Cancer Risks After Radiation Exposure of Children – Overview of Epidemiological Studies

Richard Wakeford

Professor in Epidemiology

Centre for Occupational and Environmental Health

The University of Manchester, UK

(Richard.Wakeford@manchester.ac.uk)

MANCHESTER 1824

EU Article 31 Expert Group Scientific Seminar, 1 December 2020

The University of Manchester Centre for Occupational and Environmental Health

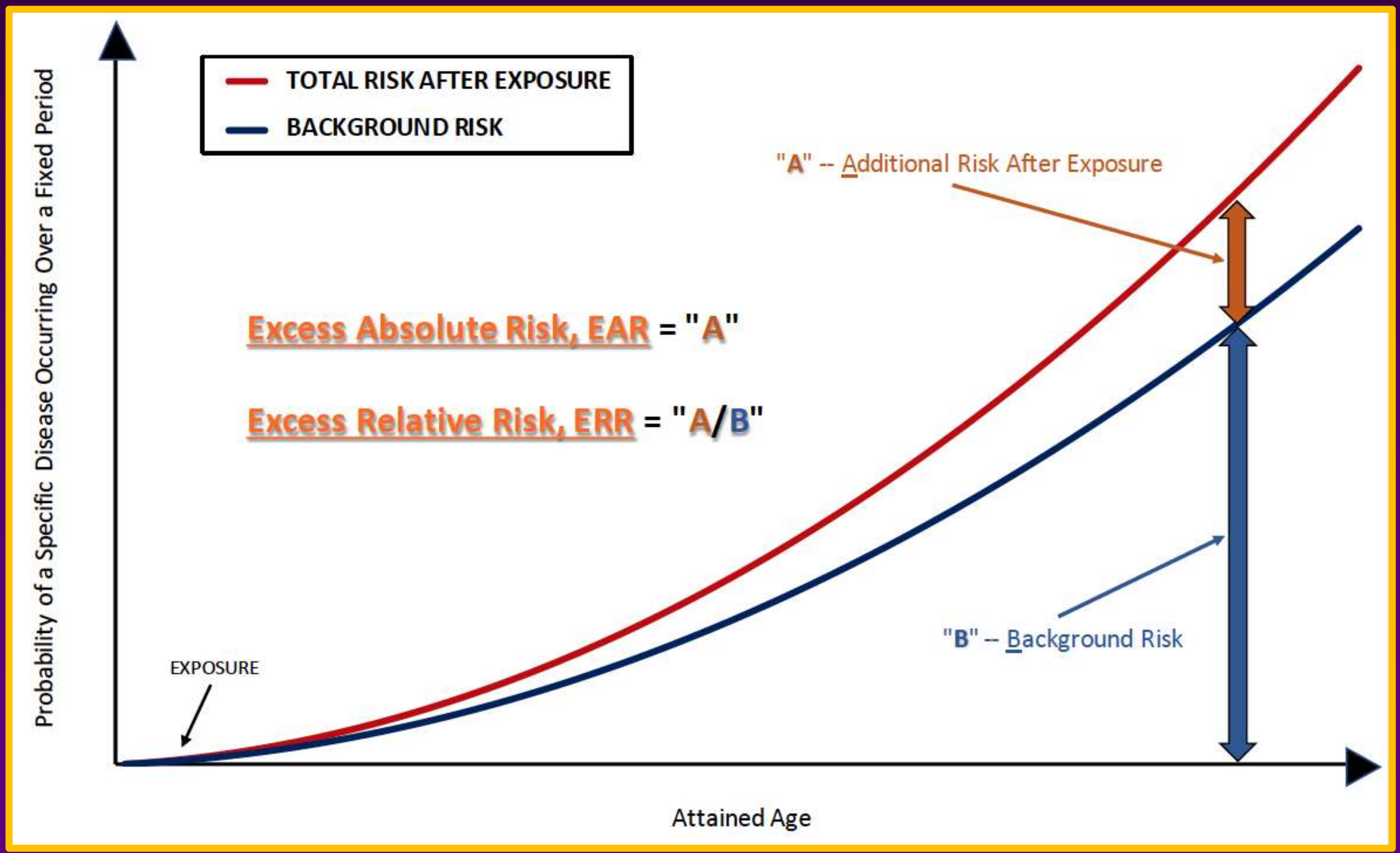
Risk Estimates – EAR and ERR

Excess Absolute Risk (EAR) and **Excess Relative Risk** (ERR)

- Cancer risk models may be expressed in terms of either the **Excess Absolute Risk** (EAR) or the **Excess Relative Risk** (ERR).
- The EAR is the **additional risk** above the background absolute risk (i.e., the risk in the absence of the exposure under consideration).
- The ERR is the **proportional increase in risk** over the background absolute risk.

EAR and ERR

Excess Absolute Risk (EAR) and **Excess Relative Risk** (ERR)

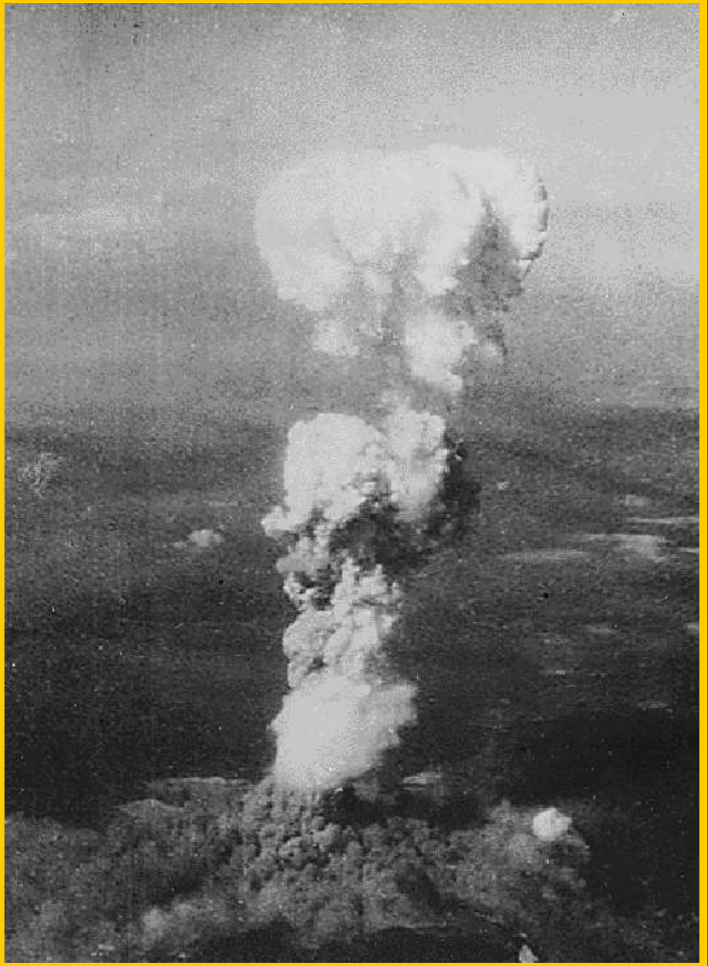


Cancer Risk Models

UNSCEAR 2006 Report, Volume I, Annex A
US NRC BEIR VII Report, 2006
Berrington de González *et al*., *J Radiol Prot* 2012; **32**: 205-22

- Cancer risk models predict the excess risk (EAR or ERR) of cancer consequent to the receipt of a certain dose of radiation.
- The risk per unit dose is modified by factors such as
  - Sex
  - Age-at-exposure (AAE)
  - Time-since-exposure (TSE)

Hiroshima and Nagasaki
6th and 9th August 1945



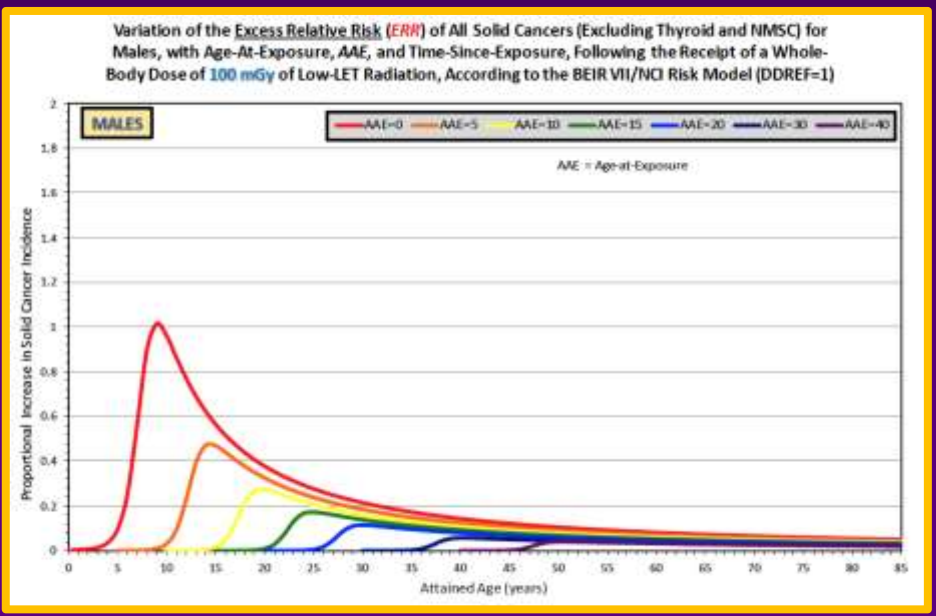
Life Span Study (LSS)

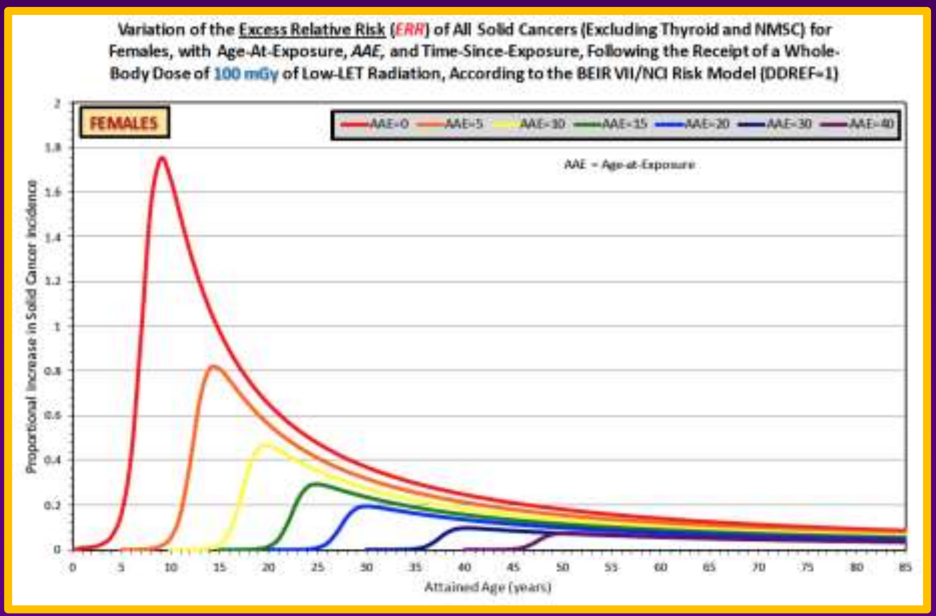
- Follow-up of ~86 500 survivors having dose estimates; ~48 000 survivors were non-trivially exposed (weighted absorbed doses >5 mGy), ~⅔ of whom received doses <100 mGy.
- Started in October 1950, still underway – 42% alive at end-2003 (88% of survivors aged <10 years ATB).
- General population of "healthy" individuals of both sexes and all ages.
- Mortality and cancer incidence investigated.
- Wide range of doses received with detailed organ dose estimates (DS02 doses – recently, DS02R1).

<u>ERR</u> – All Solid Cancers Incidence

(all cancers except leukaemia, lymphoma and multiple myeloma, but excluding thyroid cancer and NMSC)

The **<u>proportional increase in incidence risk</u>** over background (the **<u>Excess Relative Risk</u>**, ***ERR***) for males and females receiving a whole-body dose of **100 mGy** of low-LET radiation, showing the variation with age-at-exposure (*AAE*) and time-since-exposure, according to the BEIR VII/NCI risk models, with DDREF=1.



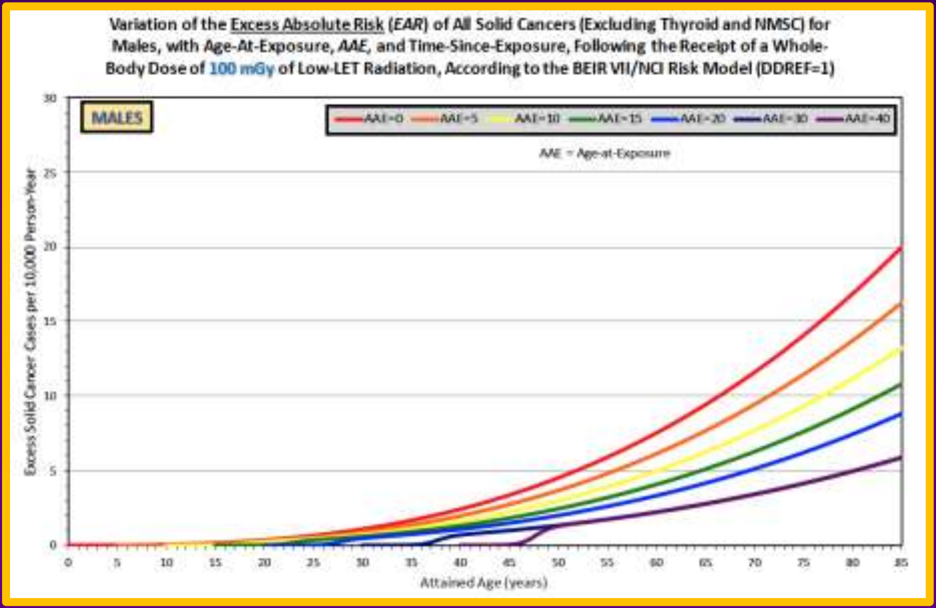


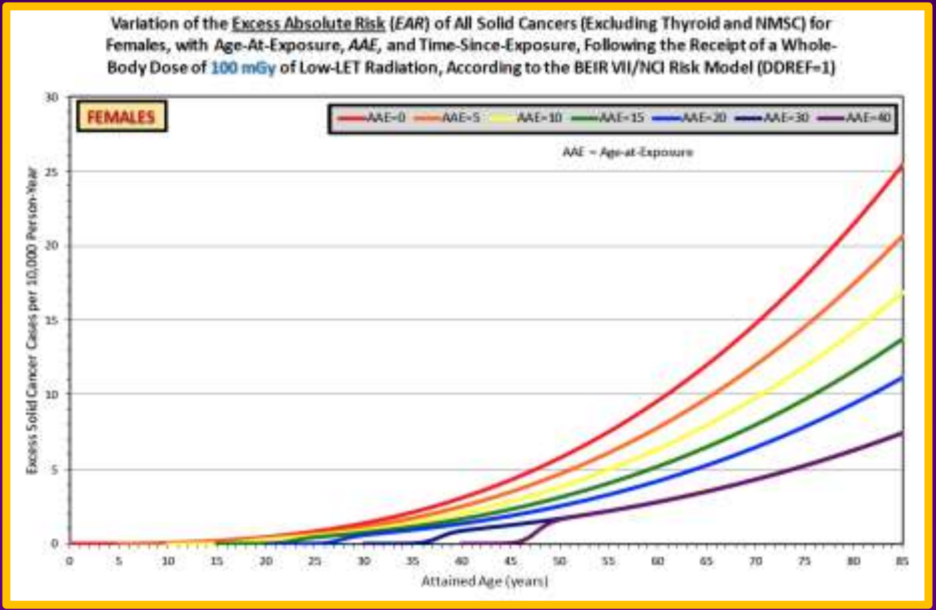
Follow-up started in 1958 (for AAE=0, attained age would be 13 years).

EAR – All Solid Cancers Incidence

(all cancers except leukaemia, lymphoma and multiple myeloma, but excluding thyroid cancer and NMSC)

The **additional incidence risk** over background (the **Excess Absolute Risk**, ***EAR***) for males and females receiving a whole-body dose of **100 mGy** of low-LET radiation, showing the variation with age-at-exposure (AAE) and time-since-exposure, according to the BEIR VII/NCI risk models, with DDREF=1.

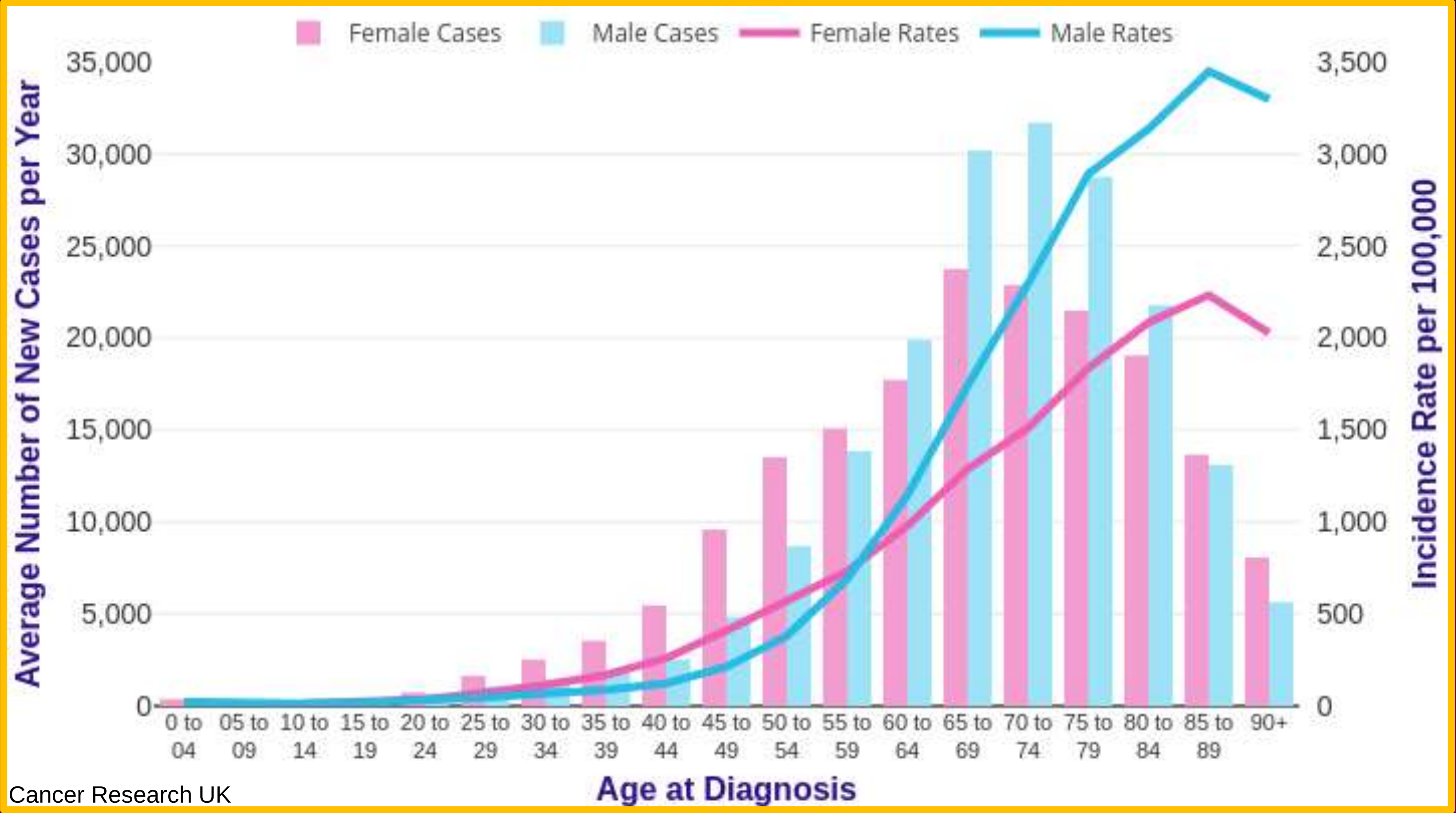




Follow-up started in 1958 (for AAE=0, attained age would be 13 years).

Incidence Rates of All Cancers

(excluding non-melanoma skin cancer, NMSC)
Cases diagnosed in the UK during 2015-2017



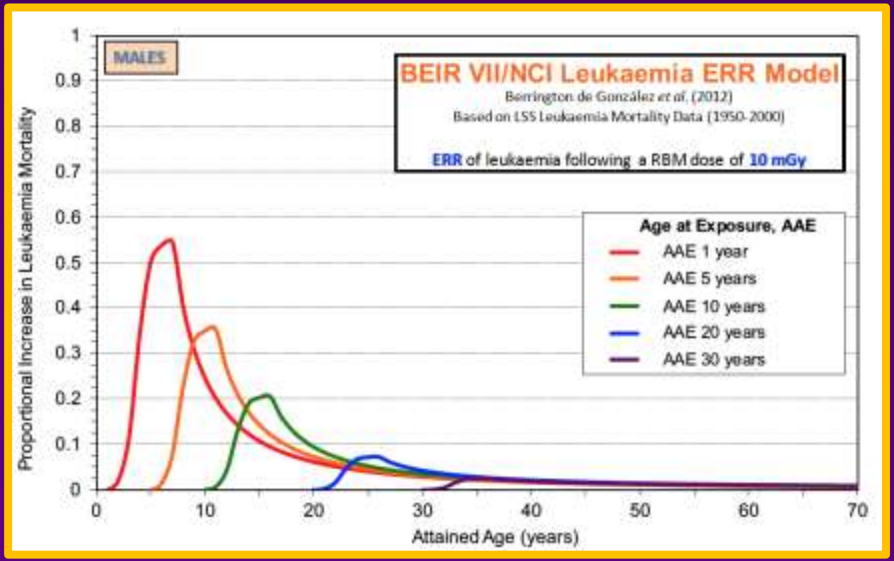
UNSCEAR 2013 Report

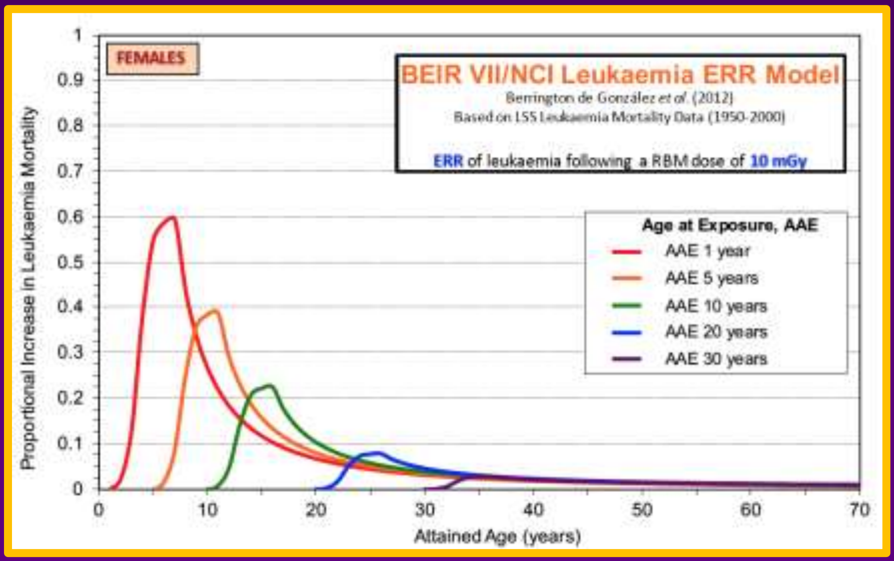
(Volume II, Scientific Annex B: Effects of Radiation Exposure of Children)

- Clear increased risk for exposure in childhood *vs* adulthood for leukaemia and thyroid, breast, skin and brain cancers (~25% of cancers).
- ~15% of cancers (e.g., bladder) appear to have about the same level of risk, while others (~10%, e.g., lung) have a lower risk.
- For ~20% of cancers (e.g., oesophagus) the evidence is too weak to draw conclusions, and for ~30% the evidence for a risk at any age at exposure is equivocal.

ERR – Leukaemia Mortality

The **proportional increase in mortality risk** over background (the **Excess Relative Risk**, ***ERR***) for males and females receiving a red bone marrow (RBM) dose of **10 mGy** of low-LET radiation, showing the variation with age-at-exposure (*AAE*) and time-since-exposure, according to the BEIR VII/NCI leukaemia risk model.

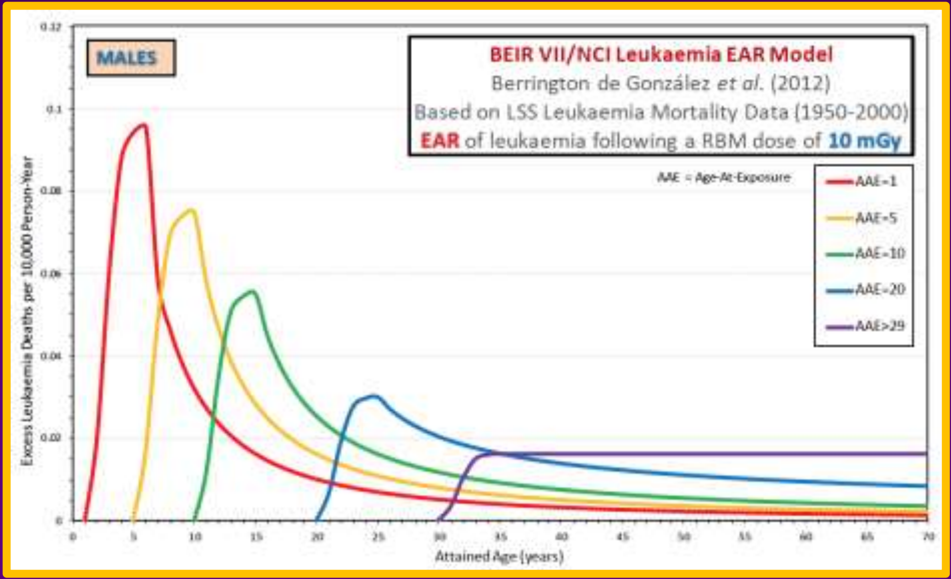


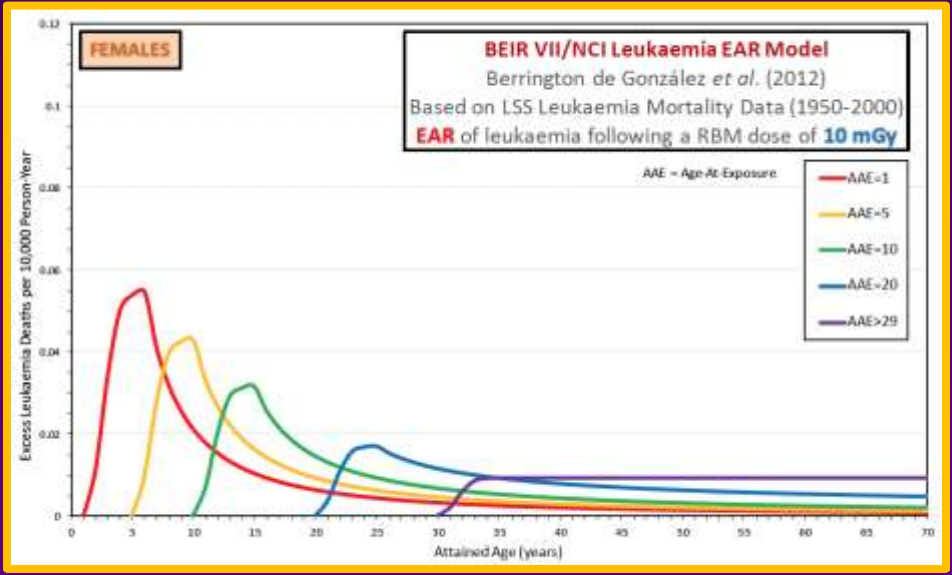


Follow-up started in 1950 (for AAE=0, attained age would be 5 years).

EAR – Leukaemia Mortality

The **additional mortality risk** over background (the **Excess Absolute Risk**, ***EAR***) for males and females receiving a red bone marrow (RBM) dose of **10 mGy** of low-LET radiation, showing the variation with age-at-exposure (*AAE*) and time-since-exposure, according to the BEIR VII/NCI leukaemia risk model.

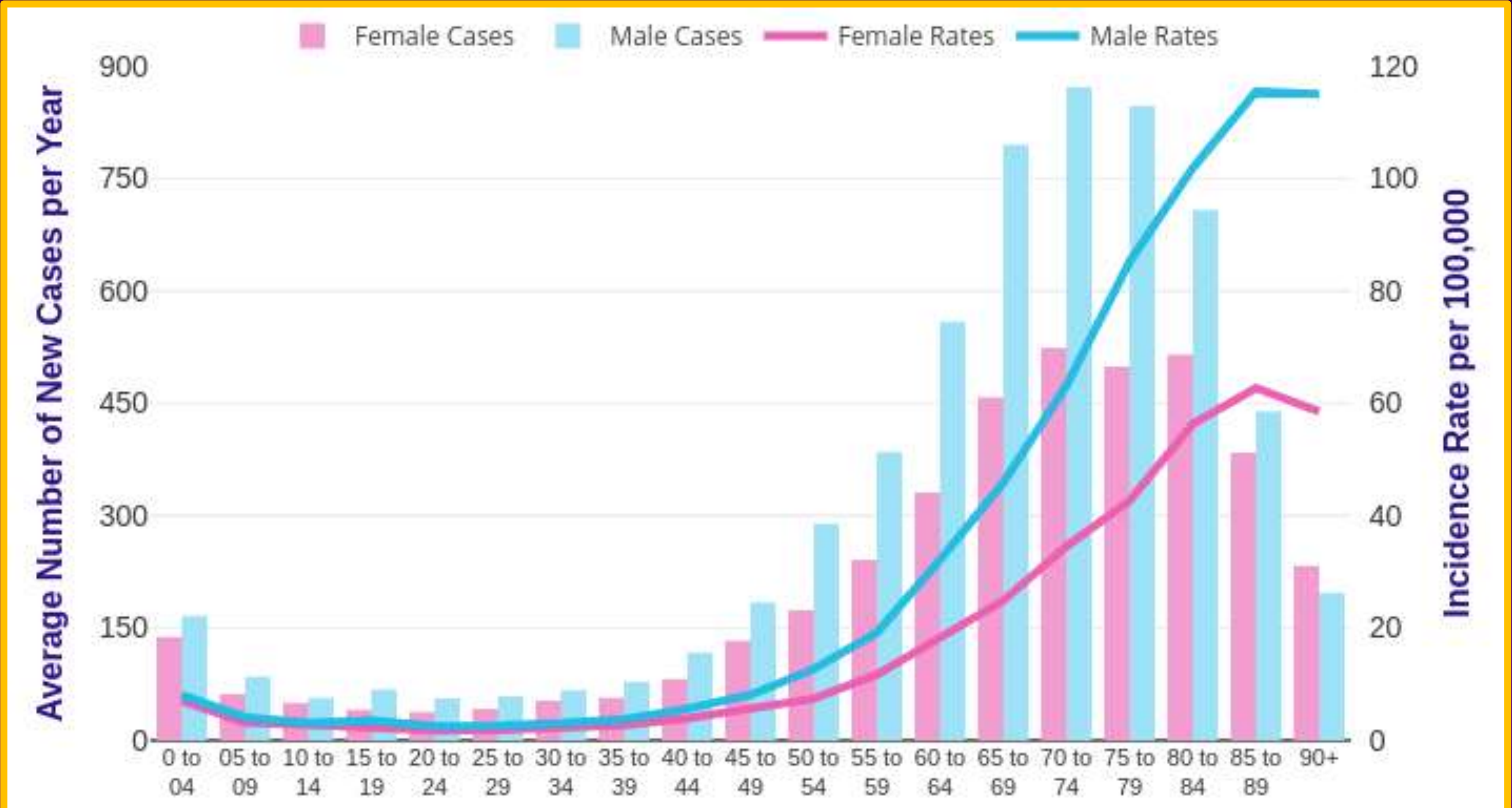




Follow-up started in 1950 (for AAE=0, attained age would be 5 years).

Leukaemia Incidence Rates

Cases diagnosed in the UK during 2015-2017



Cancer Research UK

A Word of Caution on Modelling

(Walsh & Kaiser, *Radiat Environ Biophys*, 2011; **50**: 21-35)

- The LSS leukaemia mortality data for childhood exposure are limited.
- For survivors dying of leukaemia
  – In the attained age range of 5-9 years (i.e., an age at exposure 0-4 years*) there were 4 deaths, all with weighted RBM doses >1 Gy
  – In the attained age range of 10-14 years (i.e., an age at exposure 5-9 years*) there were 6 deaths with a weighted RBM dose range 0-3.4 Gy

* Follow-up began in October 1950

Natural Background Radiation

(Wakeford *et al.*, *Leukemia* 2009; **23**: 770-6.
Little *et al. J Radiol Prot* 2009; **29**: 467-82.
Kendall *et al.*, *Leuk Res* 2011; **35**: 1039-43.)

- Recent risk models for radiation-induced leukaemia suggest that perhaps ~15-20% of cases of childhood (<15 years of age) leukaemia in Great Britain may be caused by natural background radiation.
  - red bone marrow dose ~1.4 mSv per annum
- Past epidemiological studies have been unable to reliably demonstrate this source of risk
  - probably have insufficient statistical power

Natural Background Radiation

(Little *et al. Radiat Res* 2010; **174**: 387-402)

- Power calculations show that *large* studies are required to detect the predicted excess risk
  - to achieve 80% statistical power, >8000 cases are needed in a case-control study covering the whole of Great Britain (England, Wales and Scotland).
- Greatest effect is from γ-rays, <u>not</u> radon.
- The extensive data from the National Registry of Childhood Tumours make such a study feasible in respect of power to detect the predicted excess risk of childhood leukaemia.

Natural Background Radiation

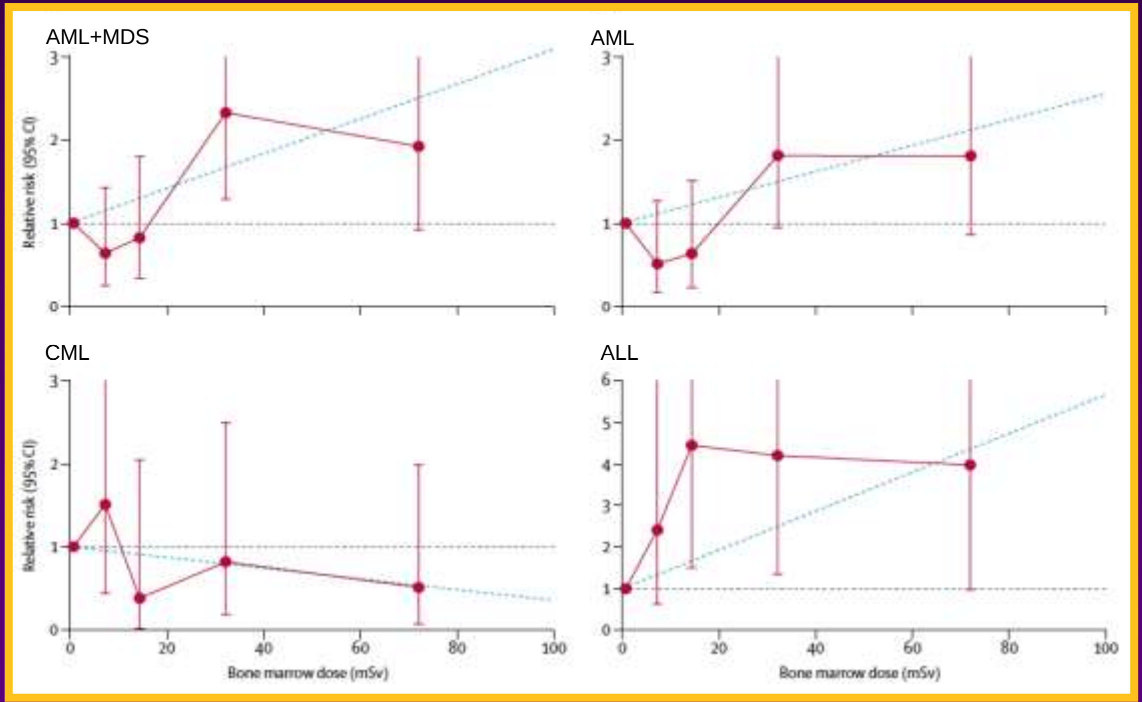
(Kendall *et al.*, *Leukemia* 2013; **27**: 3-9
Demoury *et al.*, *Environ Health Perspect* 2017; **125**: 714-20
Mazzei-Abba *et al*., *J Radiol Prot* 2020; **40**: R1-R22)

- Some large nationwide studies of childhood leukaemia incidence and natural background gamma radiation have been conducted, with mixed results.
- A British study finds an association between childhood leukaemia incidence and gamma radiation dose at the predicted level, but a French study does not.
- More work is required.

Pooled Leukaemia Analysis

(Little *et al*., *Lancet Haematol* 2018; **5**: e346-e358)

Analysis of pooled data from nine cohorts of persons exposed to external sources of radiation in childhood (but not as a treatment for cancer) – 262,573 individuals with **mean RBM doses <100 mGy**.

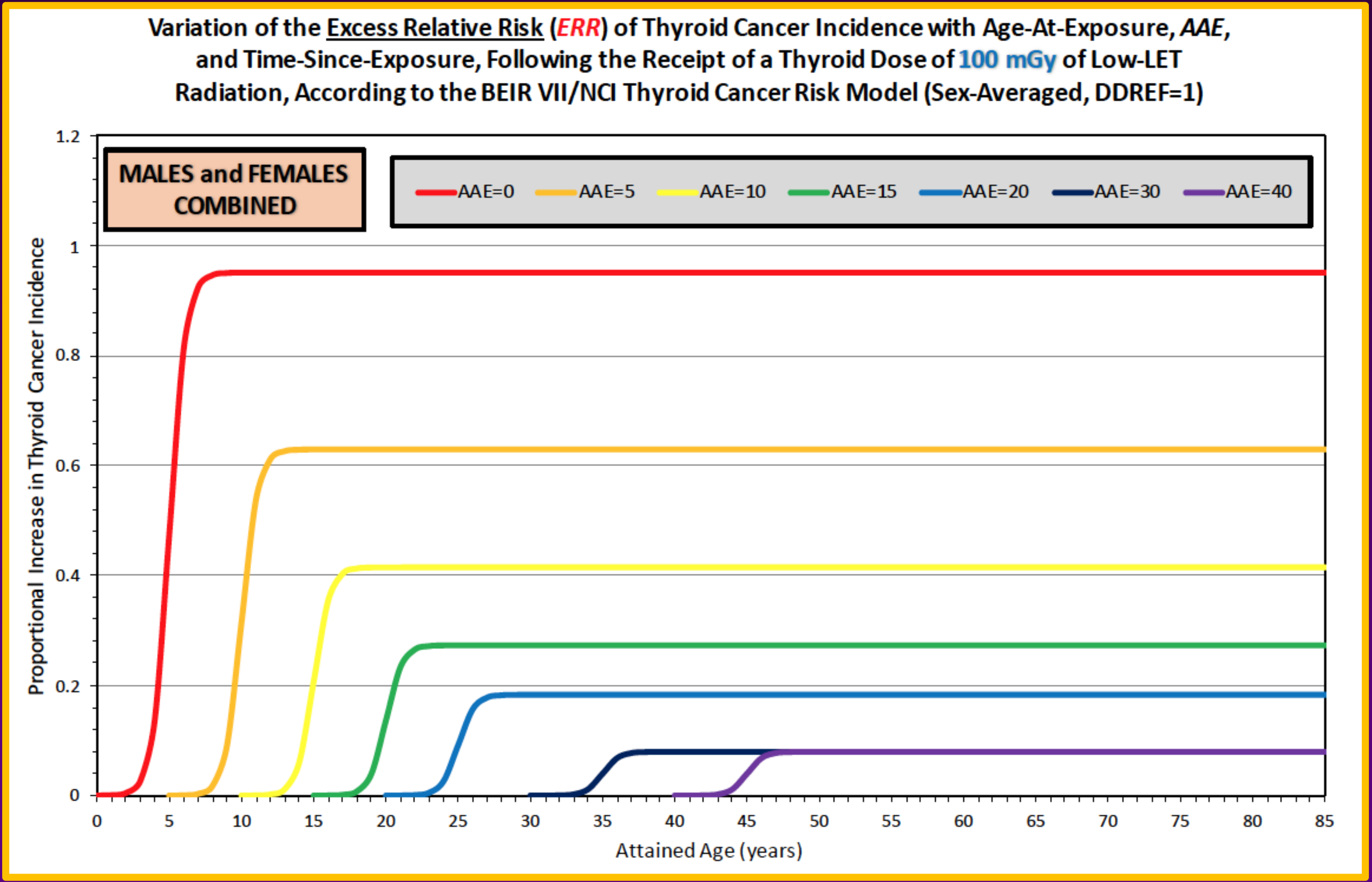


MDS = myelodysplastic syndrome

ERR/Sv:	Leukaemia (excluding CLL):	8.4 (95% CI: -0.3, 20.8)
	Acute Myeloid Leukaemia (AML):	15.6 (95% CI: 0.9, 40.6)
	Acute Lymphoblastic Leukaemia (ALL):	46.6 (95% CI: 3.5, 187.1)
	Chronic Myeloid Leukaemia (CML):	-6.4 (95% CI: <-6.4, 13.6)

<u>ERR</u> – Thyroid Cancer Incidence

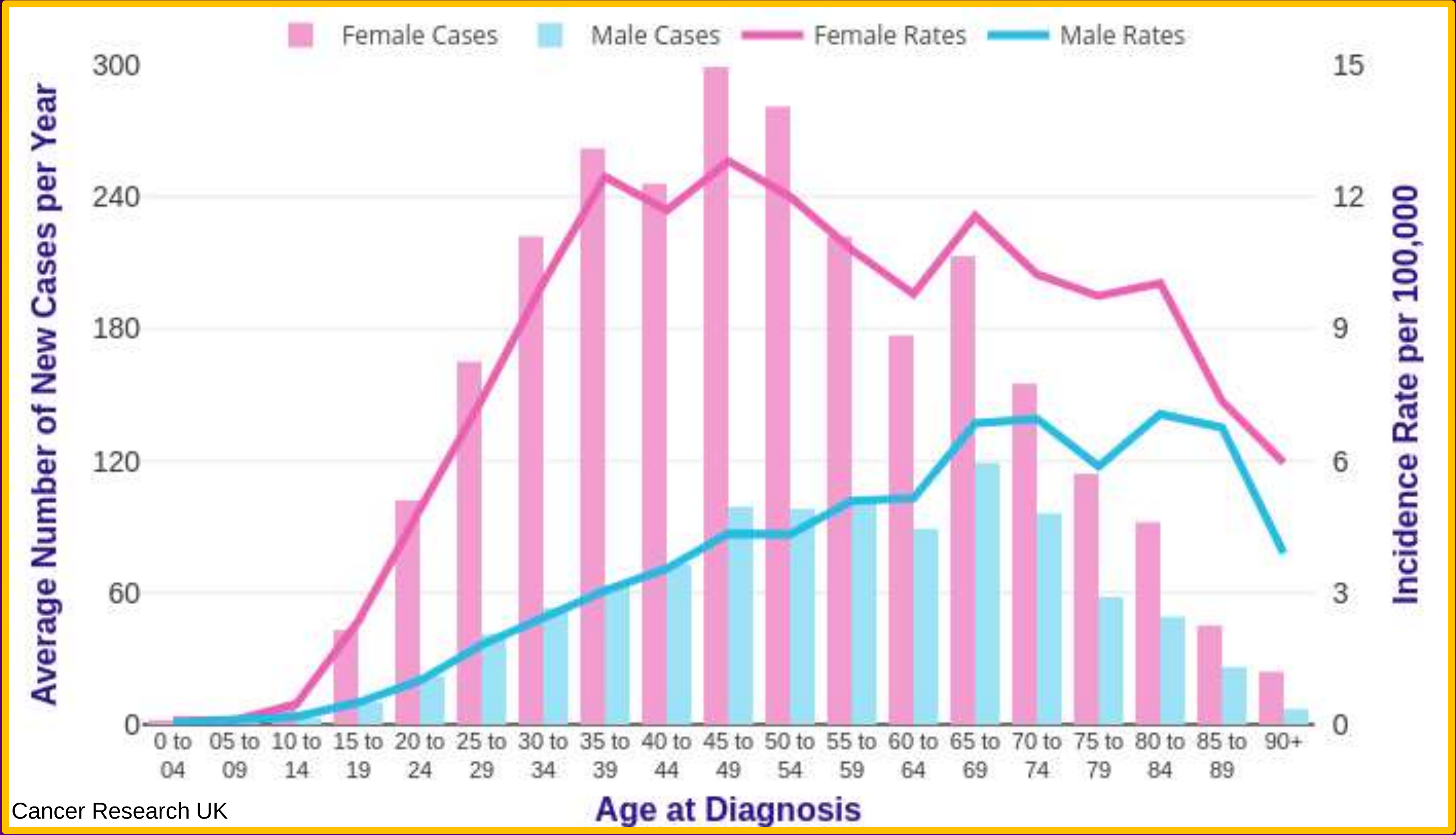
(BEIR VII/NCI Thyroid Cancer ERR Model; **100 mGy** Thyroid Dose)



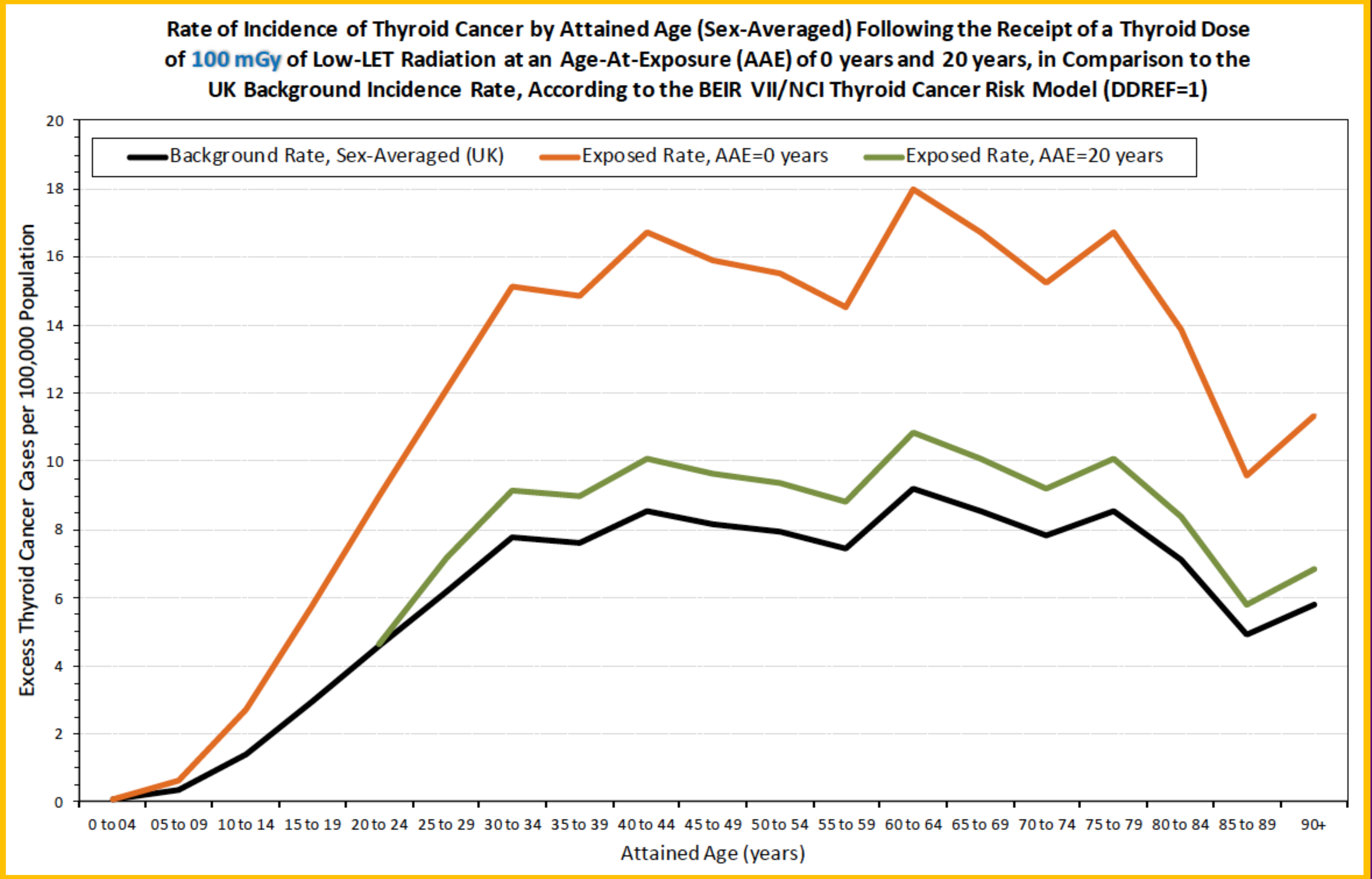
ERR model based upon the results of an analysis of pooled data from seven cohort studies (Ron *et al.*, 2005).

Thyroid Cancer Incidence Rates

Cases diagnosed in the UK during 2015-2017



Excess Thyroid Cancer Rates



Chornobyl Unit 4 – 26 April 1986

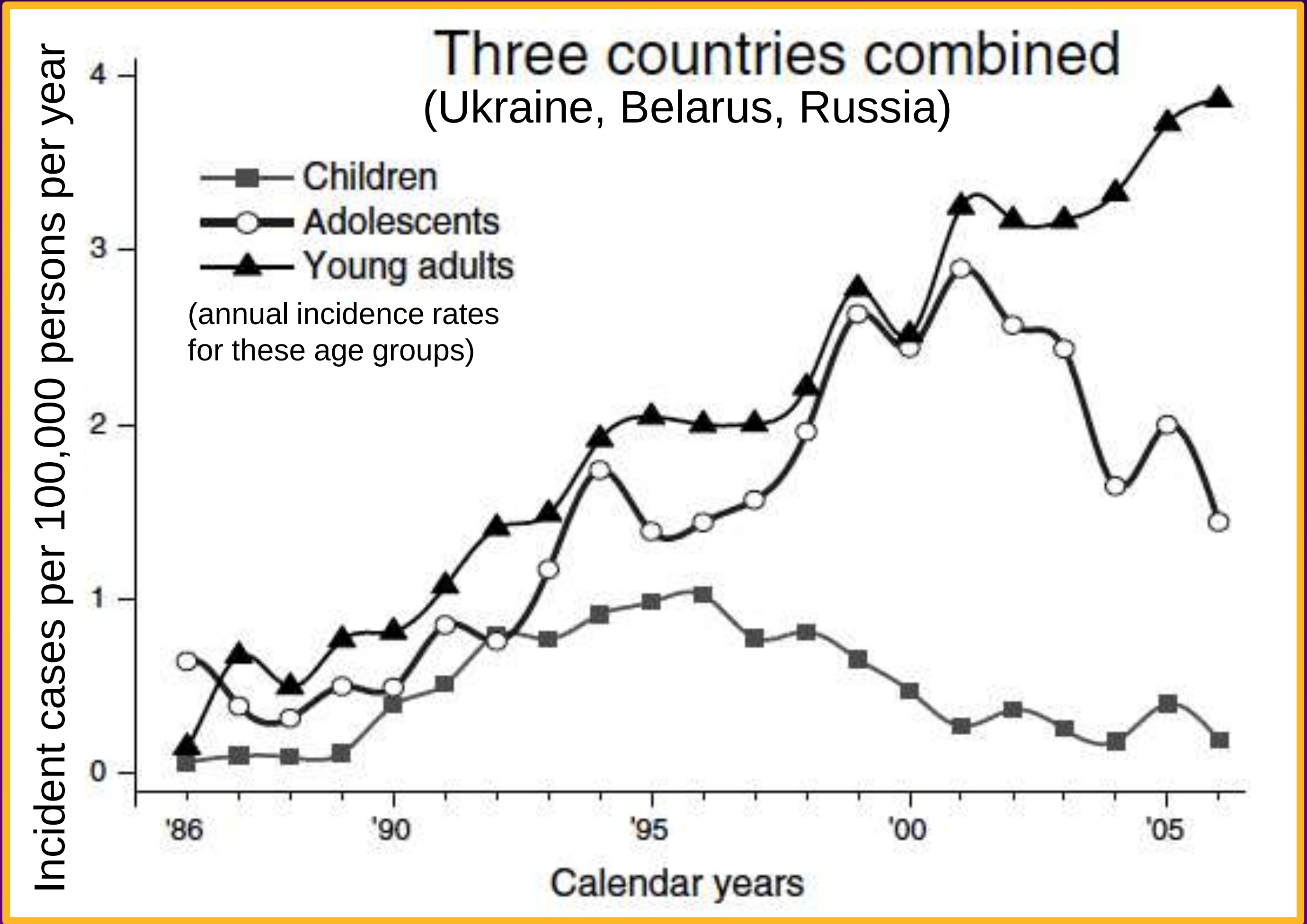
(UNSCEAR 2008 Report, Volume II, Annex D)

- Total activity release of ~14 EBq*
- ~50% of the activity released from Chornobyl was as radioisotopes of noble gases, and
- ~1.8 EBq* of ^{131}I,
- ~85 PBq of ^{137}Cs,
- ~10 PBq of ^{90}Sr,
- ~0.1 PBq of Pu α-emitting isotopes.

* 1.8×10^{18} Bq

Chornobyl – Annual Thyroid Cancer Incidence Rates

(Yamashita, *Health Phys* 2014; **106**: 166-80)



Thyroid Cancer Incidence

(<15 years of age at exposure)

Exposure	Study	ERR/Gy (95% CI)
External	Pooled Analysis Ron *et al.*, *Radiat Res* 1995; **141**: 259-277	7.7 (2.1, 29)
External	Pooled Analysis Veiga *et al.*, *Radiat Res* 2016; **185**: 473-484	6.5 (5.1, 8.5)
Chornobyl	Case-control (Belarus & Russia) Cardis *et al.*, *J Natl Cancer Inst* 2005; **97**: 724-32	4.5 (1.2, 7.8)
Chornobyl	Case-control (Bryansk, Russia) Kopecky *et al.*, *Radiat Res* 2006; **166**: 367-374 * <20 years of age at exposure	48.7 (4.8, 1151)
Chornobyl	Cohort* (Ukraine) Tronko *et al.*, *J Natl Cancer Inst* 2006; **98**: 897-903 * <18 years of age at exposure	5.2 (1.7, 27)
Chornobyl	Cohort* (Belarus) Zablotska *et al.*, *Br J Cancer* 2011; **104**: 181-187 * <18 years of age at exposure	2.2 (0.8, 5.5)
Chornobyl	Cohort* (Ukraine) Brenner *et al.*, *Environ Health Perspect* 2011; **119**: 933-939 * <18 years of age at exposure	1.9 (0.4, 6.3)

Chornobyl – Thyroid Cancer

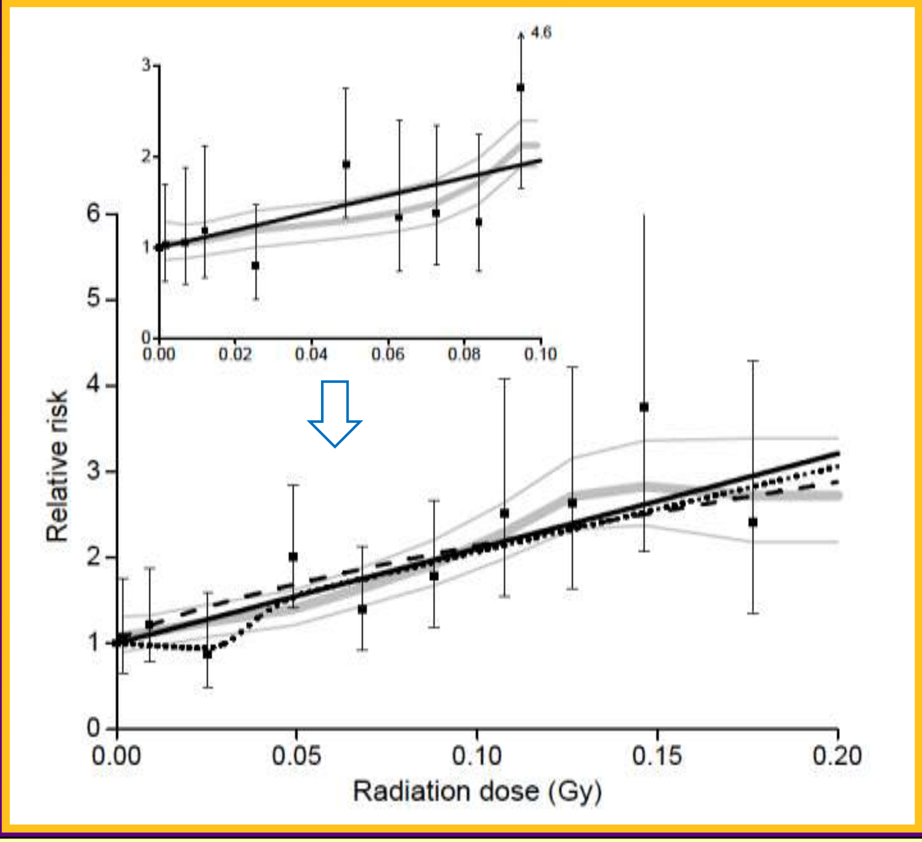
(Furukawa *et al*., *Int J Cancer* 2013; **132**: 1222-6)

- The eventual number of excess cases of thyroid cancer among those exposed at a young age will largely depend on how long the excess risk persists and how (and if) the ERR varies with time since exposure.
- A dose-related excess of thyroid cancer is still present among the Japanese atomic bomb survivors 60 years after exposure, although some evidence exists for a decrease in ERR.

Pooled Thyroid Cancer Analysis

(Lubin *et al.*, *J Clin Endorinol Metab* 2017; **102**: 2575-83)

Analysis of pooled data from nine cohorts of persons exposed to external sources of radiation in childhood – 107,595 individuals with **thyroid doses <200 mGy**.



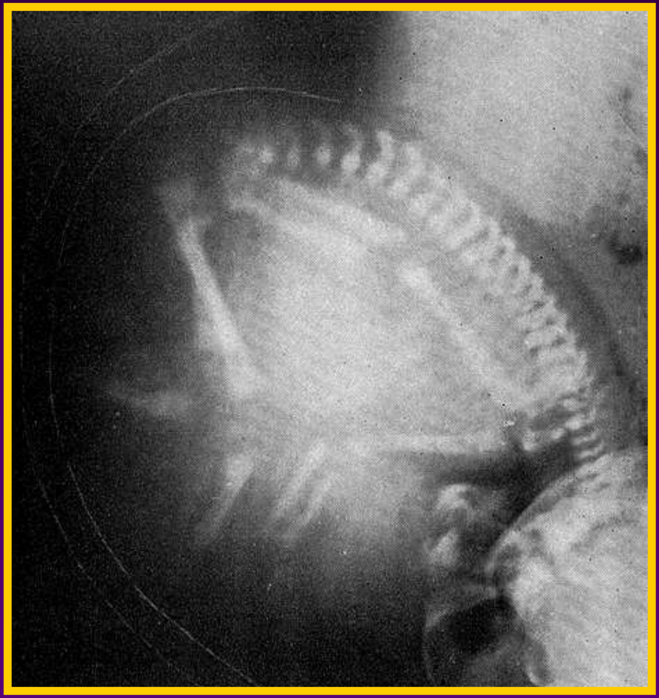
ERR/Gy: 11.1 (95% CI: 6.6, 19.7)	(<0.2 Gy)
9.6 (95% CI: 3.7, 17.0)	(<0.1 Gy)

MANCHESTER 1824

The University of Manchester Centre for Occupational and Environmental Health

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 <u>childhood</u> (<15 years of age) cancer incidence following fetal exposure:

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

Bomb Survivors Irradiated *In Utero*

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

- 0 case of childhood leukaemia observed (O), but only 0.2 expected (E)

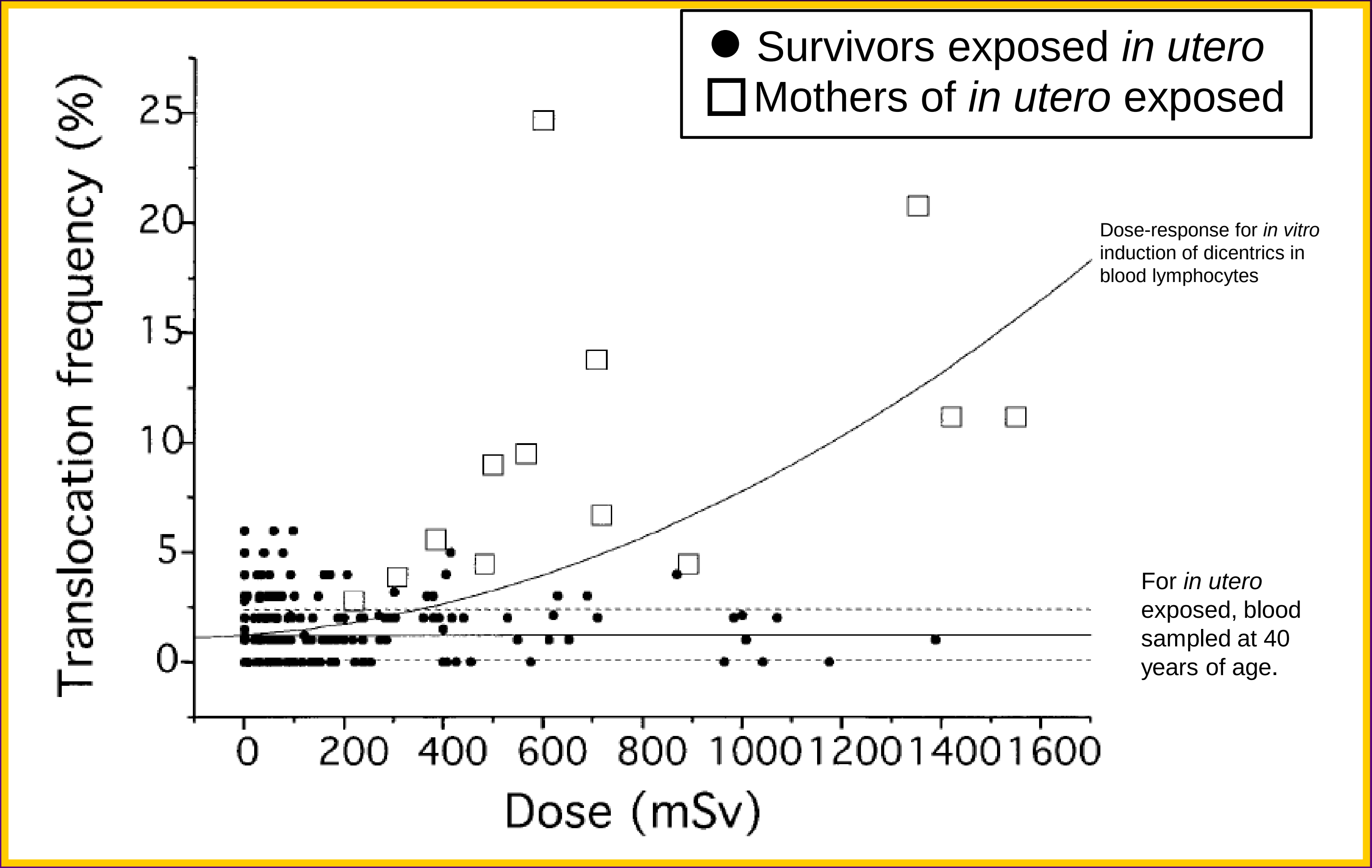
  O/E = 0, but with a 95% CI of (0, 15)

- 2 cases of other childhood cancers observed (O), against 0.28 expected (E)

  O/E = 7.1 (95% CI: 1.2, 24)

- 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)

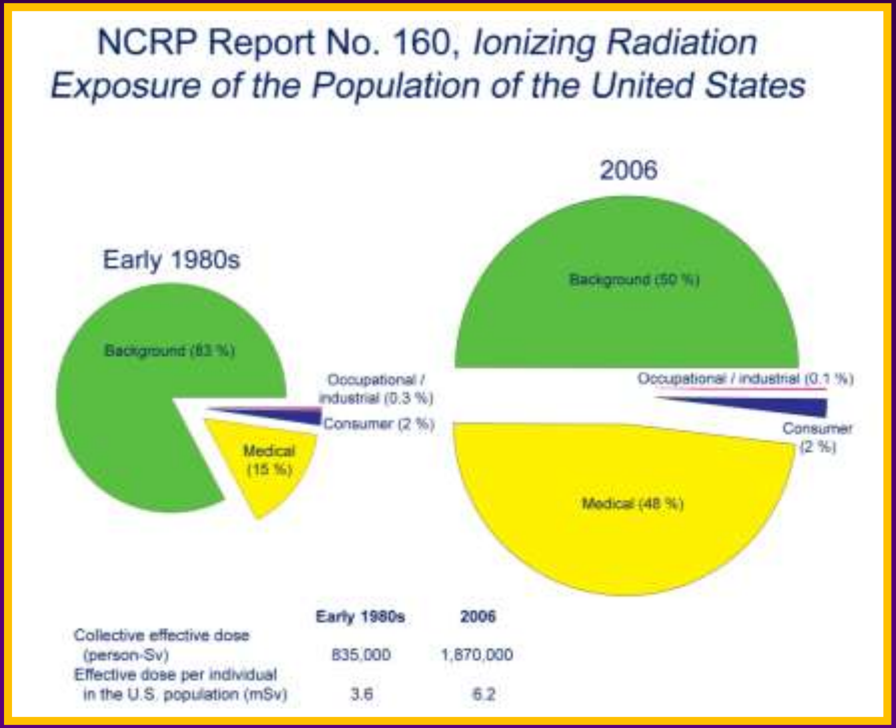


Medically Exposed Groups

- 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 bias the risk estimates obtained from medical studies (e.g., reverse causation and confounding by indication) – selection effects are a distinct possibility
  - Accurate dose estimates are often lacking

CT Scanning


Discovery


NCRP Report No. 160, *Ionizing Radiation Exposure of the Population of the United States*
Early 1980s
Background (83 %)
Medical (15 %)
Occupational / industrial (0.3 %)
Consumer (2 %)
2006
Background (50 %)
Occupational / industrial (0.1 %)
Consumer (2 %)
Medical (48 %)
Early 1980s
2006
Collective effective dose (person-Sv)
835,000
1,870,000
Effective dose per individual in the U.S. population (mSv)
3.6
6.2

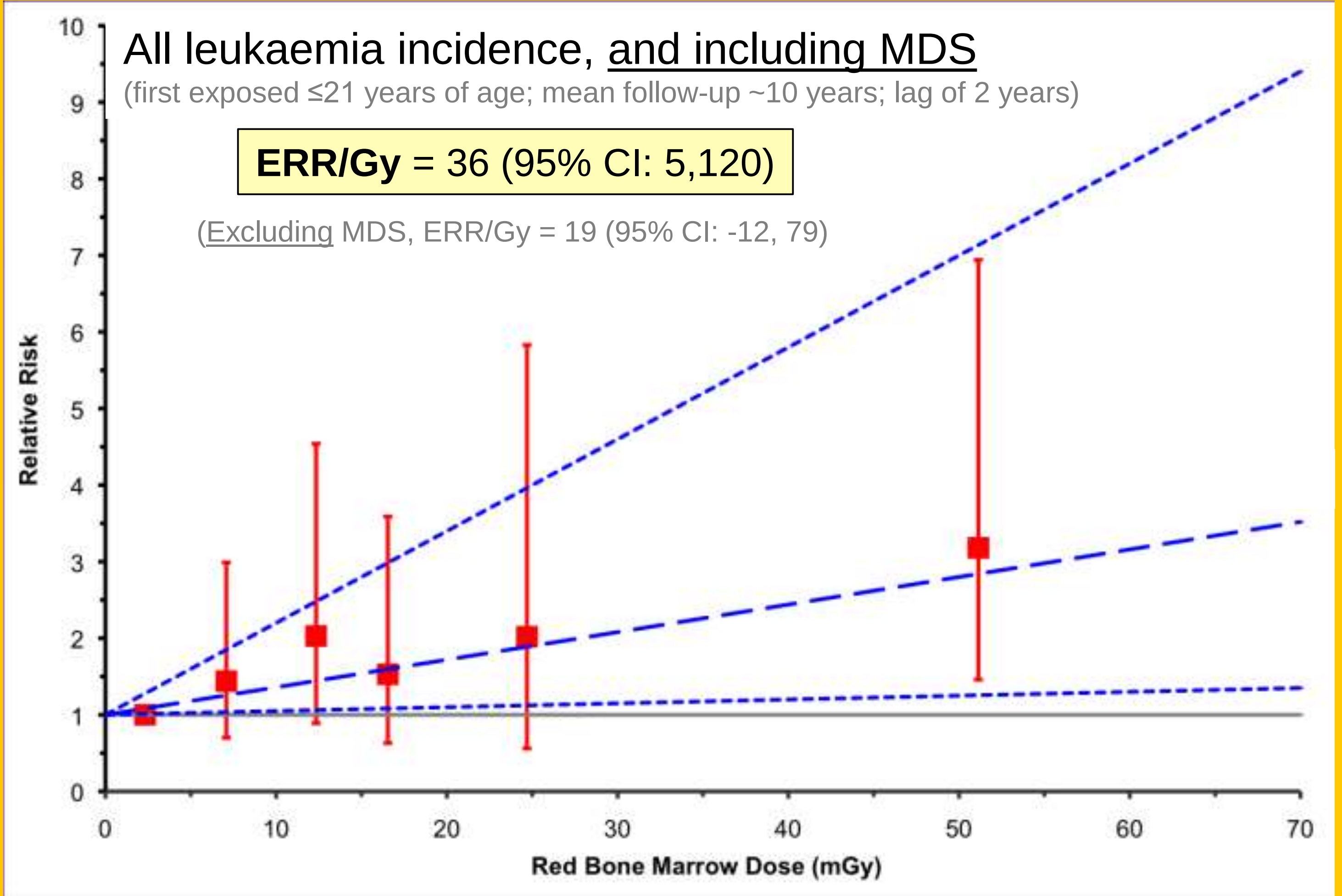
British CT Scan Cohort Study

(Pearce *et al*., *Lancet* 2012; **380**: 499-505)

- Cohort study of ~176,500 patients first examined with CT in Great Britain during 1985-2002 when ≤21 years of age.
- Cancers diagnosed during 1985-2008 identified through UK national cancer registry.
- Initial analysis of leukaemia (lag, 2 years) and brain tumours (lag, 5 years), using estimates of RBM and brain doses per CT scan from details contained in medical records.

British CT Scan Cohort Study

(Pearce *et al.*, *Lancet* 2012; **380**: 499-505)
(Berrington de Gonzalez *et al.*, *Br J Cancer* 2016; **114**: 388-394)
(Journy *et al.*, *Br J Radiol* 2016; **89**: 20160532)



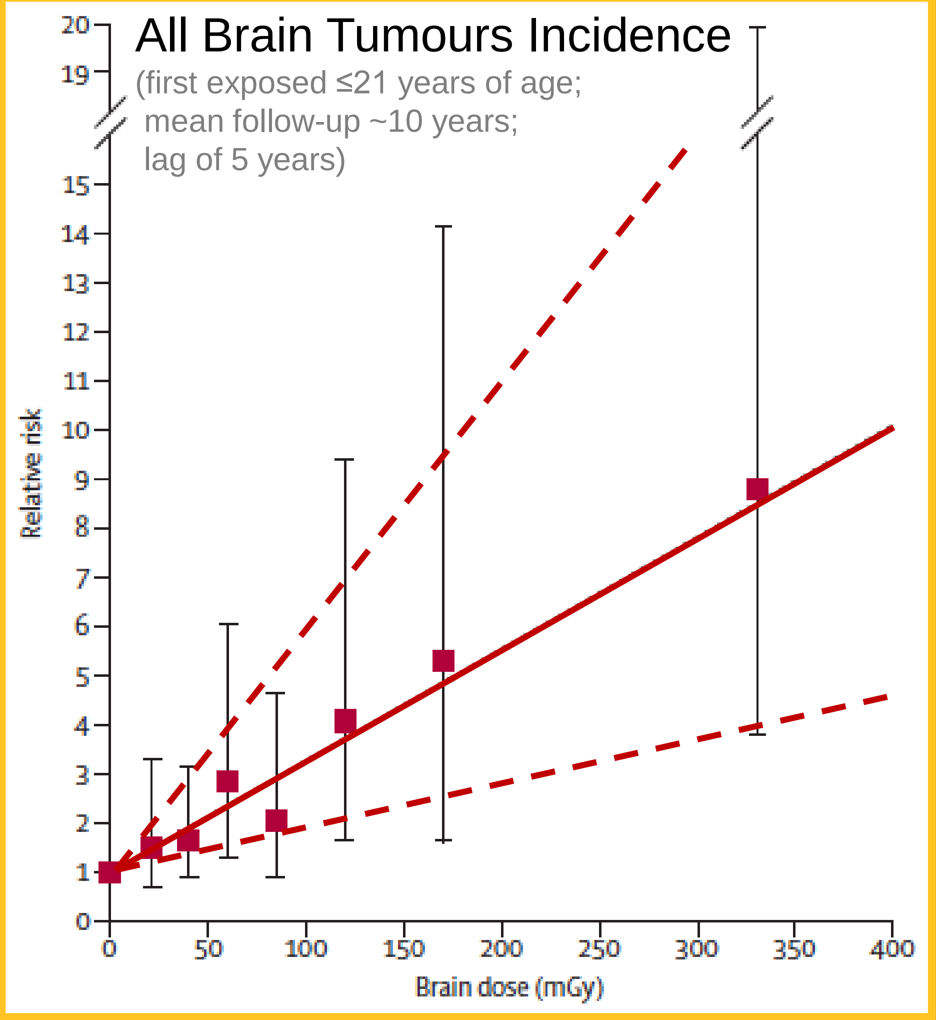
Using Japanese LSS incidence data (for leukaemia only); <20 years of age at exposure, 5-14 years since exposure:

ERR/Sv = 45 (95% CI: 16, 188)

MDS = myelodysplastic syndrome

British CT Scan Cohort Study

(Pearce *et al*., *Lancet* 2012; **380**: 499-505)
(Berrington de Gonzalez *et al*., *Br J Cancer* 2016; **114**: 388-394)
(Journy *et al*., *Br J Radiol* 2016; **89**: 20160532)



ERR/Gy = 23 (95% CI: 10, 49)

Using the Japanese LSS incidence data for brain cancer; <20 years of age at exposure, 13-19 years since exposure:

ERR/Sv = 6.1 (95% CI: 0.1, 63.9)

Atmospheric Nuclear Weapons Testing

Peaking in late-1950s and early-1960s.

MANCHESTER 1824

The University of Manchester Centre for Occupational and Environmental Health

Nuclear Weapons Testing

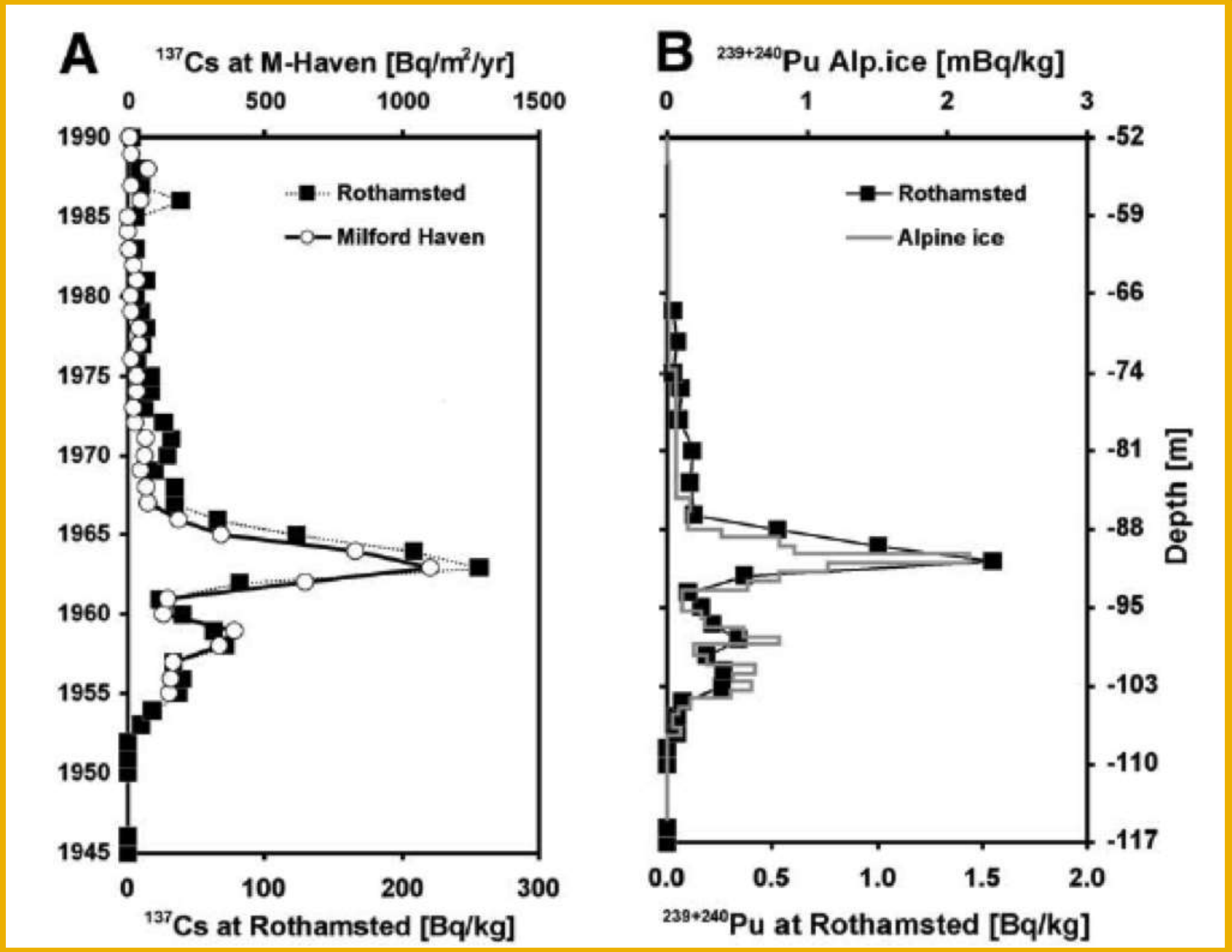
(UNSCEAR 2000 Report, Volume I, Annex C, Table 9)

Comparison of Activity Releases (PBq) from Atmospheric Nuclear Weapons Testing and the Chornobyl Accident

Radionuclide	Nuclear Weapons Testing (PBq)	Chornobyl Accident (PBq)
I-131	675,000	1800
Cs-137	948	85
Sr-90	622	10
Pu (α-activity)	11	0.1

Cs-137 and Pu in Fallout

(Warneke *et al.*, *Earth Planet Sci Lett* 2002; **203**: 1047-57)

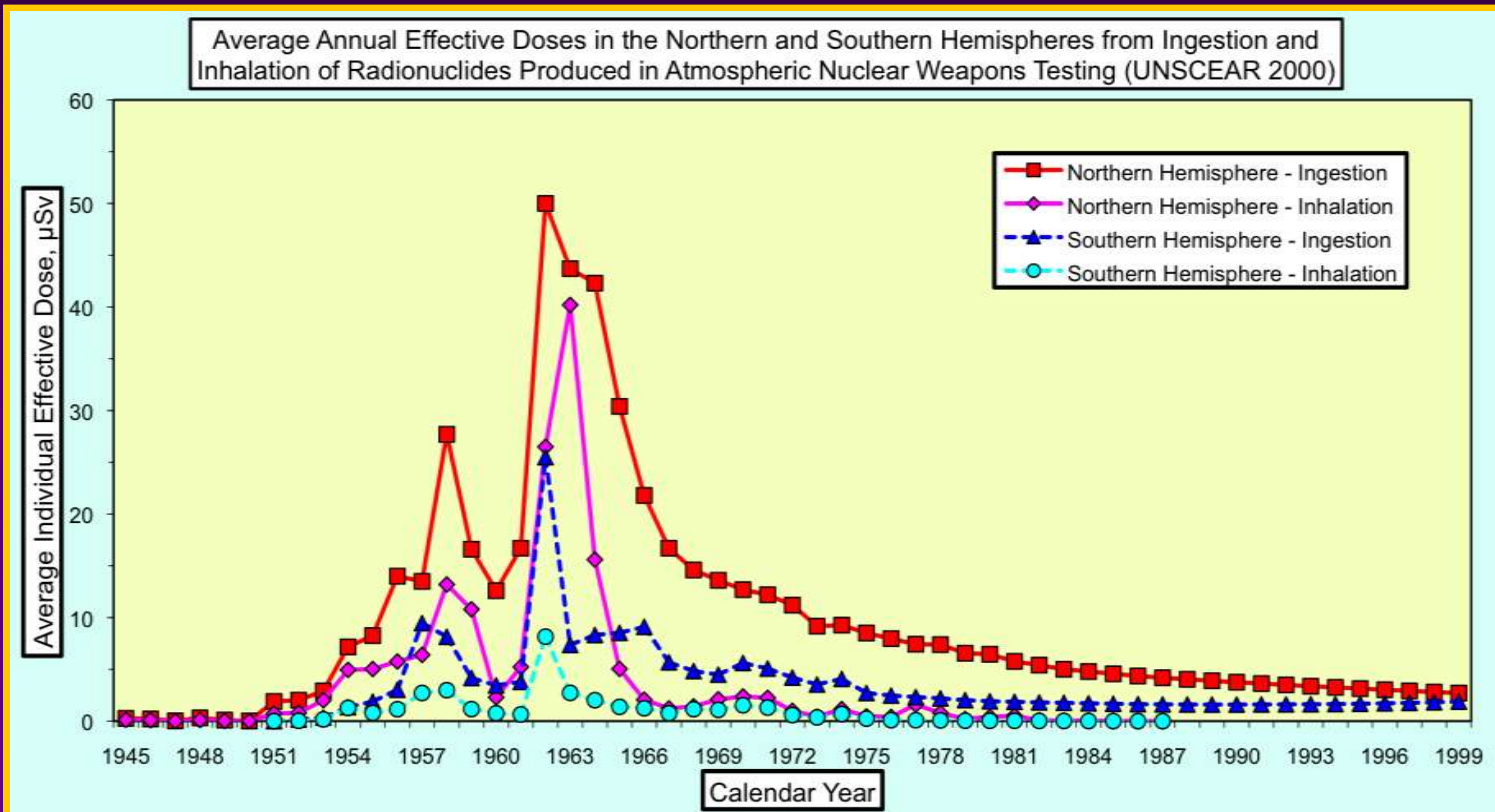


MANCHESTER 1824

The University of Manchester Centre for Occupational and Environmental Health

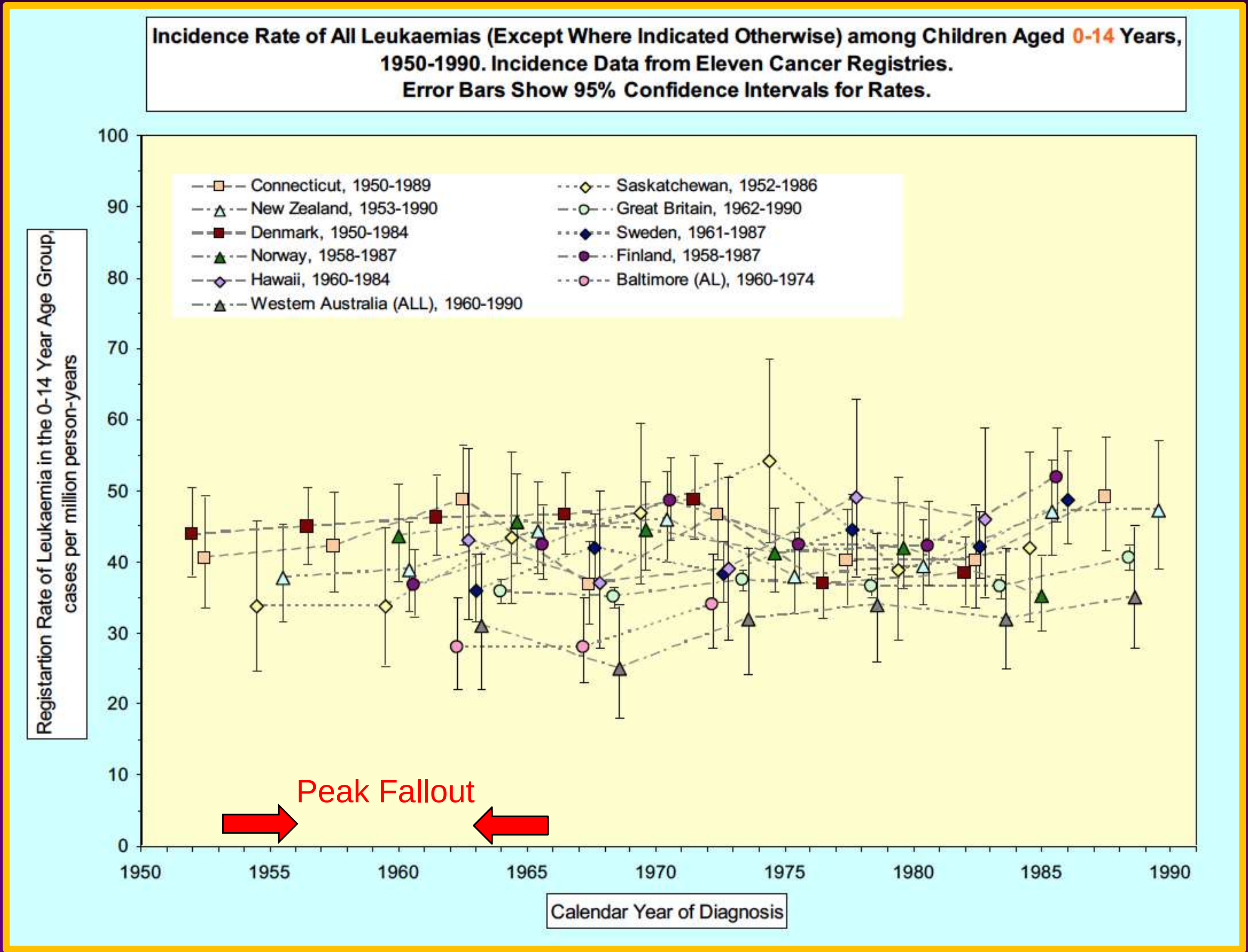
Weapons Testing Fallout

(UNSCEAR 2000 Report, Volume I, Annex C)



Childhood Leukaemia Incidence

(Wakeford *et al. Radiat Environ Biophys* 2010; 49: 21-27)



Fin

Richard.Wakeford@manchester.ac.uk

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