In Utero Exposure

(with an emphasis on low doses)

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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.

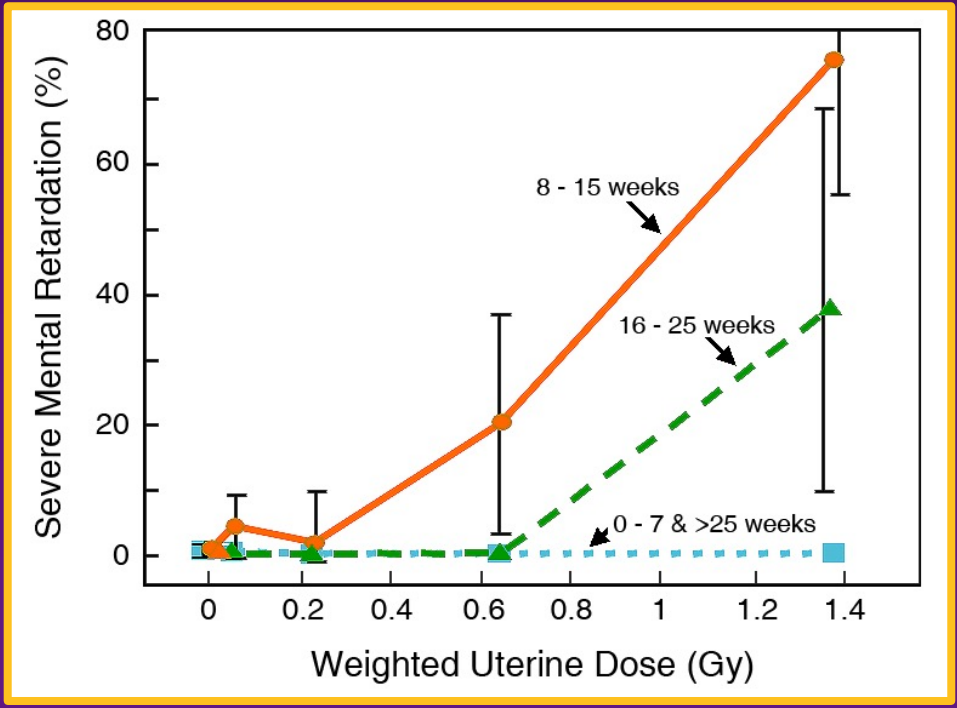
- These are teratogenic (developmental) effects, such as congenital malformations and mental retardation.

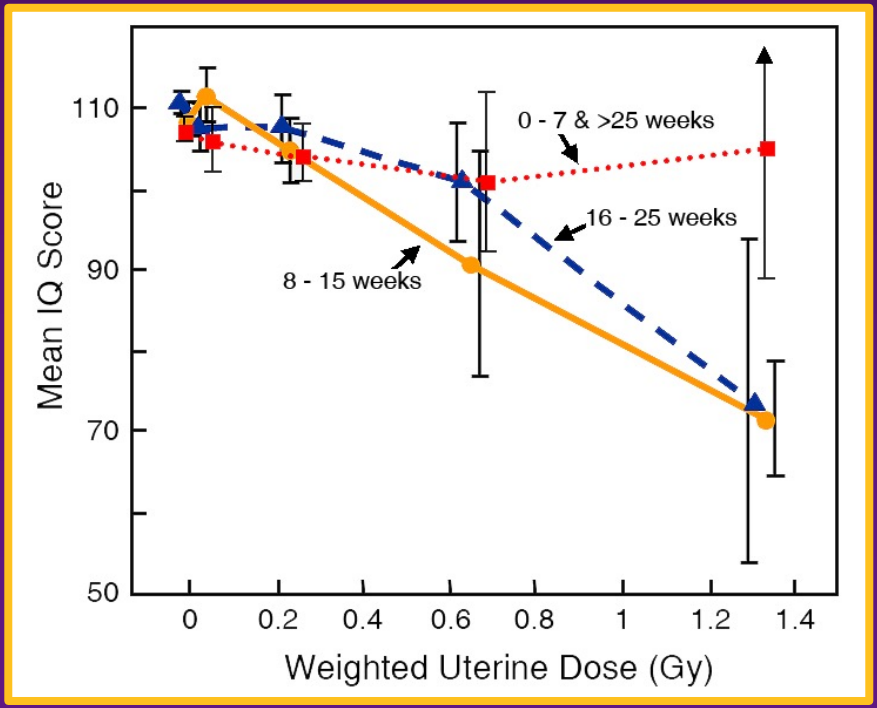
Severe Mental Retardation and Reduction in IQ

(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)





Diagnostic Intrauterine Irradiation

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

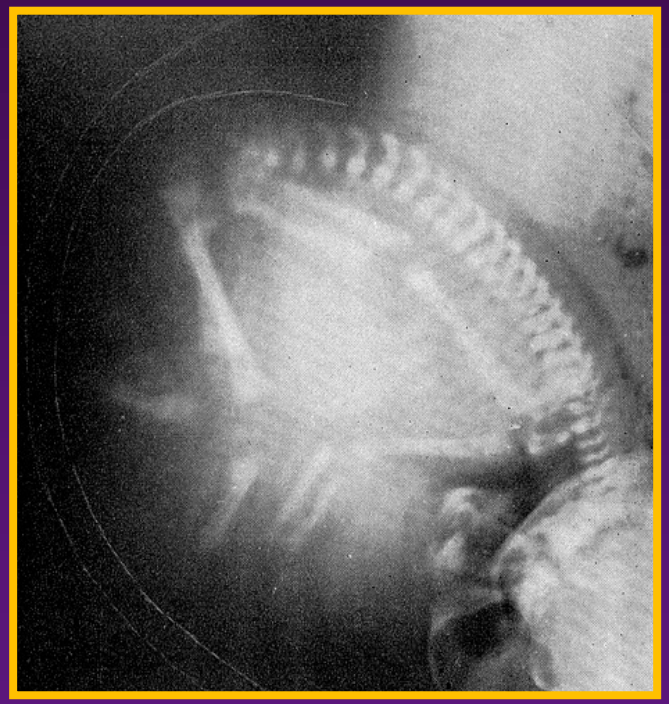
Deaths from Childhood Cancer during 1953-1955						
Maternal irradiation during relevant pregnancy	Leukaemia*			Other Cancers*		
	Cases	Controls	Relative Risk (95% confidence interval)	Cases	Controls	Relative Risk (95% confidence interval)
Abdomen	42	24	1.92 (1.12, 3.28)	43	21	2.28 (1.31, 3.97)
Other	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

Important conformation of the association from the case-cohort study of MacMahon
(MacMahon, *J Natl Cancer Inst* 1962; **28**: 1173-91)

Antenatal Radiography

(Mole, *Br J Cancer* 1990; **62**: 152-168
Doll & Wakeford, *Br J Radiol* 1997; **70**: 130-139
Wakeford & Little, *Int J Radiat Biol* 2003; **79**: 293-309)



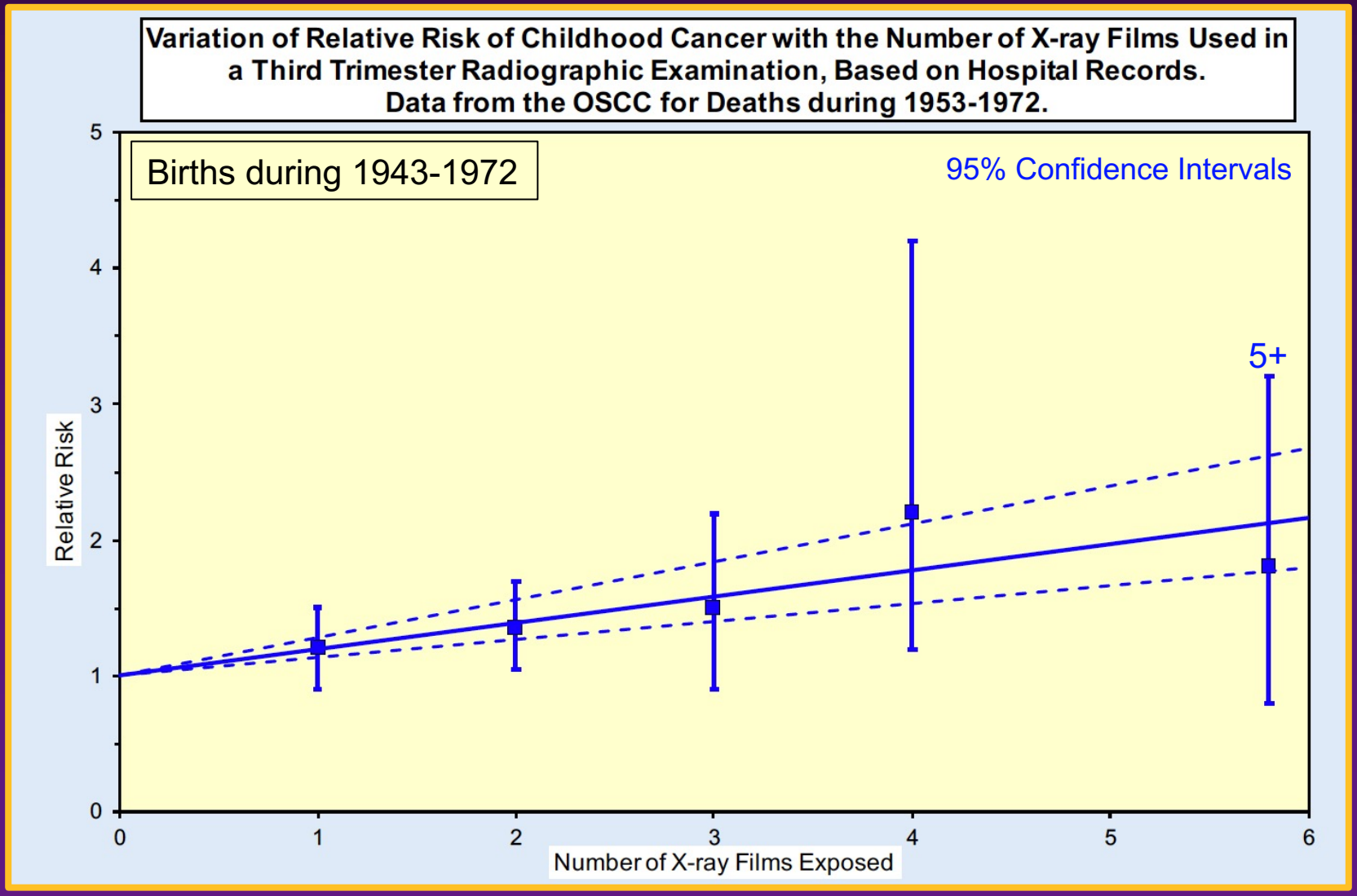
During 1950-1975, the frequency of abdominal X-raying of pregnant women in the UK was 10-15 % (>90% during the third trimester). The fetal dose received was variable, but would have been around 10 mGy of X-rays – average fetal dose in the UK in 1958 was 6.1 mGy. This was the subject of the Oxford Survey of Childhood Cancers (OSCC).

The OSCC data can be used to derive a risk estimate for childhood (<15 years of age) cancer incidence following fetal exposure:

ERR = 0.5 (95% CI: 0.3, 0.8) at 10 mGy (X-rays)

Exposure-Effect Relationship

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



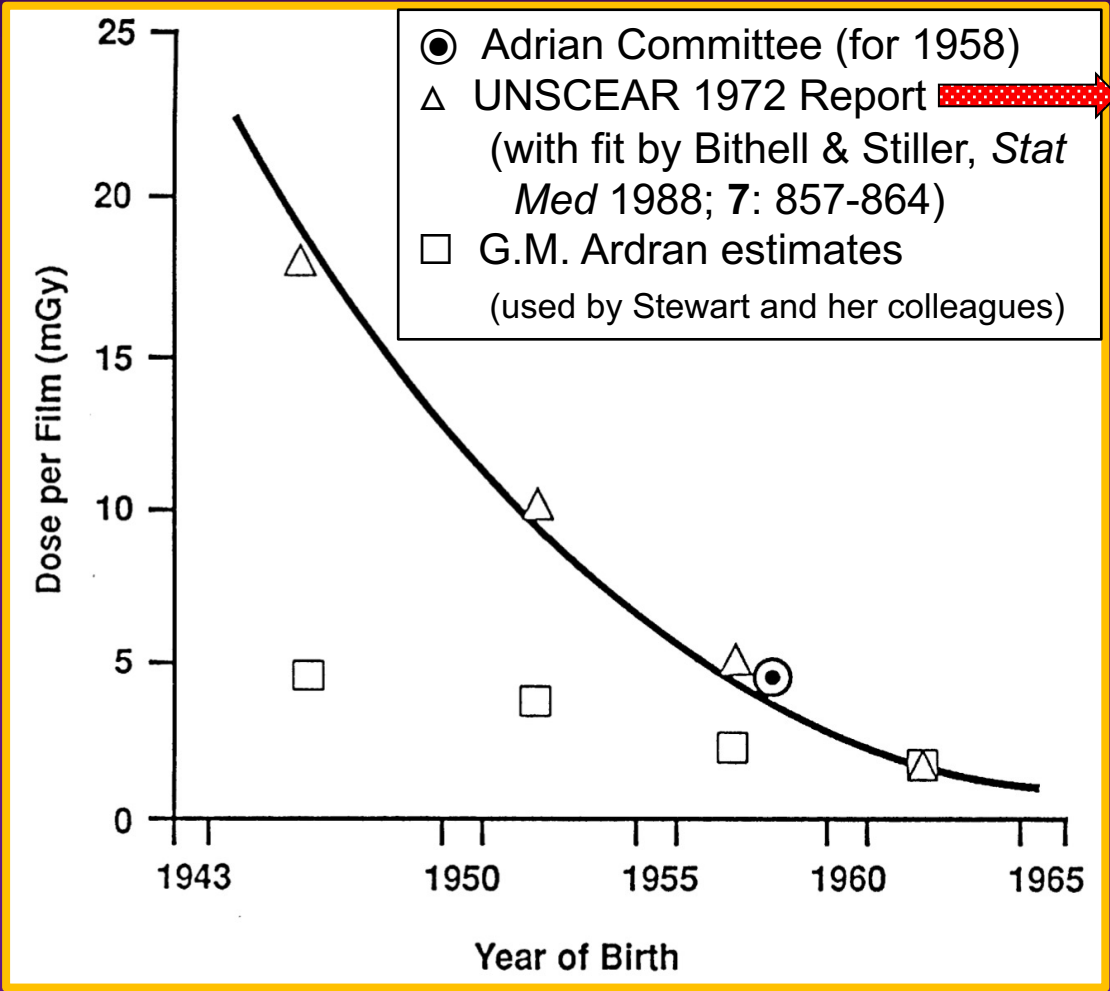
Risk Coefficient

- 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 in any detail 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)

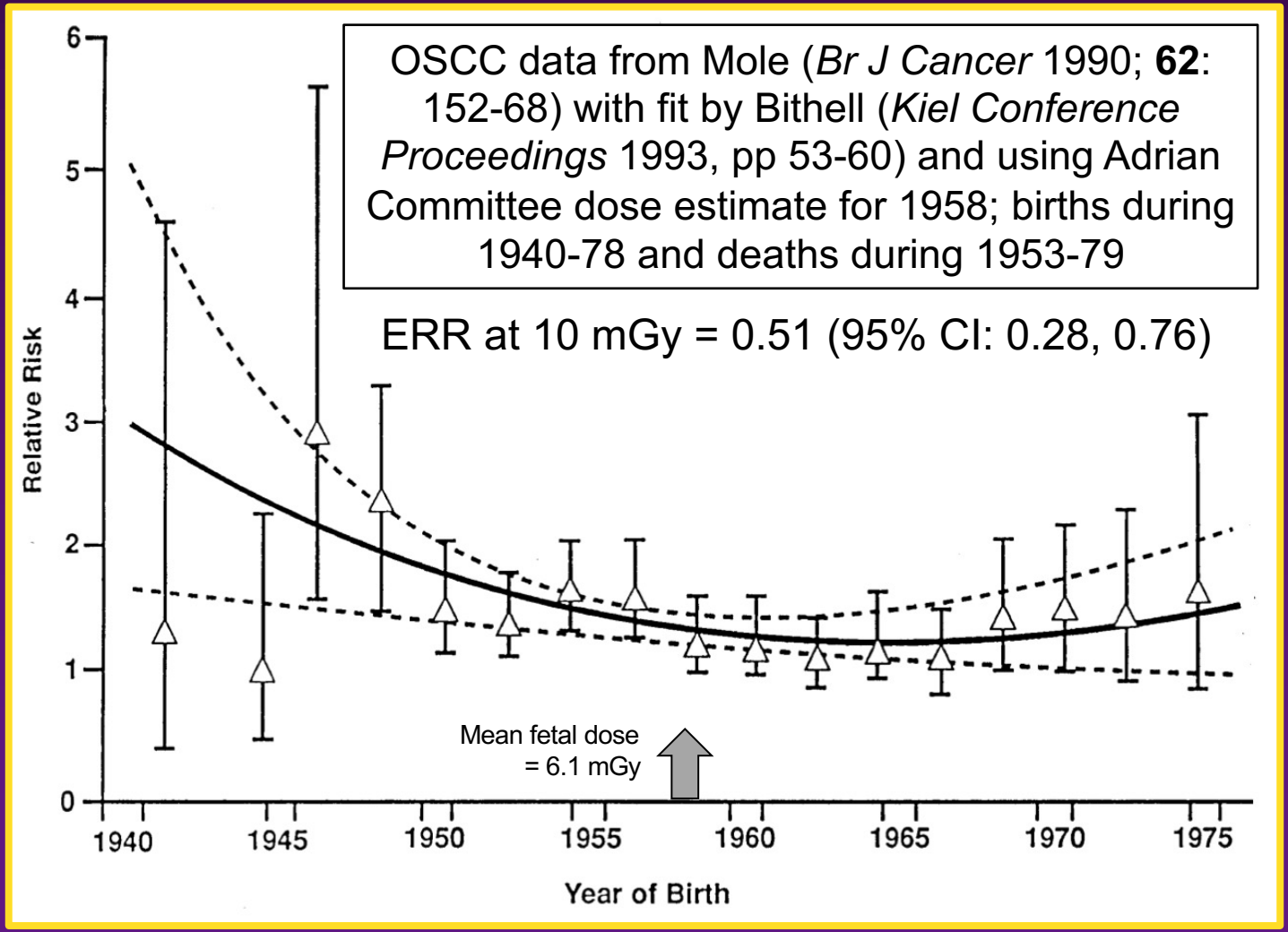


But see:
Mole, *Br J Cancer* 1990; **62**: 152-68
and
Mole, *J Radiol Prot* 1990; **10**: 199-203

RR of Childhood Cancer by Birth Cohort

(OSCC data for births during 1940-78 and deaths during 1953-79)

(Error bars and band show 95% confidence intervals)



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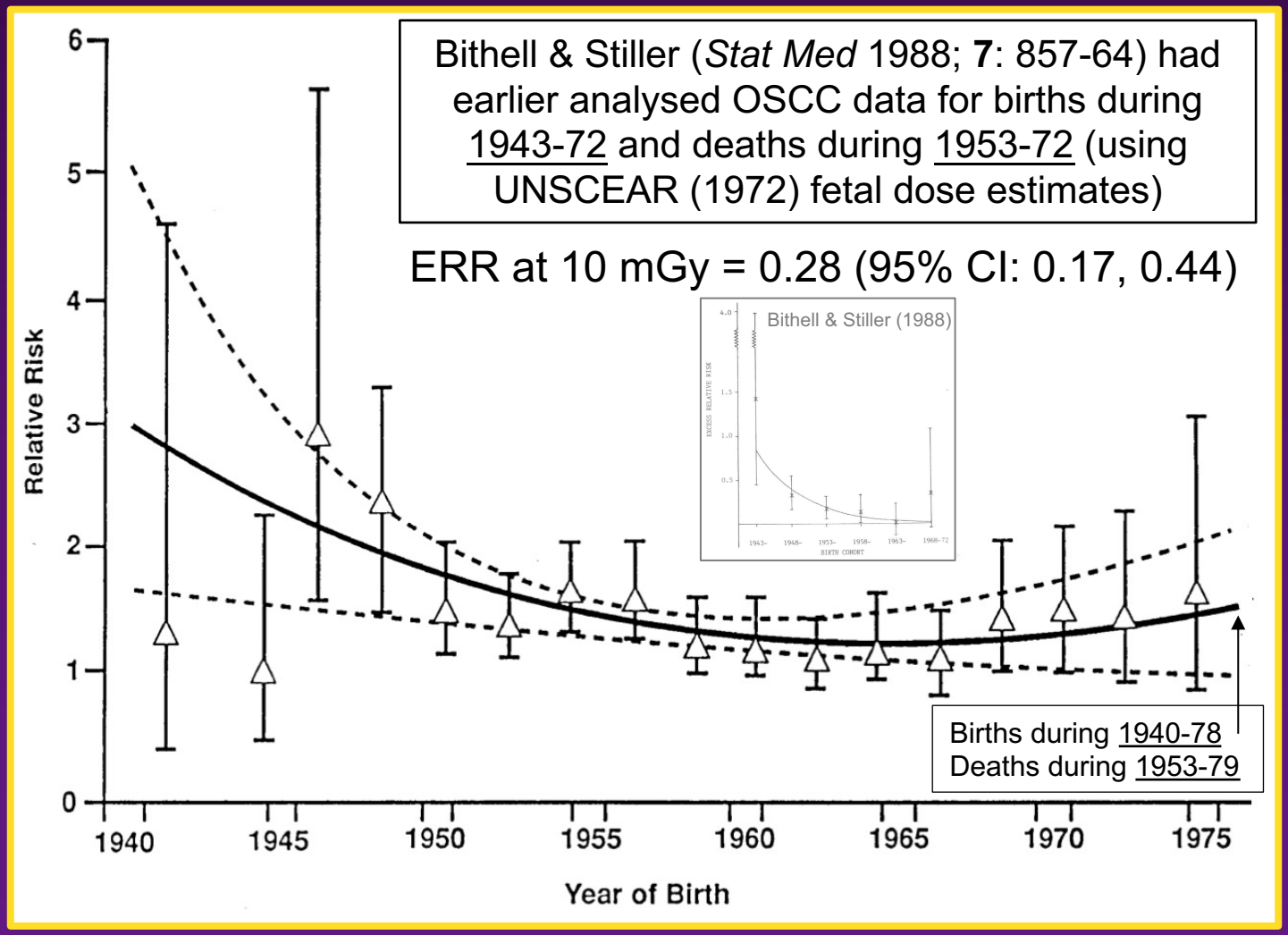
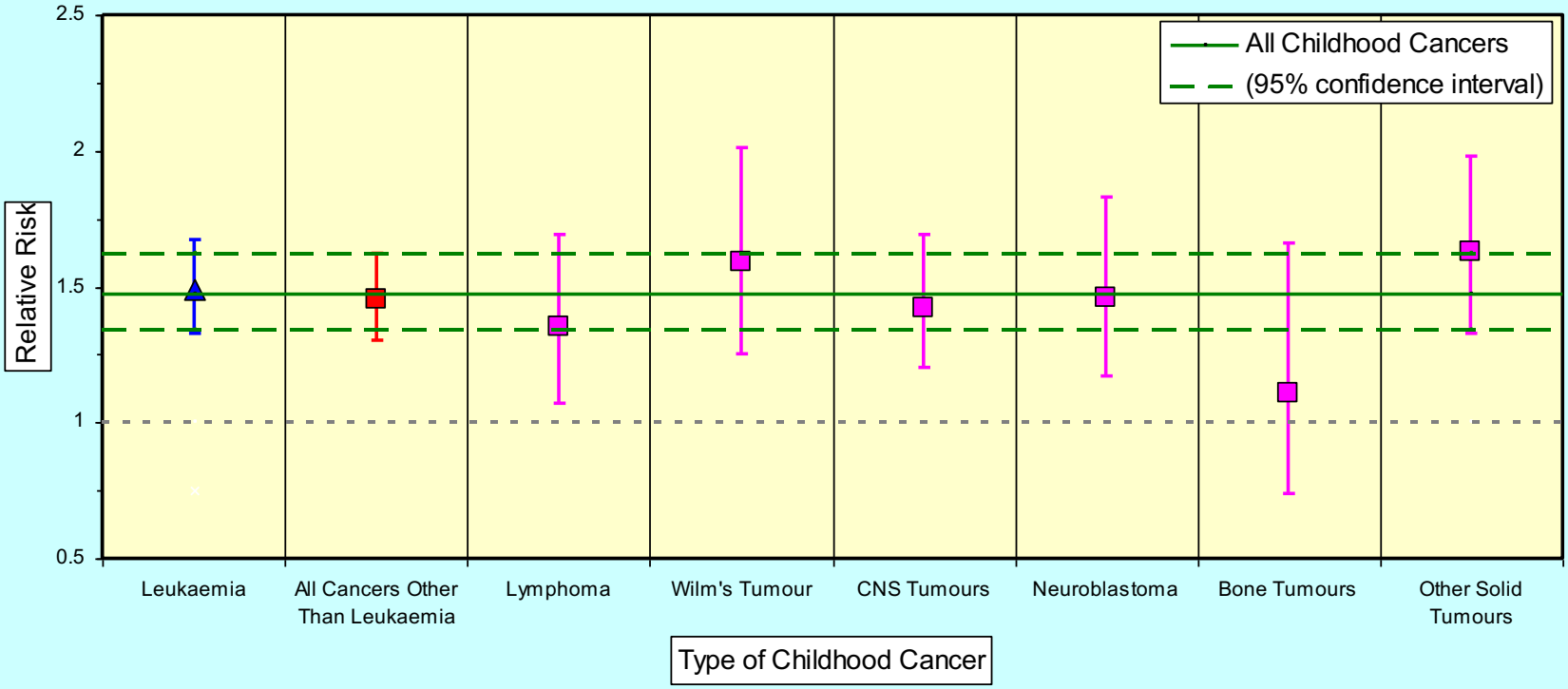


Type of Childhood Cancer

(Bithell & Stewart, *Br J Cancer* 1975; **31**: 271-87)

Relative Risk of Specific Types of Childhood Cancer Associated with an Antenatal Abdominal X-ray Examination.
OSCC Data for Deaths during 1953-1967 (Bithell and Stewart, 1975).
Error Bars and Band Show 95% Confidence Intervals.



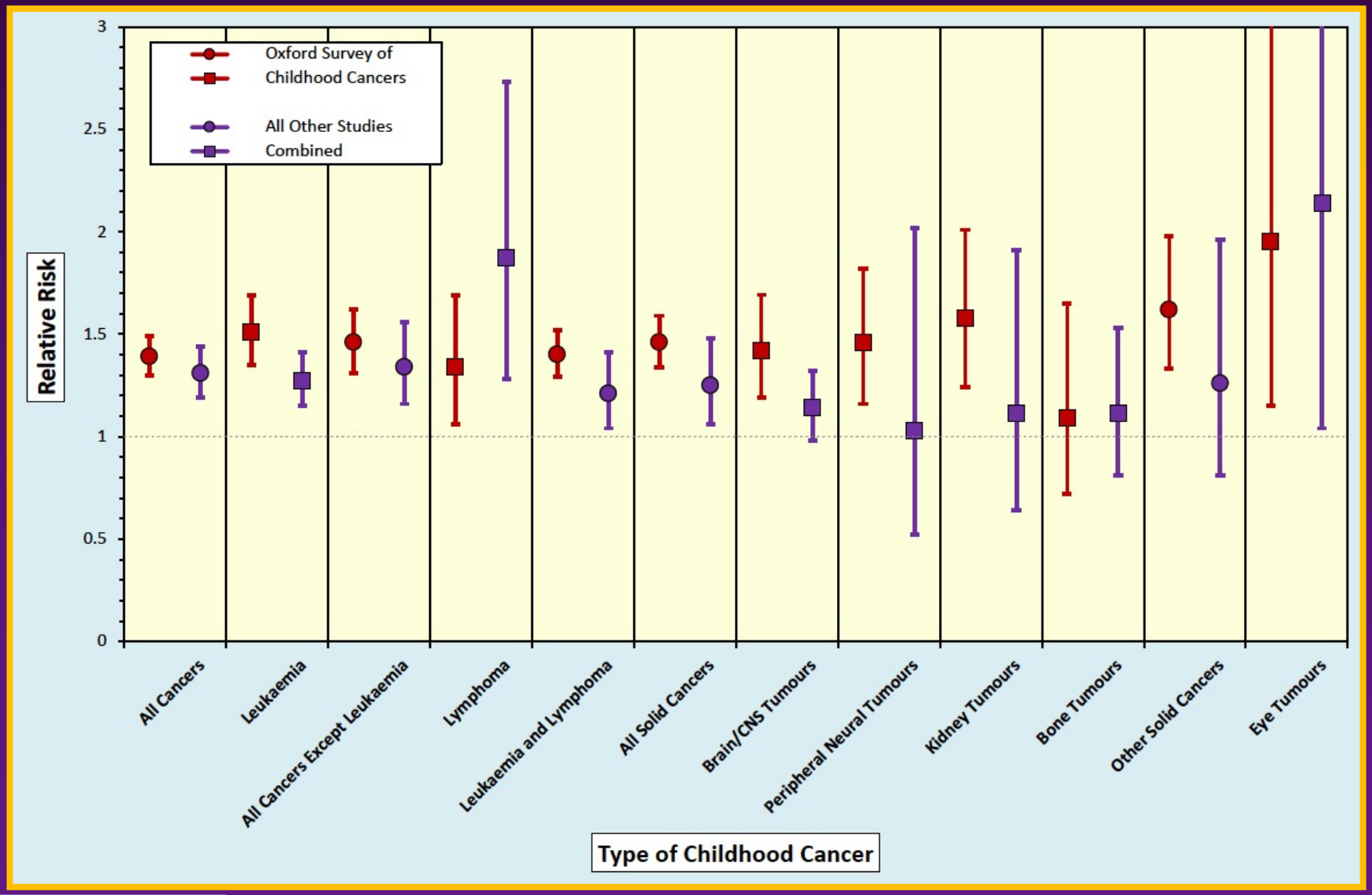
Relative Risk of Childhood Cancer Associated with Antenatal Diagnostic Exposure to Radiation found by Case-Control Studies

(Wakeford & Bithell, *Int J Radiat Biol* 2021; **97**: 571-92)

Case-control Study	Cases (Exposed/Total)	Statistical Information (Precision)	Relative Risk	95% Confidence Interval
All Childhood Cancers				
OSCC	2281/15276	852	1.39	(1.30, 1.49)
All Except OSCC	688/10,042	401	1.31	(1.18, 1.44)
Childhood Leukaemia				
OSCC	620/4122	308	1.51	(1.35, 1.69)
All Except OSCC	746/10,989	391	1.27	(1.15, 1.40)
All Childhood Cancers Except Leukaemia				
OSCC	672/4552	325	1.46	(1.31, 1.62)
All Except OSCC	246/4535	163	1.34	(1.15, 1.56)

OSCC *vs* Other Studies

(Wakeford & Bithell, *Int J Radiat Biol* 2021; **97**: 571-92)



Childhood Cancers

- Why should most common types of childhood cancer be affected to a similar extent by radiography predominantly conducted during the last few months of pregnancy?
- Little evidence exists that the typical cancers of childhood (other than childhood leukaemia) are sensitive to induction by radiation exposure after birth.

Other Childhood Cancers

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

- It may be that the primitive cells that give rise to most of the typical cancers of childhood may remain active throughout pregnancy (including during the third trimester when most obstetric X-ray examinations take place).
- However, these cells (apart from those in which leukaemia originates) may not remain susceptible to malignant transformation by radiation for long after birth, if at all.

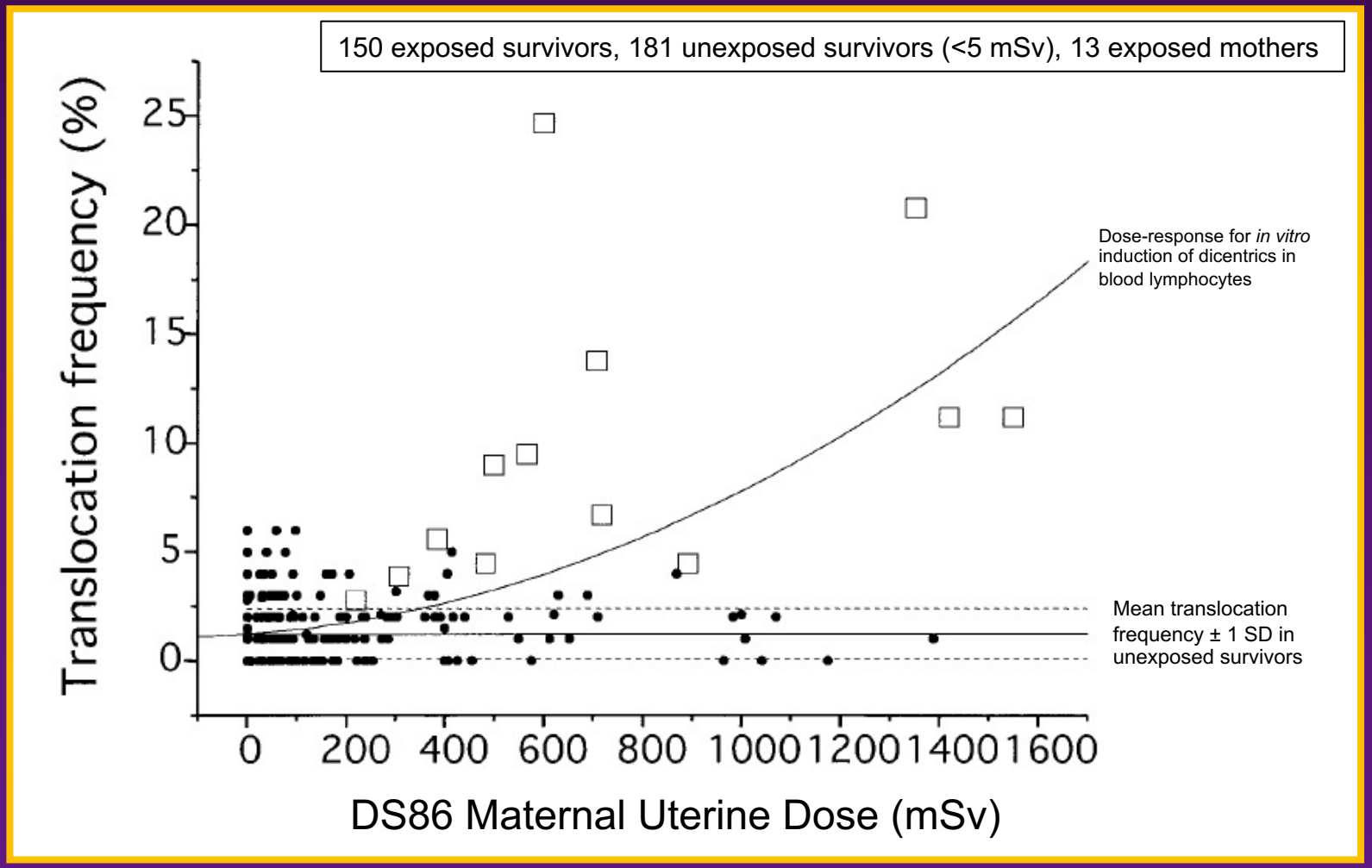
Bomb Survivors Irradiated *In Utero*

(Wakeford & Little, *Int J Radiat Biol* 2003; 79: 293-309
Sugiyama *et al*., *Eur J Epidemiol* 2021; 36: 415-28)

- 908 Japanese atomic-bomb survivors were irradiated *in utero*, who received DS02R1 uterine doses of at least 5 mGy (average dose, 0.254 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, 0.42 case expected from contemporary Japanese rates.
- No case of childhood leukaemia, but only, at most, 0.18 case expected.

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
Hamasaki & Nakamura, *Curr Stem Cell Rep* 2019; **5**: 92-9)



Adulthood Cancers

(Preston *et al.*, *J Natl Cancer Inst* 2008; 100: 428-36
Sugiyama *et al.*, *Eur J Epidemiol* 2021; 36: 415-28)

- Growing evidence from the Japanese atomic-bomb survivors irradiated *in utero* (with DS02R1 uterine dose estimates) of an increased risk of cancer in adult life.
- Solid cancer mortality (to end-2012) –

Women: ERR/Gy = 2.10 (95% CI: 0.26, 5.61) (21 deaths)

Men: ERR/Gy = -0.08 (95% CI: <-0.82, 1.36) (24 deaths)

- The level of risk of cancer in adulthood following exposure *in utero* in comparison to that following exposure from the atomic-bombings in childhood is unclear at the moment, and more data are required from continued follow-up of both groups of survivors.
- Of 908 survivors receiving an intrauterine dose >5 mGy only 132 (15%) had died by end-2012.

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