THE UNIVERSITY OF MELBOURNE

MELBOURNE SCHOOL OF POPULATION HEALTH

Cancer risks following low-dose radiation from CT scans in childhood

New insights into effects of age at exposure and attained age

John Mathews

CSRP 2016

Acknowledgments

Particular thanks are due to the 15 co-authors of our BMJ publication.

Data access and linkage was facilitated by

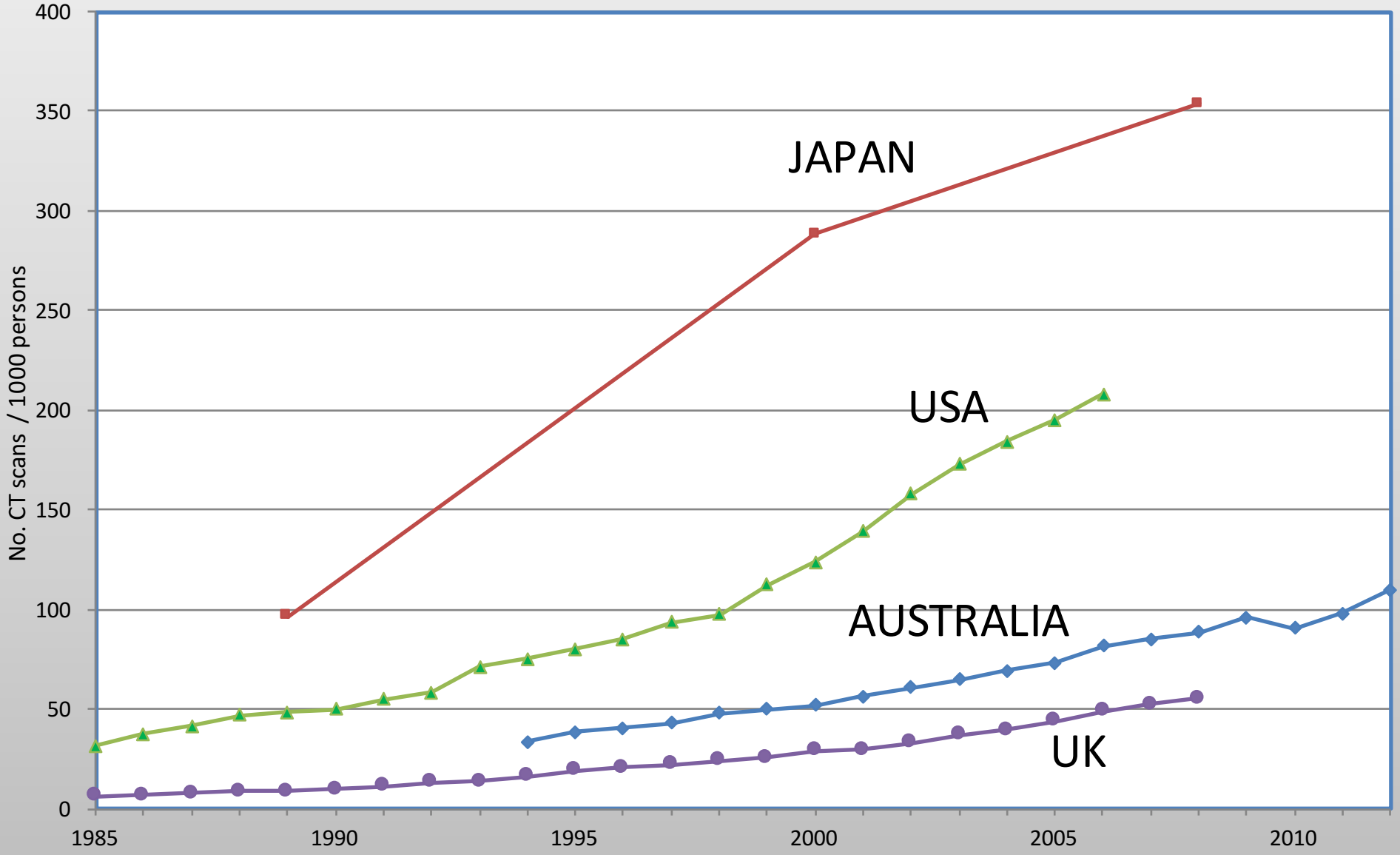
- Health & Ageing, Medicare Australia
- Australian Institute of Health and Welfare
- State and Territory governments and cancer registrars

This report includes valuable contributions from Darren Wraith (now at the Queensland University of Technology), Marissa Bartlett (Queensland Health), Anna Forsythe, and Zoe Brady

Themes for the talk

1. CT (computed tomography) X-ray scans are important in medical diagnosis;
2. However, radiation doses from CT scans are typically greater than the annual dose of background radiation;
3. Cancer risks are increased following diagnostic CT scan radiation before the age of 20 years.
4. Is this due to bias from reverse causation?
5. Why are the risk estimates for low-dose radiation from CT scans greater than those estimated in the LSS of atomic survivors?
6. What does this mean for low dose radiation effects from environmental contamination, as at Fukushima?

Per capita CT usage varies by Country



Context and significance of CT exposed cohorts

- Theoretical papers by Brenner and others from 2000 predicted an increased risk following childhood CT based on results from the Life Span Study (LSS) of atomic survivors.
- Pearce et al (2012) used UK data to show an actual increase in brain cancer & leukaemia following childhood CT
- Our Australian study (Mathews et al, 2013) showed actual increases in brain cancer, leukaemia, and other solid cancers. Our study had:
  - About 4 times the exposure of the UK study
  - About 4-5 times as much low dose exposure as LSS
- **Longer follow-up of medically-exposed cohorts will soon answer the "low-dose" radiation question.**

Cancer after CT scans - Study design

Exposure

Records of CT scans funded by Medicare for all persons aged 0-19 years in 1985-2005

Outcome

First diagnoses of cancer more than 12 months after CT exposure

Data linkage in high security unit of the Australian Institute of Health & Welfare

Analysis of de-identified data at the University of Melbourne

A large study

CT exposed

680,211

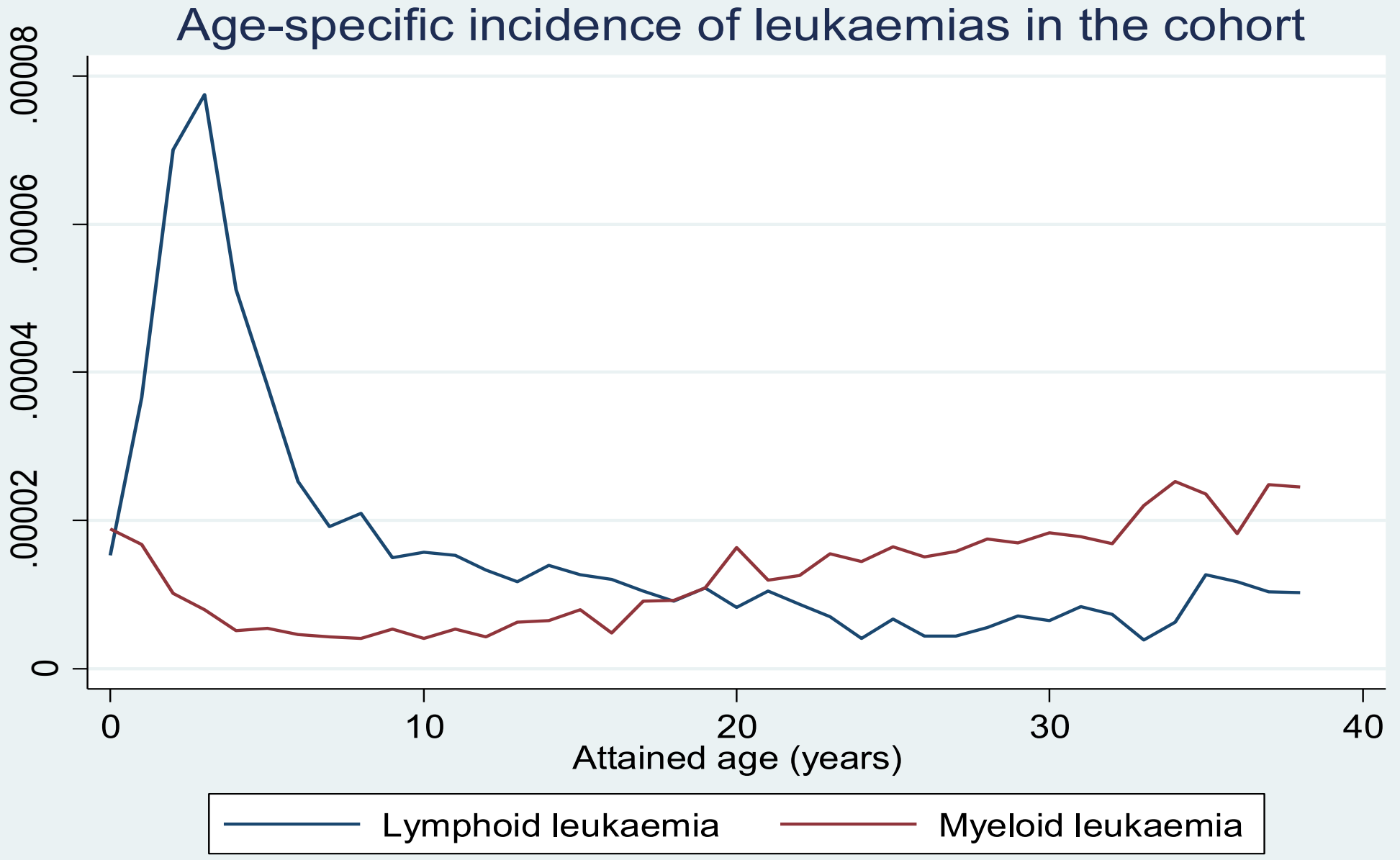
- Exposure more than 12 months prior to any cancer diagnosis
- When aged 0-19 years
- In period 1985-2005
- Follow-up to 31/12/2007

Non-exposed

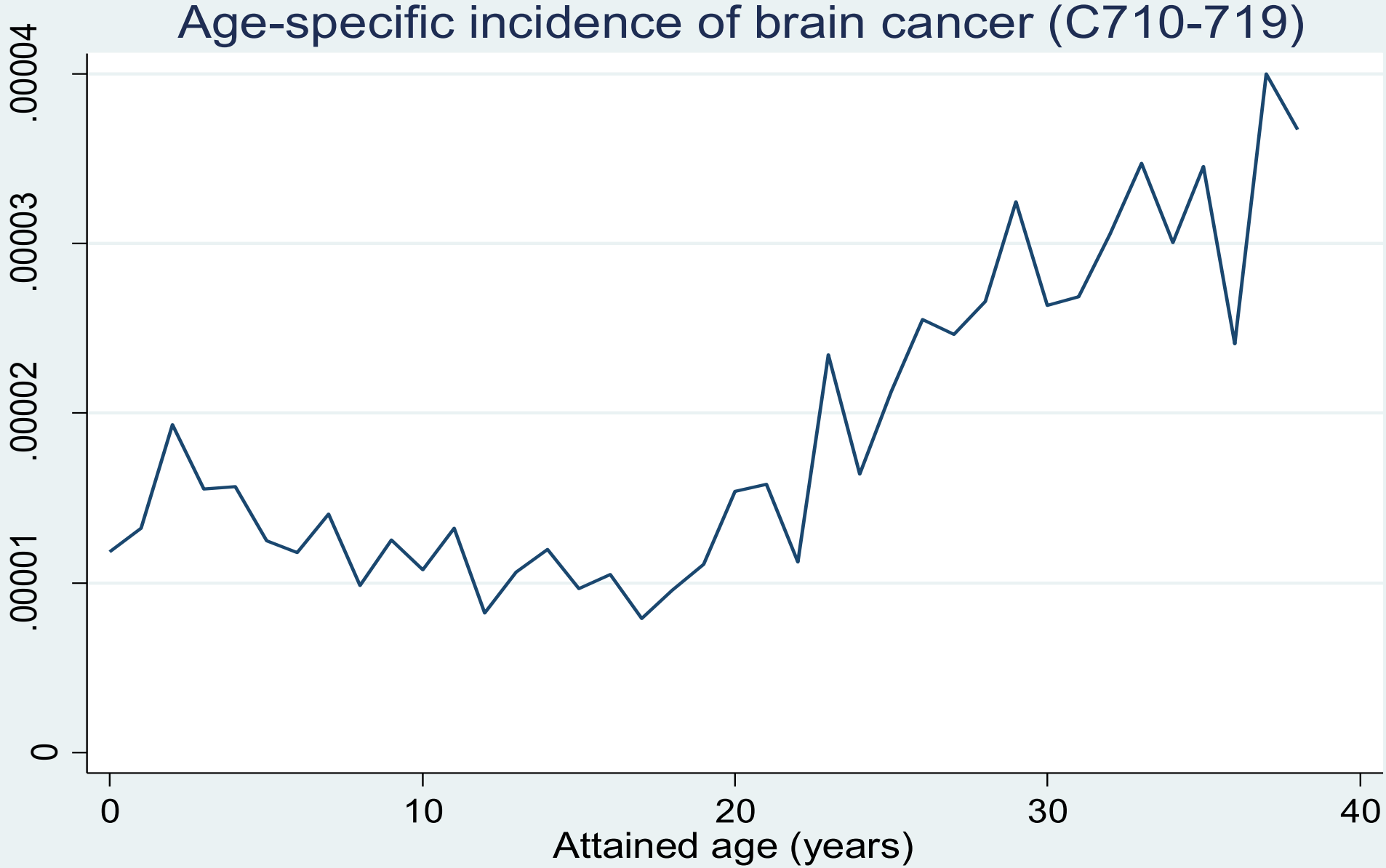
10,259,469

- No Medicare record of any CT scan
- When aged 0-19 years
- In period 1985-2005
- Follow-up to 31/12/2007

Leukaemias in our cohort



Brain cancer in our cohort



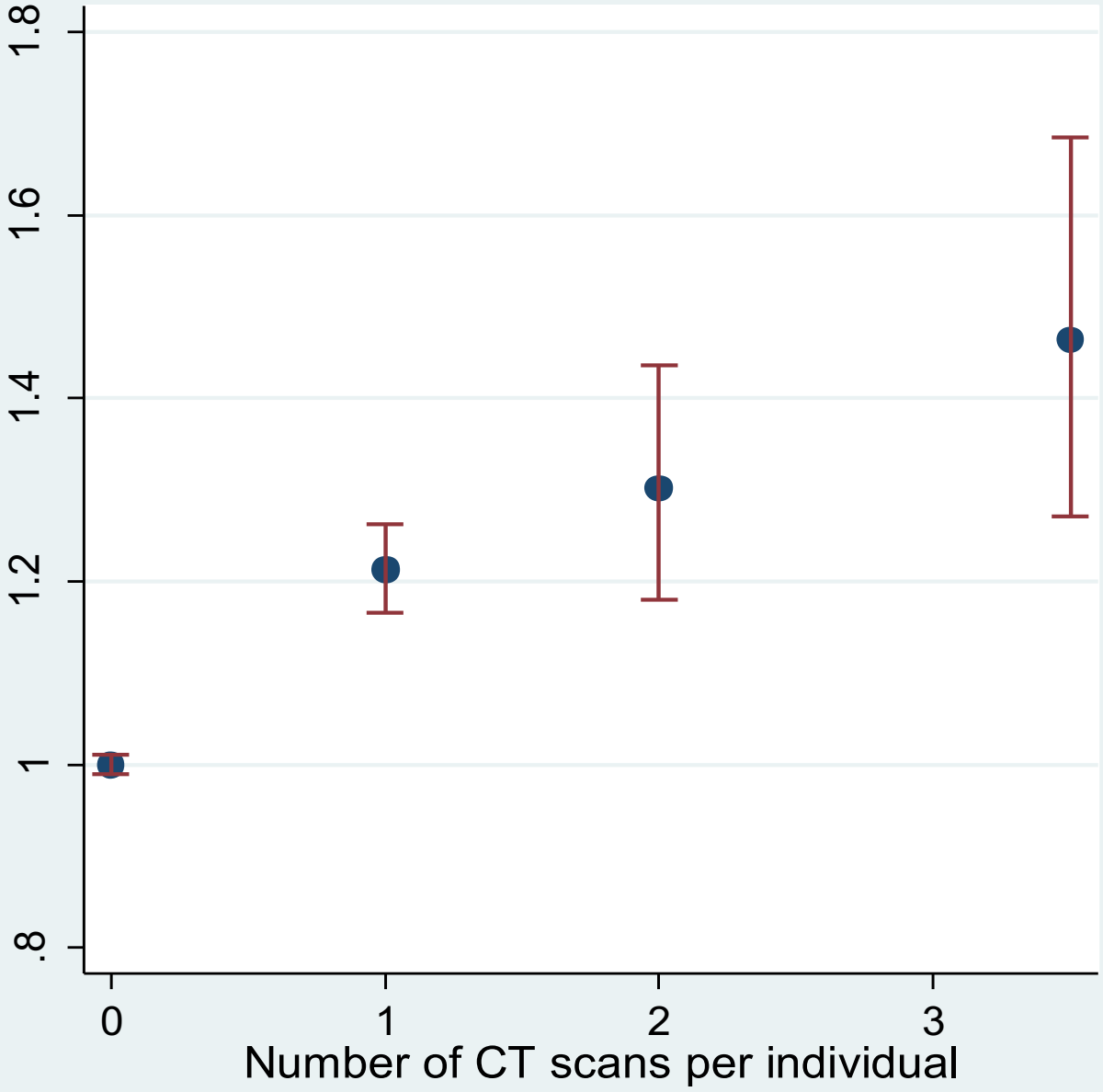
Cohort follow-up details

Characteristic (at one year lag)	Exposed persons	Unexposed persons
Number of person years of follow-up	6 486 548	177 191 342
Mean length of follow-up (years)	9.5	17.3
Number of cancers	3150	57 524

So what did we find?

	1 year lag	5 year lag	10 year lag
Observed cancers in exposed	3,150	2,365	1,405
Expected cancers in exposed	2,542	1,963	1,196
Incidence rate ratio (IRR) & 95 % CI	**1.24 (1.20,1.29)**	**1.21 (1.16,1.26)**	**1.18 (1.11,1.24)**

Cancer risk by number of CT scans (All cancers & all exposures)



The incidence rate ratio increased by 0.16 (95% CI 0.13 to 0.19) for each additional CT scan, calculated after stratification for age, sex, and year of birth

(χ^2 for trend: 131.4 , p<0.0001).

If unexposed persons are excluded the trend remains significant

(χ^2 for trend: 5.79, p = 0.02).

Different measures of CT risk

Measure	Average risk	More extreme risk
Excess relative risk	16% increase per CT	200% per CT after exposure at an early age
Absolute increase	1 extra cancer per 2000 scans	Will continue to increase over time
Attributable risk for a person with cancer after exposure	14 % per CT	67% for a person with brain cancer after exposure at a young age

Understanding Attributable Risk

An example

If a child is exposed to a CT head scan before the age of 5 years, then in the years that follow, the average rate of brain cancer is 3 times as great as for "unexposed".

We are interested in the **attributable risk -** probability that the cancer was caused by exposure. This is calculated as:

A.R. = Excess rate in exposed/Overall rate in exposed

= (3-1)/3 = 2/3 = 67%

Cancers after head CT – 5 year lag

Type of cancer	No. exposed cancers	Incidence rate ratio (IRR)	IRR 95% confidence interval
Brain cancer	123	2.03	(1.69-2.43)
Soft tissue	46	1.55	(1.15-2.08)
Thyroid	130	1.36	(1.14-1.62)
Leukaemia	100	1.25	(1.02-1.53)
Other solid	536	1.12	(1.03-1.22)
All cancers	**1532**	**1.21**	**(1.15-1.27)**

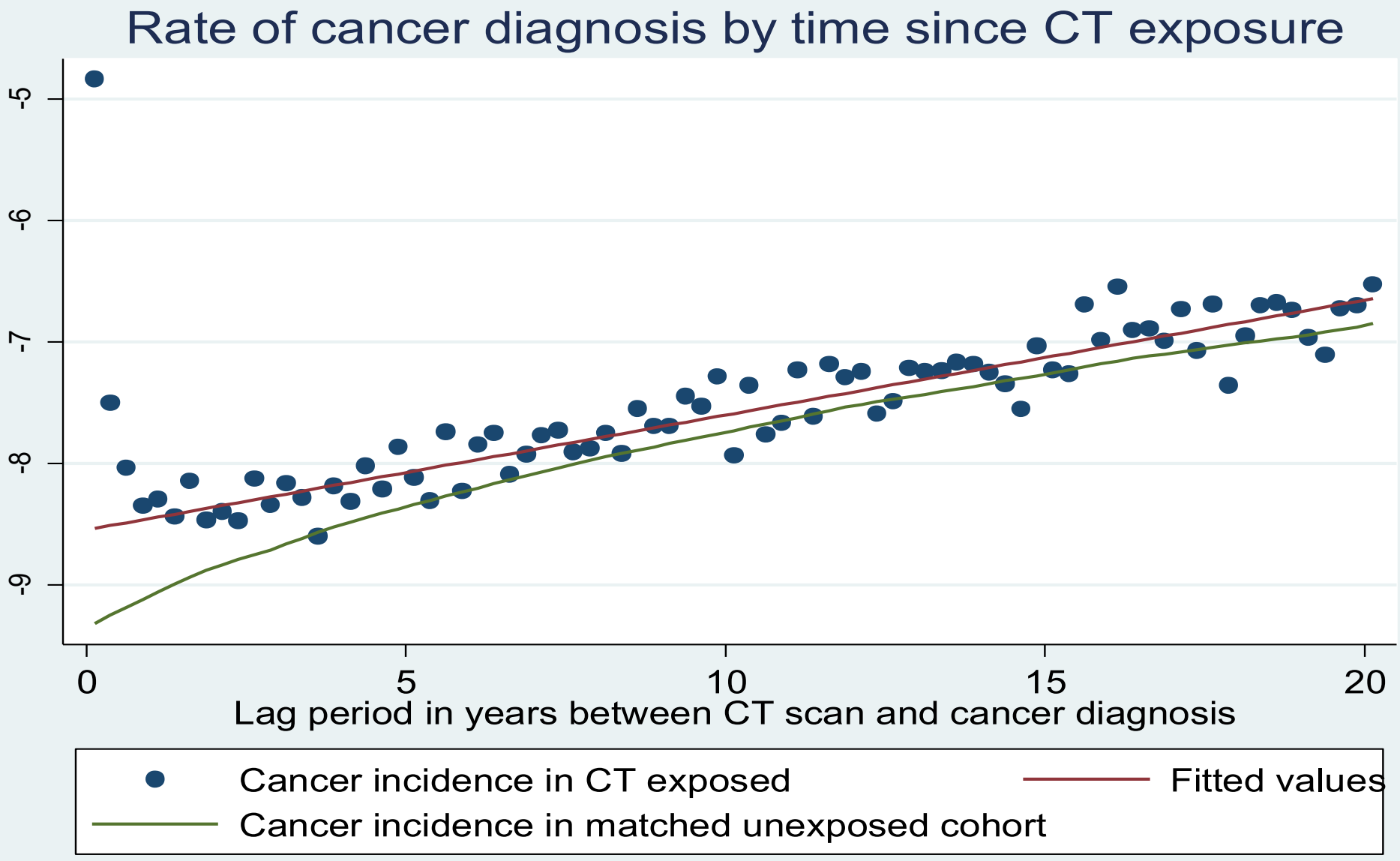
What about "reverse causation"?

Cancers at the shortest lag periods following CT scans are almost certainly due to **"reverse causation"**, as when symptoms of cancer or a pre-cancerous condition prompt the CT scan.

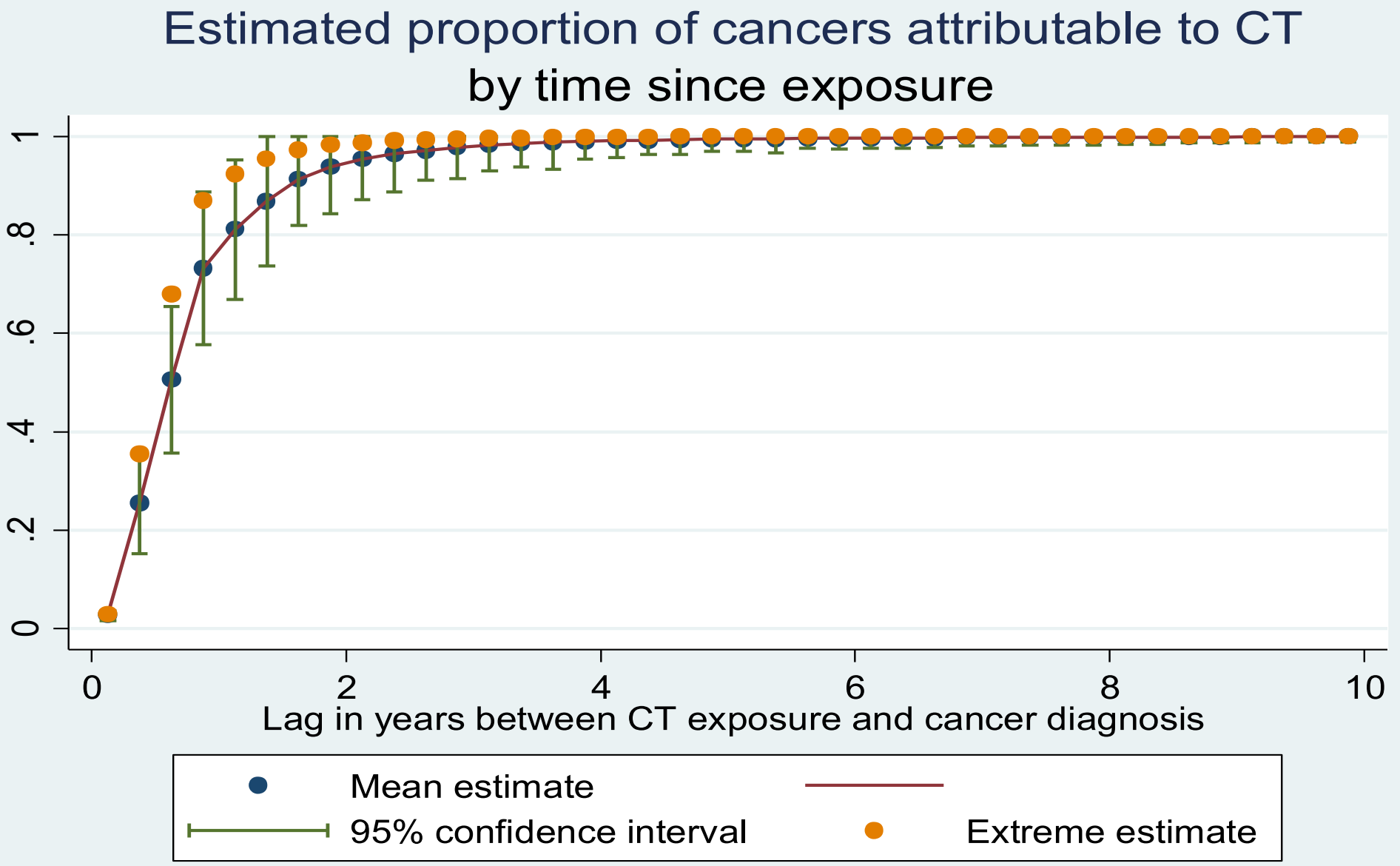
It was for this reason that in our BMJ paper we chose to exclude cancers occurring at a lag of less than 12 months after exposure.

Can we be more precise about cancers due to reverse causation at different lag periods?

What about reverse causation?



Reverse causation is over by 2 yrs



Comparing Risk Estimates

Exposure details	Typical dose (mSv)	Excess relative risk per Sv		Reference
		Leukemia	Solid cancers	
Prenatal X-rays	10	49 (33-67)	45 (30-62)	Doll & Wakeford (29)
Childhood exposures (0-19 years)				
Life Span Study	100-250	45 (16-188)	3 (2-6)	Table 9 in Mathews et al. (8)
CT (UK study)	6	36 (5-120)	-	Pearce et al. (9)
CT (Australia)	6	39 (14-70)	27 (17-37)	Mathews et al. (8)
Background	5-10	70 (10-130)	-	Kendall(30)
Adult exposures				
Life Span Study	100-250	3.2 (1.9-4.6)	0.6 (0.5-0.7)	BEIR VII (2)
Radiation workers	15	3 (1.2-5.2)		Leuraud et al. (31)
	19		0.97 (0.3-1.8) 0.58 (-0.1-1.4)*	Cardis et al. (32)

How do we explain the increased risk of solid cancers after CT?

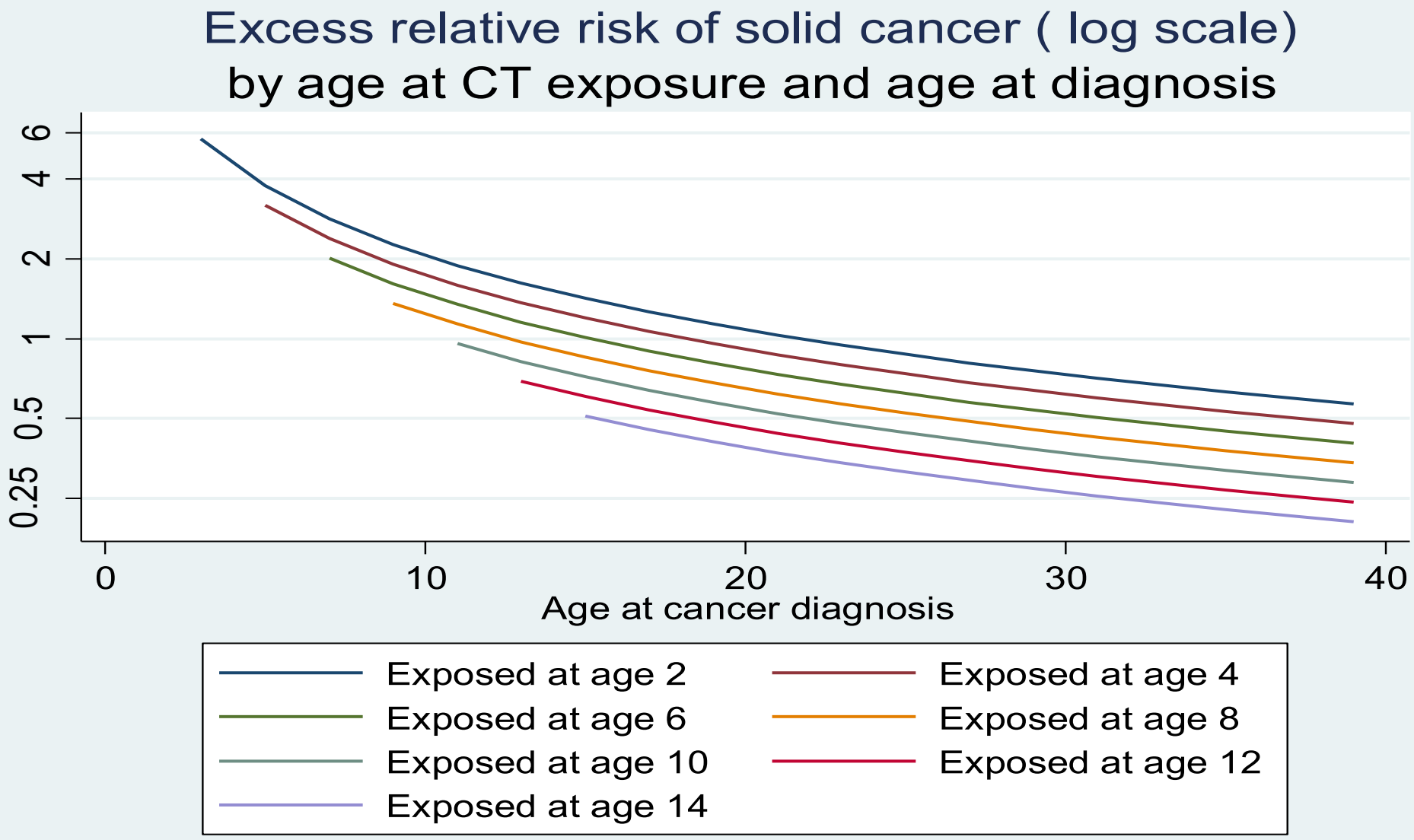
Is it due to:

1. Reverse causation

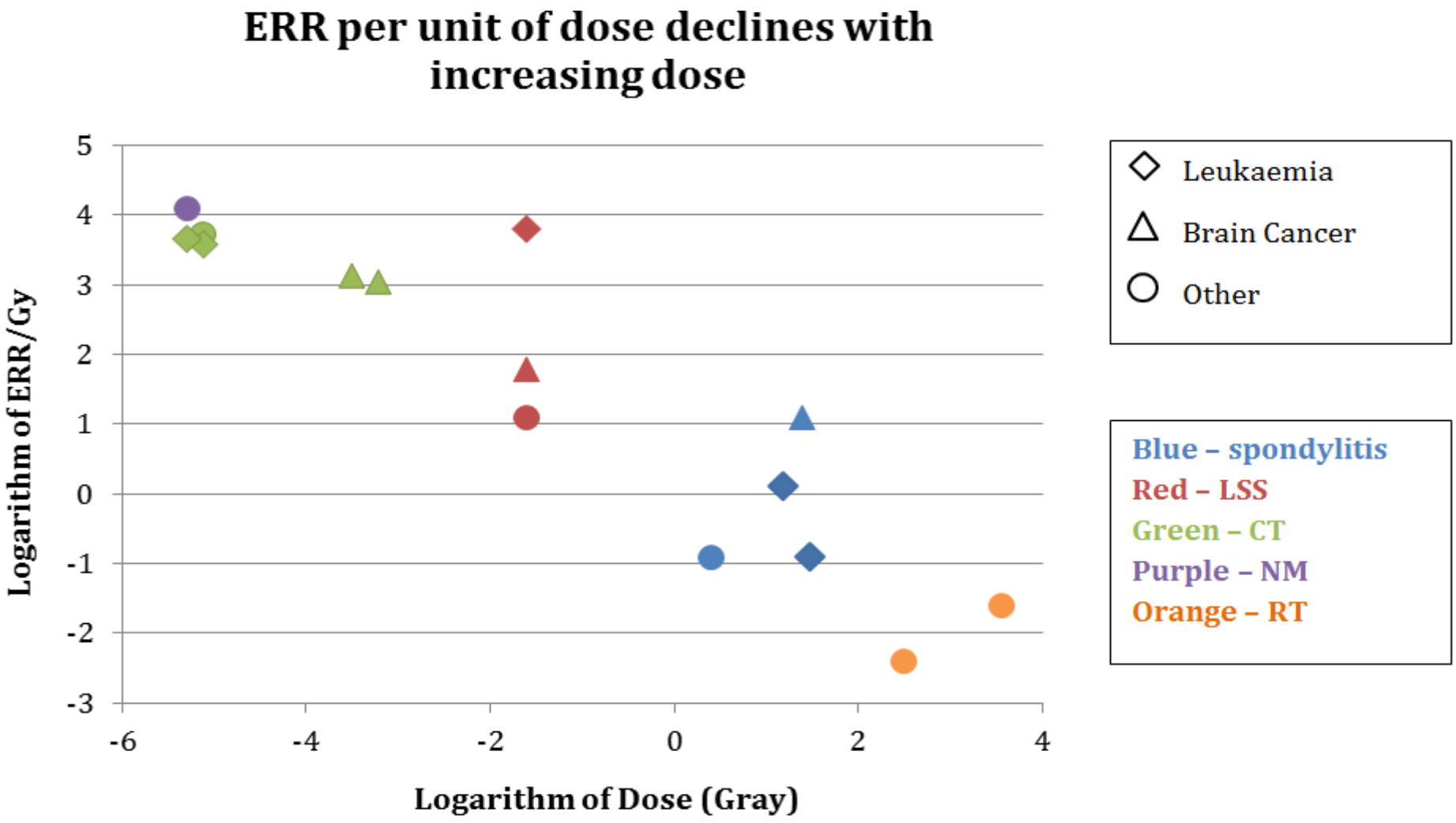
2. A greater causal effect in the early years after exposures at young ages

3. A greater effect, per unit of dose, at low doses (i.e. a non-linear dose response)

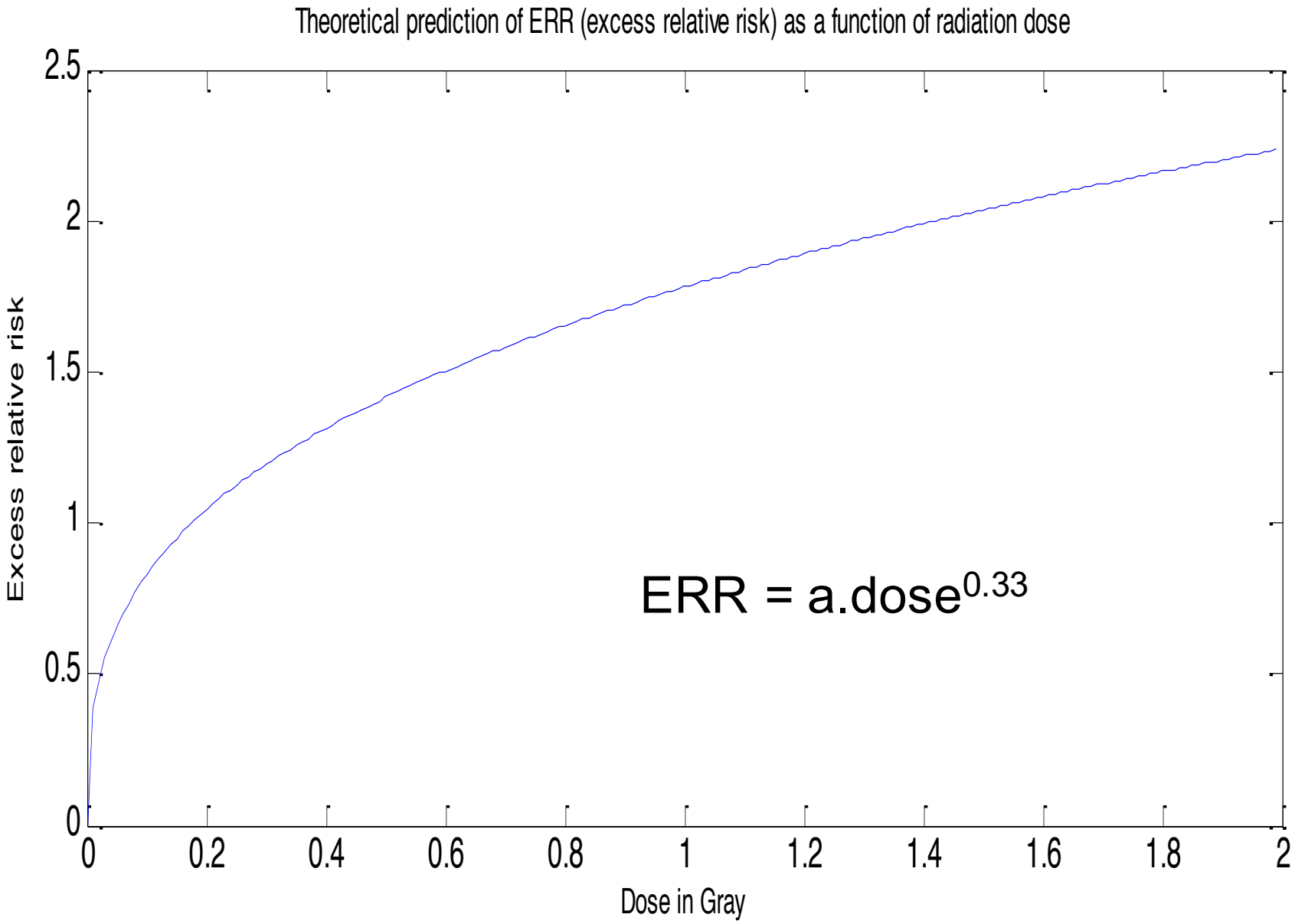
Risk is much greater in early years after exposure at young ages



ERR/Gy is less at higher doses



Dose response may be non-linear



SUMMARY 1

- There are no compelling reasons to doubt the findings from the Australian CT study.
- The Australian CT cohort was exposed to more low dose radiation (<100 mGy) than the LSS.
- The excess cancers at more than 12-24 months after CT are mostly caused by CT-scan radiation
- Risks of leukaemia following CT scan radiation are consistent with risks from LSS of atomic survivors.
- Excess risks of solid cancers per unit of dose are greater after CT scans than in LSS survivors presumably because of lower doses, and because early cancers were missed in the LSS.

SUMMARY 2

- Excess cancers in the early years after radiation exposure at young ages probably occur in susceptible persons
- Susceptibility is likely due to inherited or somatically mutated cancer genes
- The dose response curve for radiation is steeper at lower doses and at short lags because of:
  - Genetic susceptibility and stochastic selection
  - Homeostatic mechanisms such as the bystander response
  - Cell killing at higher doses
- Important implications for radiation protection!