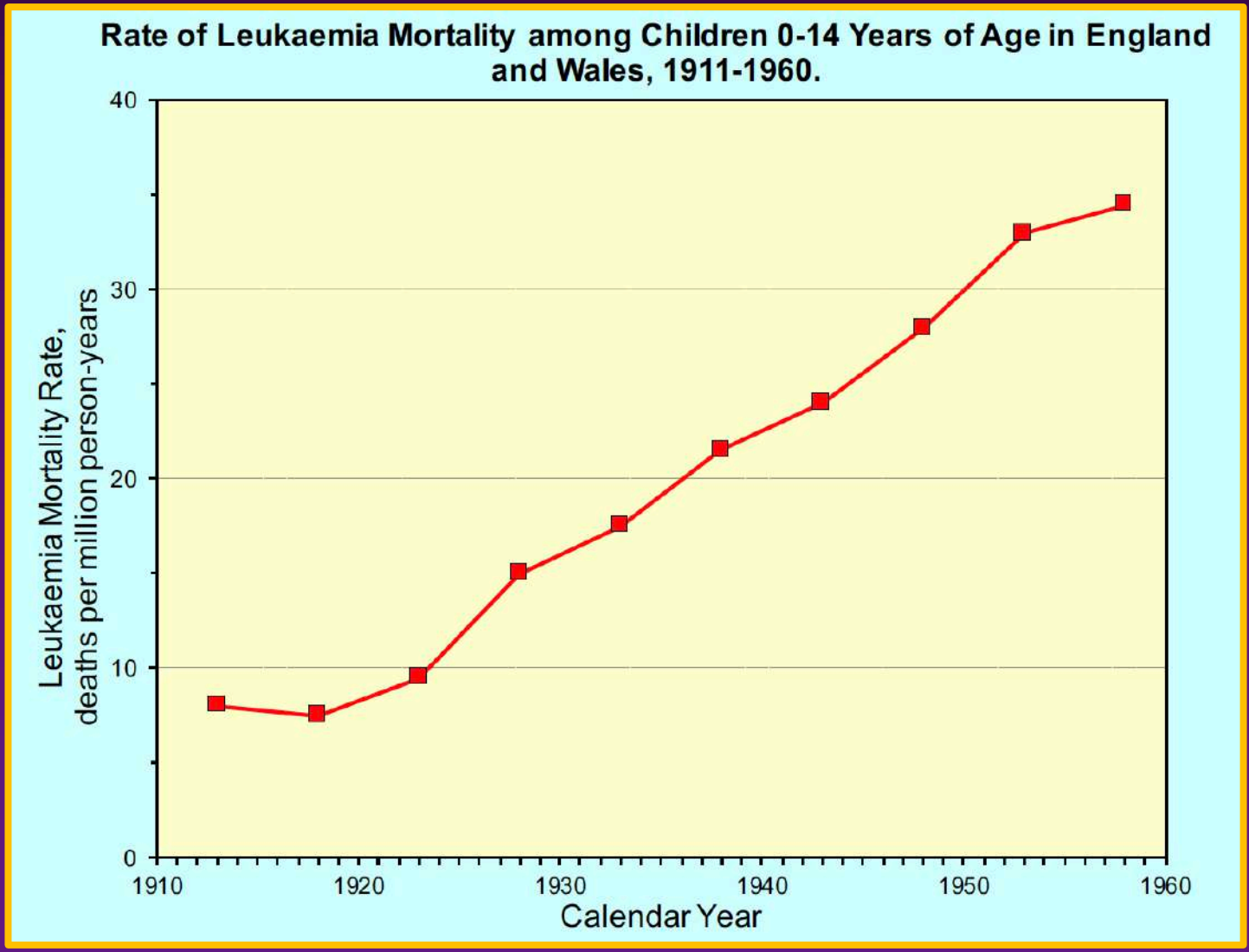
Japanese atomic-bomb survivors exposed *in utero*
(weeks since conception; DS86 uterine doses)





Childhood Leukaemia Trend

(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 childhood cancer mortality 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

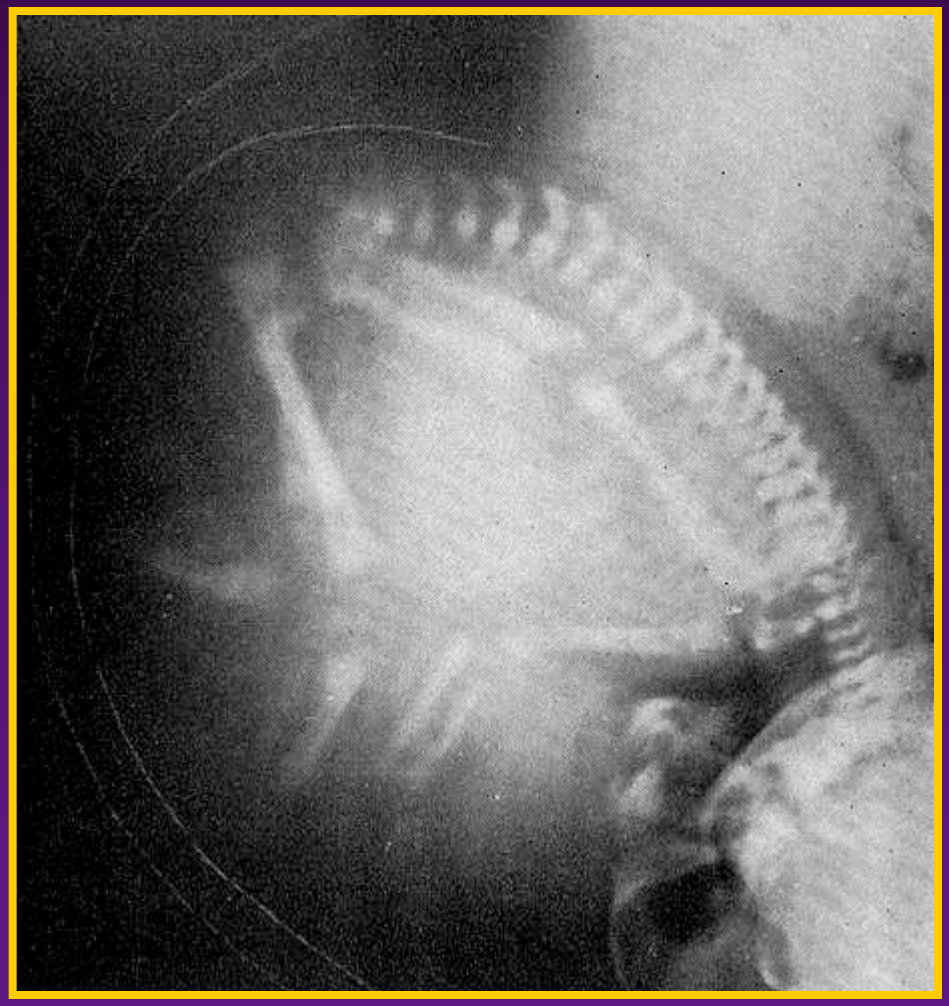
(Stewart *et al.*, *Lancet* 1956; **ii**: 447)

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

Obstetric Radiography

(Mole, *Br J Cancer* 1990; **62**: 152-68)



During 1950-1975, the frequency of abdominal X-raying of pregnant women in the UK was 10-15 % (>90% of these during the third trimester). The fetal dose received was variable, but would have been around 10 mGy of X-rays.

Medically Exposed Groups

- Although medically exposed groups offer a valuable complement to evidence derived from the Japanese atomic-bomb survivors care in interpretation is required:
  - Exposure occurs because of known or suspected disease and this may affect the risk estimates obtained from medical studies, e.g., through "confounding by indication" (including "reverse causation") – selection effects are a distinct possibility
  - Radiotherapy involves high and localised doses
  - Accurate dose estimates are often lacking

Initial Reaction to Association

- The preliminary findings of Stewart *et al.* (1956) were received with scepticism.
  - Doubts were raised about control selection – possible selection bias.
  - Information on X-ray exposures was obtained from maternal interviews − possible recall bias.
  - It was not believed that low doses of X-rays could induce cancer, especially solid cancers − possible confounding by indication (e.g., maternal ill health).

Further Findings

- Preliminary findings confirmed by the results of an extended OSCC study reported in the *British Medical Journal* 1958; **i**: 1495-1508.
- Concerns over control selection bias and maternal recall bias met by case-cohort study of MacMahon, *J Natl Cancer Inst* 1962; **28**: 1173-91 in the North-East USA based on contemporary hospital records of antenatal X-ray examinations.
- Maternal recall in OSCC largely confirmed by medical records of X-ray exposures.

OSCC

(Gilman *et al.*, *J Radiol Prot* 1989; **9**: 93-101)

- Oxford Survey of Childhood Cancers (OSCC – a case-control study of childhood cancer mortality) ended in 1981 and finally included 15,276 case-control pairs.
- The overall Relative Risk (RR) of childhood (<16 years of age) cancer mortality associated with an antenatal X-ray examination:

Relative Risk (RR) = 1.39 (95% CI: 1.30, 1.49)

a *highly* statistically significant association.

All Childhood Cancers

(Doll & Wakeford, *Br J Radiol* 1997; **70**: 130-9
Wakeford & Bithell *in review*)

OSCC *vs* Combined Other Studies

Case-control Study	Cases (Exposed/Total)	Statistical Information (Precision)	Relative Risk	95% Confidence Interval
OSCC	2281/15,276	852	**1.39**	**(1.30, 1.49)**
All Except OSCC	688/10,142	401	**1.30**	**(1.18, 1.43)**

Childhood Leukaemia

- The most recent result from the OSCC for childhood leukaemia mortality as a separate category was reported by Bithell and Stewart, *Br J Cancer* 1975; **31**: 271-87:

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

- Results for childhood leukaemia 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)**
Fajardo-Gutierréz *et al.* (1993)	Mexico City; incident cases	16/80	7	1.89	(0.91, 3.95)
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)**
Meinert *et al.* (1999)	Germany; incident cases, 1980-94	3/1184	2	**0.93**	**(0.24, 3.60)**
Shu *et al.* (1994)	Shanghai; AL incident cases, 1986-91	7/166	2	**2.39**	**(0.61, 9.41)**

Childhood Leukaemia

(Wakeford, *Radiat Prot Dosim* 2008; **132**: 166-74
Wakeford & Bithell *in review*)

OSCC *vs* Combined Other Studies

Case-control Study	Cases (Exposed/Total)	Statistical Information (Precision)	Relative Risk	95% Confidence Interval
OSCC	620/4122	308	**1.51**	**(1.35, 1.69)**
All Except OSCC	749/10,997	397	**1.28**	**(1.16, 1.41)**

Other Childhood Cancers

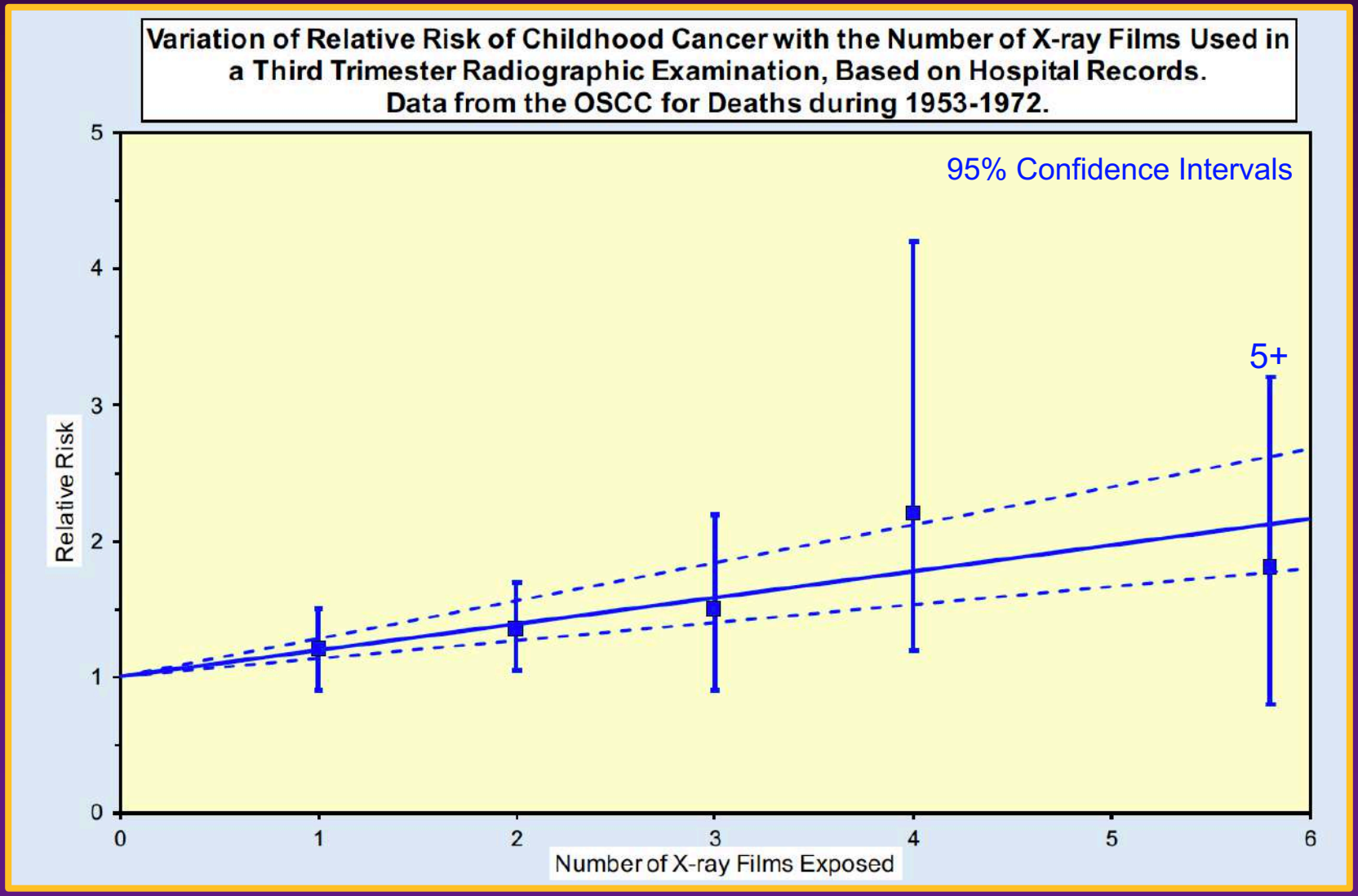
(Wakeford & Bithell *in review*)

OSCC *vs* Combined Other Studies

Case-control Study	Cases (Exposed/Total)	Statistical Information (Precision)	Relative Risk	95% Confidence Interval
OSCC	672/4552	325	1.46	(1.31, 1.62)
All Except OSCC	246/4635	163	1.31	(1.13, 1.53)

Exposure-Effect Relationship

(Bithell, *Low Dose Radiation*, 1989, pp77-87)



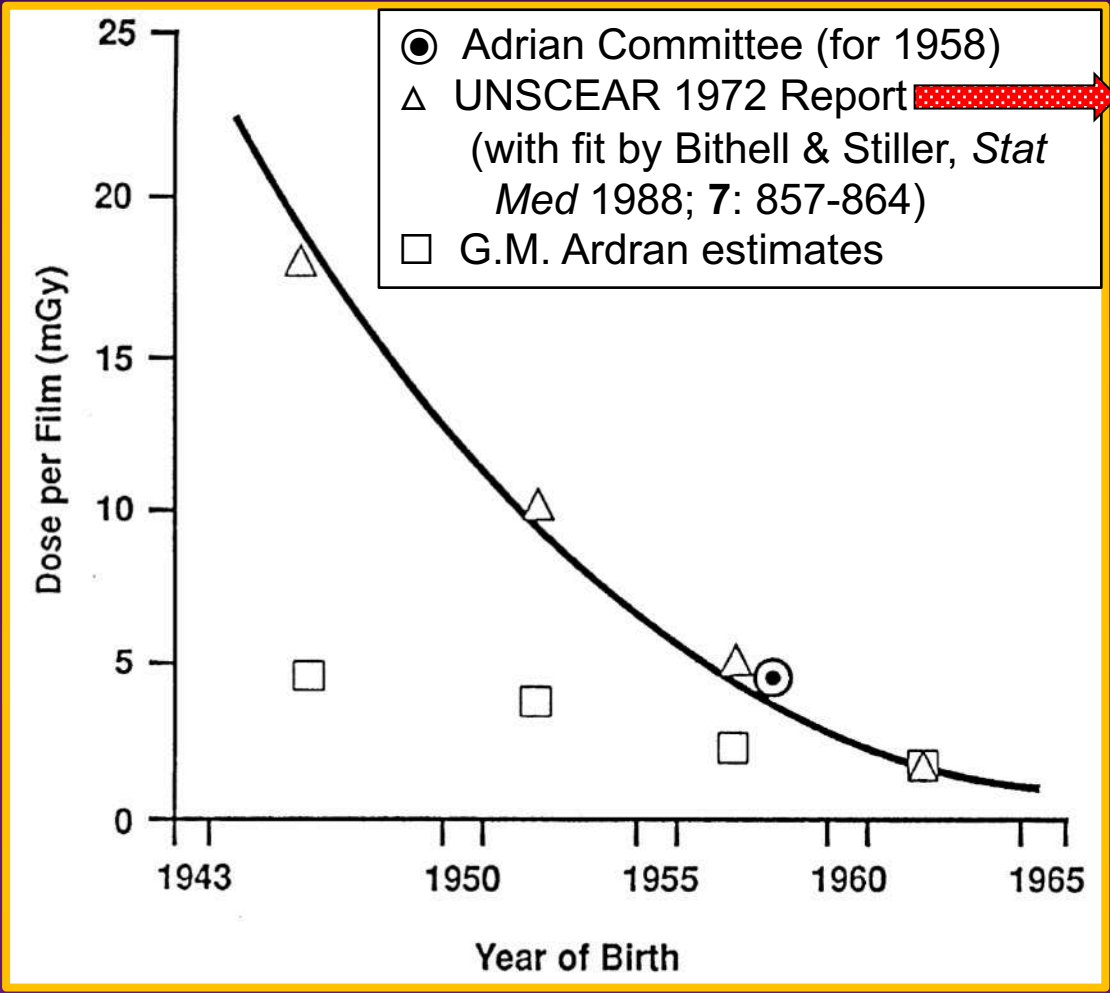
Risk Coefficient

- To derive an estimate of the excess risk of childhood cancer per unit dose received by the fetus, estimates of fetal doses are required.

- 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)

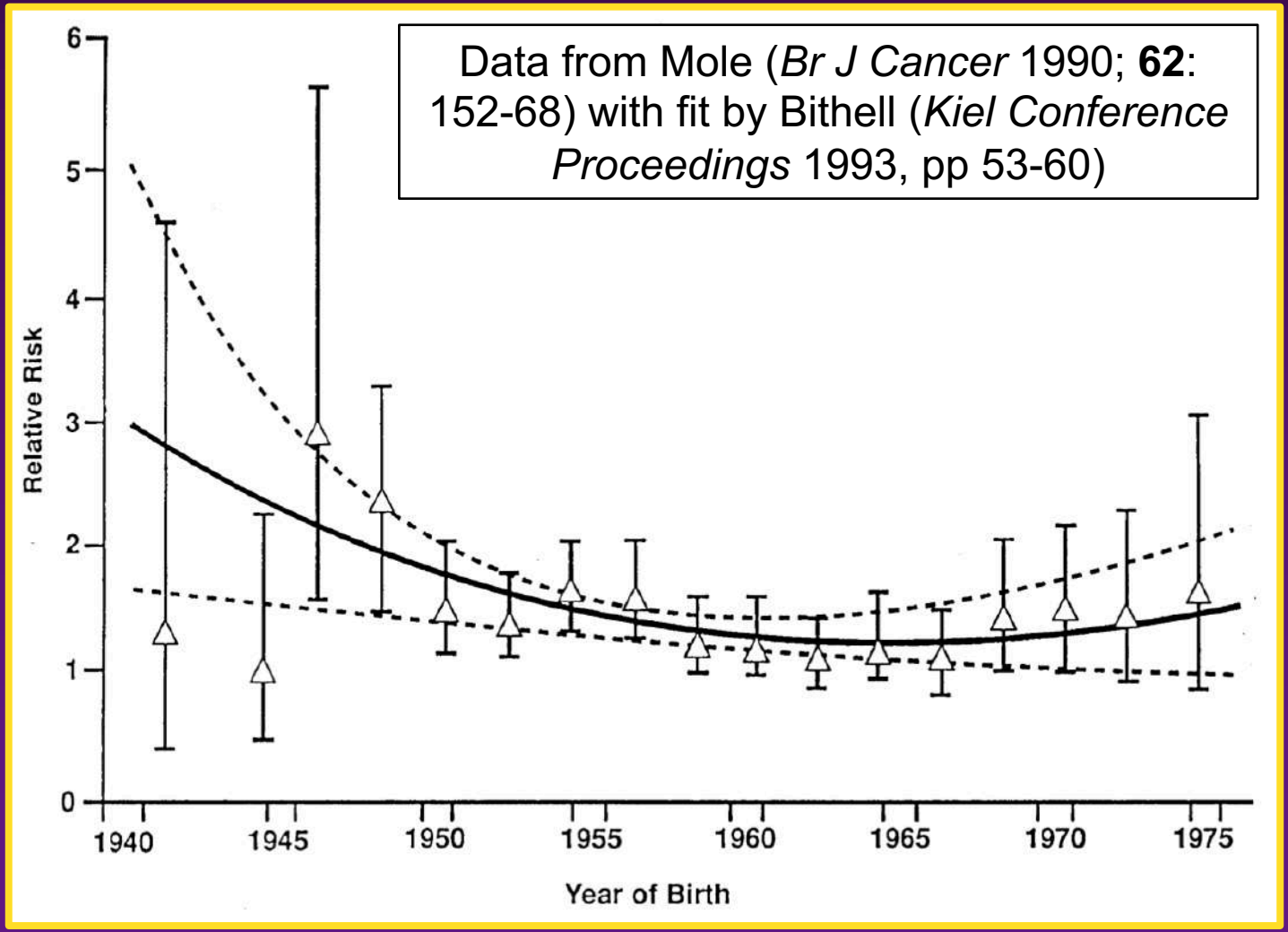


But see:
Mole, *Br J Cancer* 1990; **62**: 152-68
and
Mole, *J Radiol Prot* 1990; **10**: 199-203

RR 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)



ERR Coefficient from OSCC

(Wakeford & Little, *Int J Radiat Biol* 2003; **79**: 293-309)

- Using an Excess Relative Risk (ERR) model obtained from the OSCC birth cohort data, an ERR of childhood cancer for a birth in 1958 may be obtained.
- The Adrian Committee estimated the average fetal dose per examination in 1958 as 6.1 mGy.
- Hence, derive an ERR coefficient of

  0.51 (95% CI: 0.28, 0.76) at 10 mGy (X-rays)

  for all childhood cancers, which is taken to be the same for leukaemia and other cancers.

Risk Coefficients from OSCC

(Wakeford & Little, *Int J Radiat Biol* 2003; **79**: 293-309)

- Note that the confidence interval for this risk estimate addresses statistical errors *only*. The confidence interval does *not* incorporate uncertainties due to dosimetry, modelling and other sources.
- The upturn in ERR associated with births after 1967 may be artificial, implying that this ERR coefficient could be an overestimate by a factor of up to four.

Bomb Survivors Irradiated *In Utero*

(Wakeford & Little, *Int J Radiat Biol* 2003; **79**: 293-309)

- 807 Japanese atomic-bomb survivors were irradiated *in utero*, with DS86 uterine doses of at least 10 mGy (average dose 0.28 Gy).
- 2 incident cases of childhood (<15 years of age) cancer were observed among these survivors (1 liver tumour and 1 kidney tumour) against, at most, 0.48 case expected from contemporary Japanese rates.
- ERR per Gy (all childhood cancers)

11 (95% CI: -1, 46) Gy^{-1}

Childhood Cancer and Radiation Exposure *In Utero*

(Wakeford & Little, *Int J Radiat Biol* 2003; **79**: 293-309)

ERR per unit fetal dose (all childhood cancers)

- atomic-bomb survivors (average dose, ~280 mGy)

  11 (95% CI: -1, 44) Gy^{-1}

- OSCC (average dose, ~10 mGy)

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

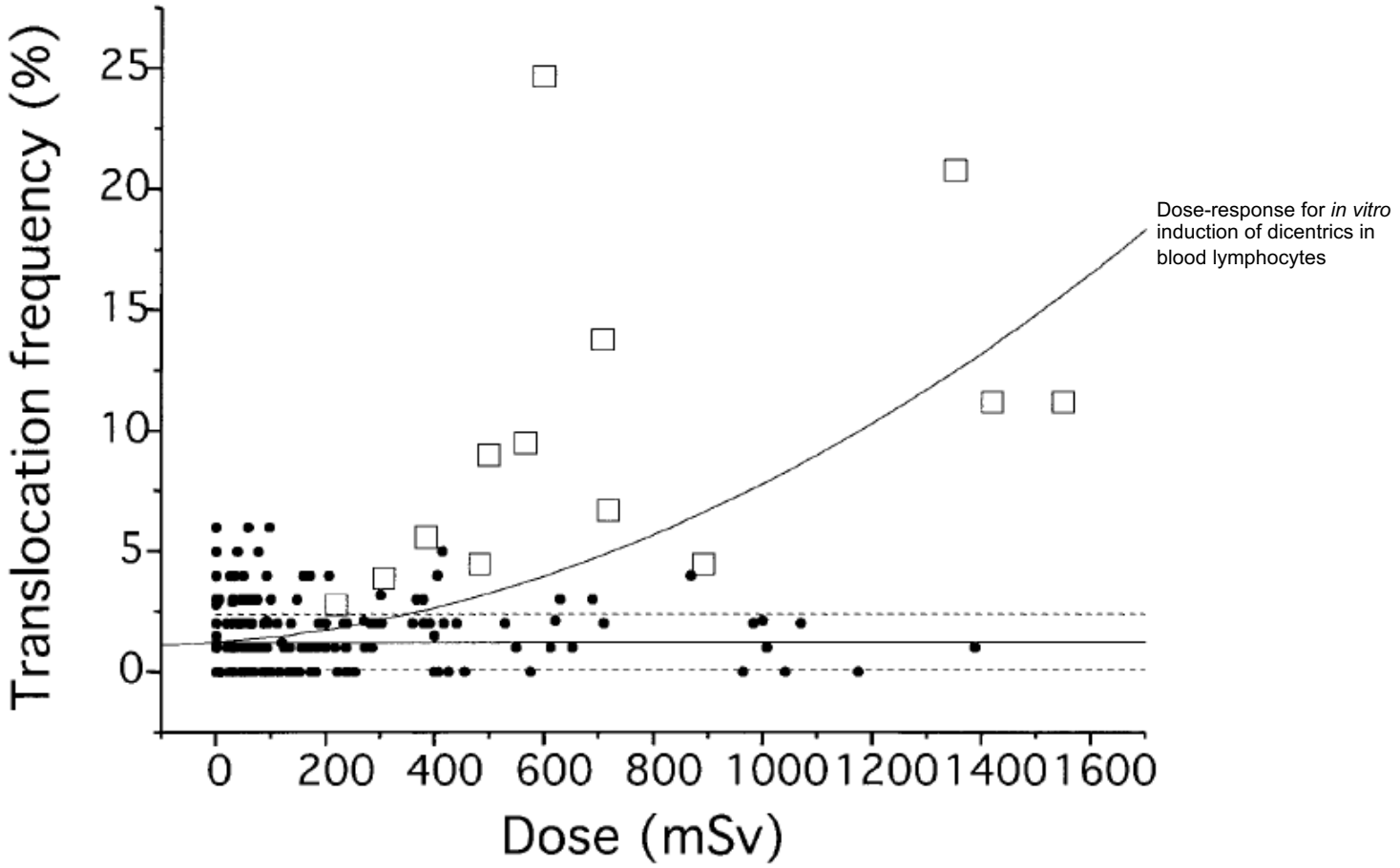
Bomb Survivors Irradiated *In Utero*

- 0 case of childhood leukaemia observed (O), but only 0.2 expected (E)
  - O/E has a Mid-P 95% CI of (0, 15), so

    ERR/Gy = <0 (95% CI: <0, 50)
- 2 cases of other childhood cancers observed (O), against 0.28 expected (E)
  - O/E = 7.1 (Mid-P 95% CI: 1.2, 24), so

    ERR/Gy = 22 (95% CI: 0.7, 81)
- Possibility that some cases of childhood cancer (particularly childhood leukaemia) occurring among the survivors before October 1950 went unrecorded or undiagnosed.

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)



Adult Cancer Deaths (1950-2012)

(Sugiyama *et al.*, *Eur J Epidemiol* 2021 *in press*)

- There is growing evidence from the 908 Japanese atomic-bomb survivors irradiated *in utero* (with dose estimates) of risks as adults.
- Increased risk of solid cancers in females:

  ERR/Gy = 1.84 (95% CI: 0.18, 4.98) (21 deaths)

  but not in males:

  ERR/Gy = -0.18 (95% CI: <-0.77, 0.94) (24 deaths)
- Further follow-up is required to properly interpret the ERR/Gy estimates.

Relative Risk of Childhood Cancer Associated with Antenatal Diagnostic Exposure to Radiation found by Case-control Studies

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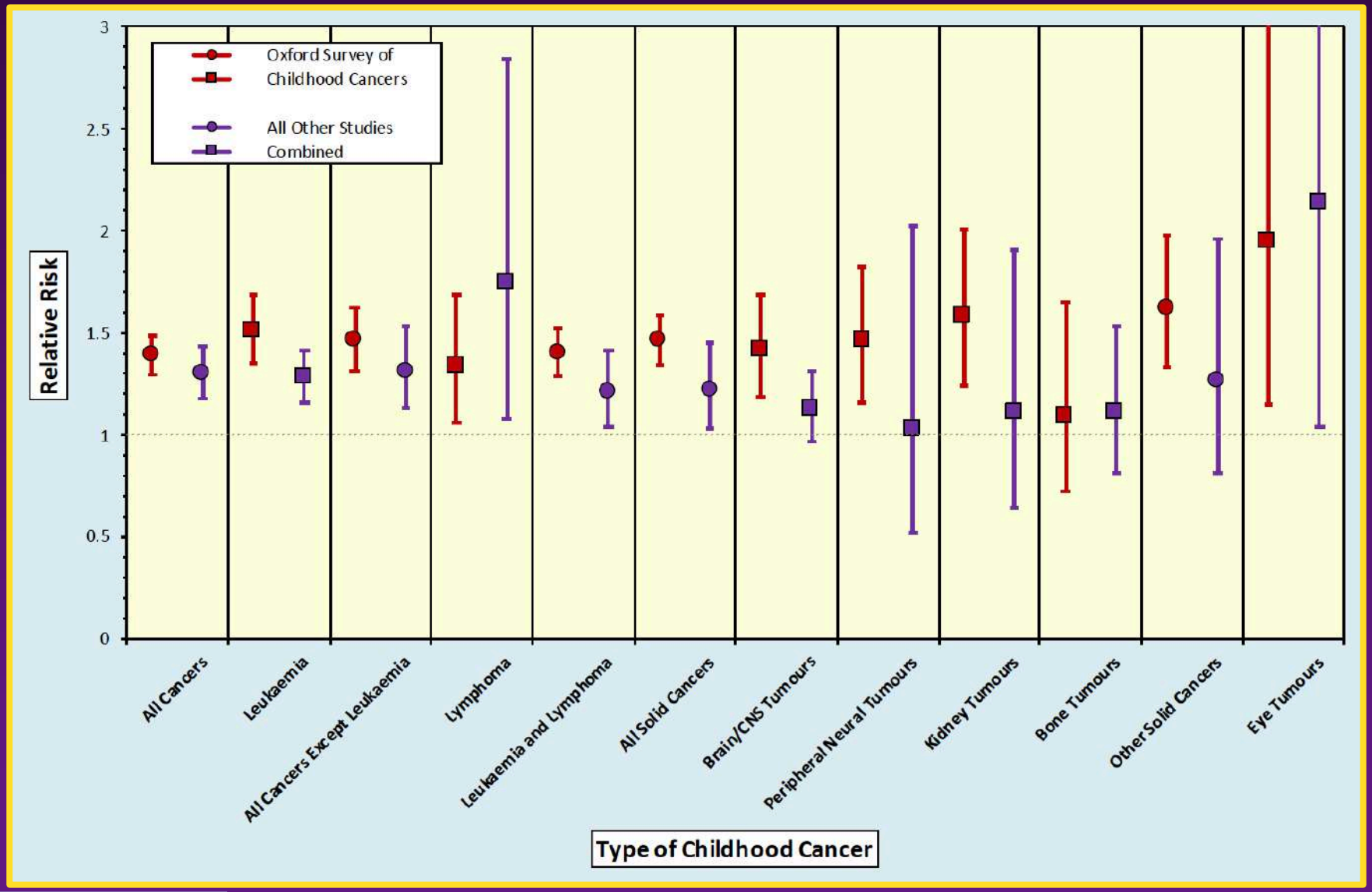

Conclusions

- There is a statistical association between an antenatal X-ray examination and the subsequent risk of childhood cancer.
- On the balance of the evidence, it seems likely that this association has a cause-and-effect interpretation.
- However, there are questions that need to be addressed to provide confidence in the validity of this inference.

Fin

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https://www.research.manchester.ac.uk/portal/en/researchers/richard-wakeford(9ae70e7a-50a9-463d-87e0-54829ecce16b).html