Modelling cancer risks from low-dose radiation: What risk from diagnostic CT scans?

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Background

- By the 1970s, radiation doses from diagnostic X-Rays had been reduced from historical levels to minimise cancer risks.
- However, radiation doses per patient tended to increase again following the widespread use of CT scans from the 1980s.
- Nevertheless, it was thought that any cancer risks from diagnostic radiation would be so small as to be undetectable.
- Our 2013 BMJ paper, based on national data linkage, showed a 24% increase in cancer incidence in young Australians exposed to CT scans.
- The causal interpretation was questioned because of the possibility of reverse causation, whereby suspicion of cancer triggers a diagnostic CT, establishing an artefactual association between exposure and cancer.
- Here we summarise recent work suggesting that diagnostic radiation does cause a real increase in cancer risk.

Understanding the Hazard Ratio (HR)

Cox regression estimates the ratio of cancer incidence in the exposed to the incidence in unexposed subjects matched for age and sex etc.

Hazard Ratio = Cancers per person year of follow-up in exposed /

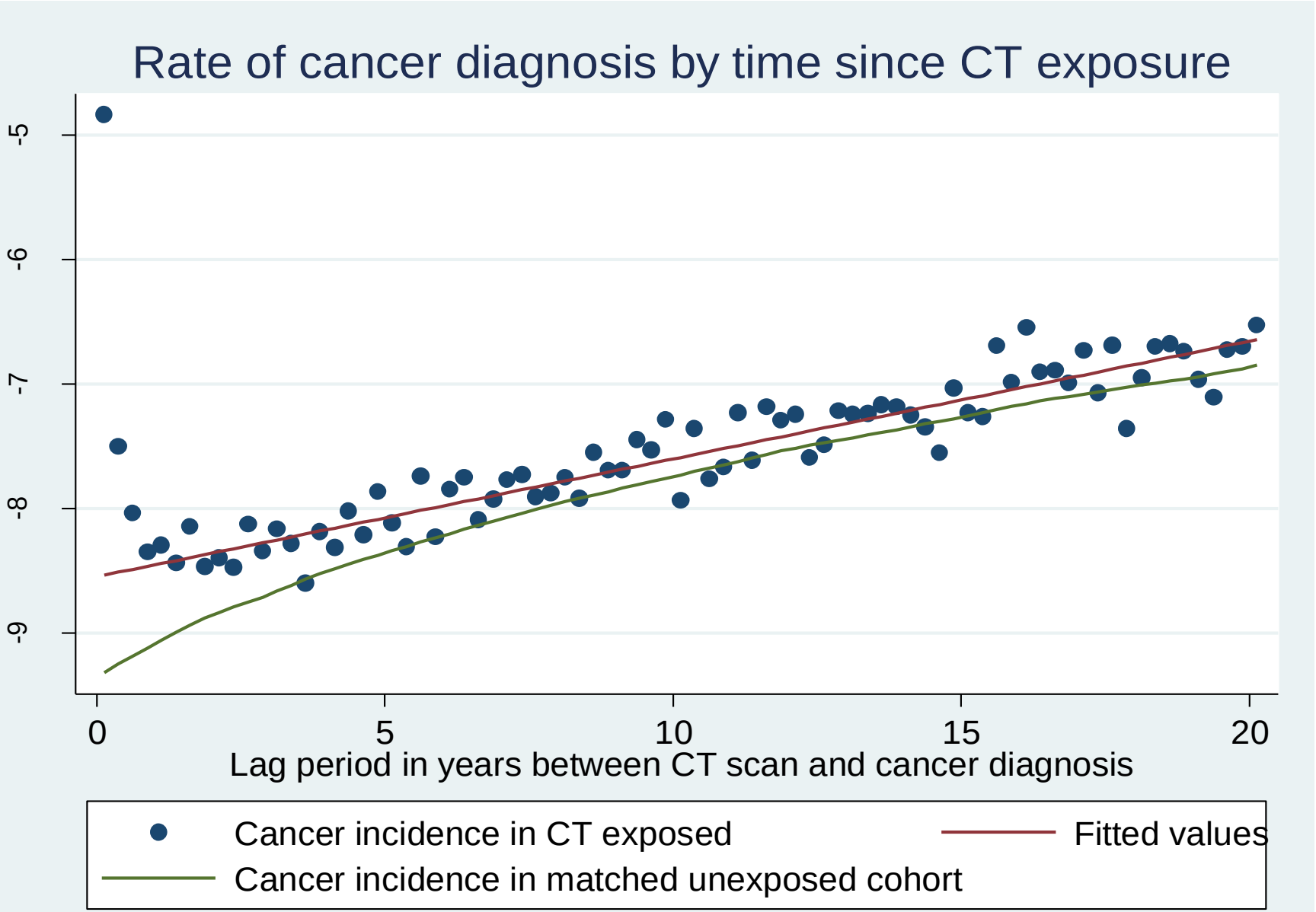
Cancers per person year of follow-up in unexposed

So if there is an excess of cancer in the exposed, the Hazard Ratio will be greater than 1.

This means either that the exposure is causing more cancers, or that there is an artefactual increase due to reverse causation bias.

Study Design and Analysis

- We showed that exclusion of CT exposures less than two years prior to cancer diagnosis would exclude almost all cases of reverse causation (Smoll et al 2020). We lagged later exposures by two years to allow for cancer latency.
- With expert colleagues (Brady et al, 2020) we estimated radiation doses to over 30 different target organs from more than 1.3 million CT scans.
- To assess the magnitude of cancer risks and biases arising from reverse causation and confounding, we have modelled excess risks by radiation dose to target organs.
- For example, using Cox and Poisson regression we showed that for brain cancers occurring at more than two years after a brain scan, the Hazard Ratio (Incidence Rate Ratio) increased with radiation dose by up to 0.8 per 100 mGy (95% CI 0.6-1.0) to the brain.
- For brain cancers with a history of CT exposure at lags of more than two years, we estimated that 40% (95% CI 29-50) are actually attributable to (caused by) CT scan radiation (Smoll et al 2023).
- Organ dose of radiation is the best predictor of excess cancers in the relevant target organ.



Dealing with Reverse Causation

This figure shows the rate of cancer diagnosis by time since CT exposure. The early cancers, due to reverse causation, are confined to the first two years after exposure. The green line shows the expected incidence in those unexposed to CT scans, but otherwise matched with the exposed cohort.

These data justify the exclusion of exposures at latencies of less than two years and lagging of exposures by two years.

We also used finite mixture modelling to show that a two-year exclusion would remove all cases of reverse causation.

Overview

The Australian Paediatric exposure to Radiation Cohort Study (Aust-PERC)

Data linkage

- Aged 0-19 years during 1985 to 2005
- Was followed up to Dec 31 2012
- Medicare + ACD + NDI
- 32 specific organ doses & effective dose

Analysis methods

- Cox regression model
- Used attained age as the time scale
- With stratification by sex, SES and year of birth
- 2-year lag period

	The exposed	The unexposed	The whole cohort
No. of people (%)	612,349 (5.25)	11,056,175	**11,521,718**
No. of solid cancer diagnosis	3,958	77,697	81,655
Total person-years (pyrs)	8,272,220	247,076,912	255,362,880
Ave. follow-up years	13.51	22.35	22.16

Risks for specific solid cancers

Fig. HR of exposed vs. unexposed.

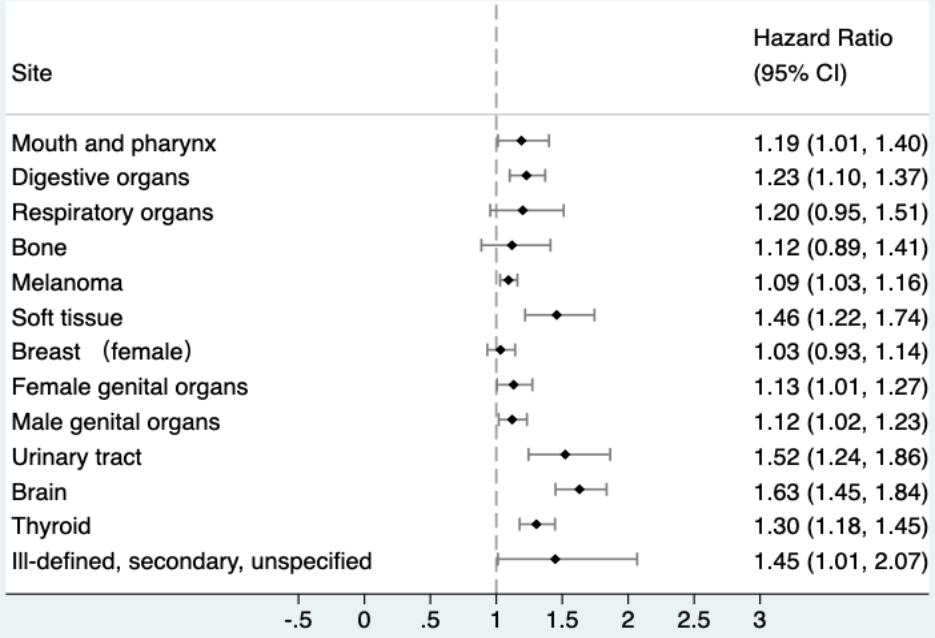
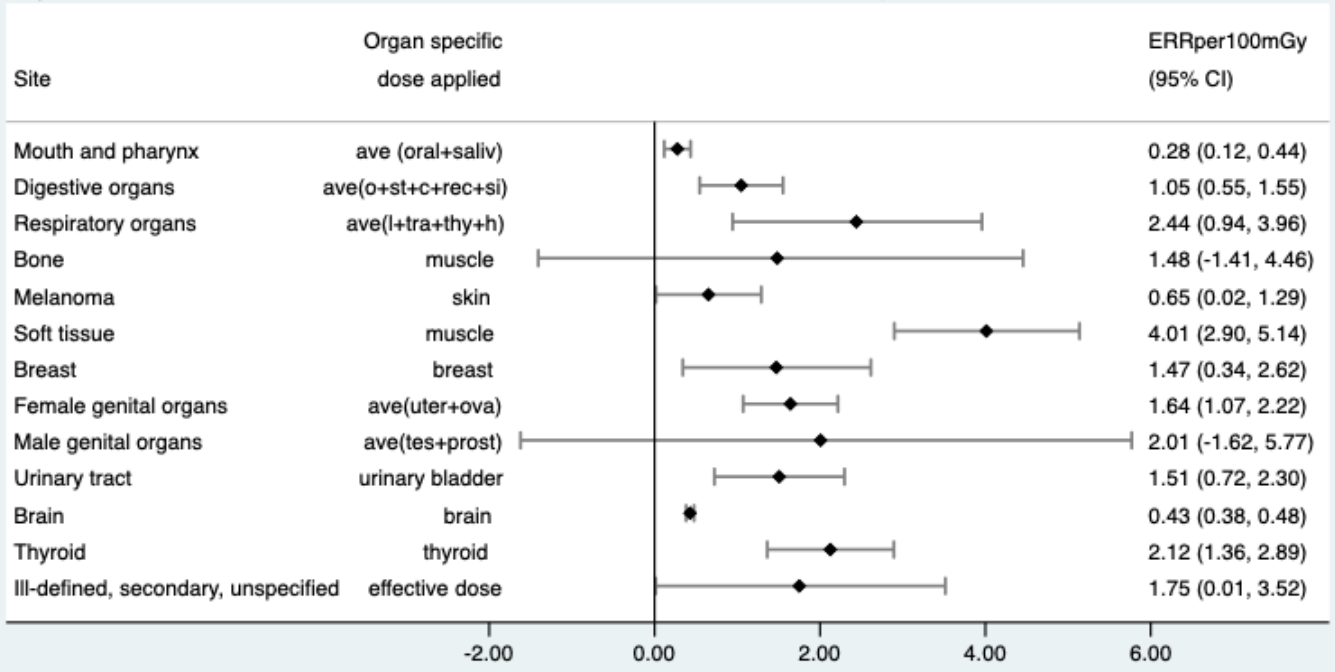


Fig. Linear dose response measured as ERR per 100 mGy, for the whole cohort.



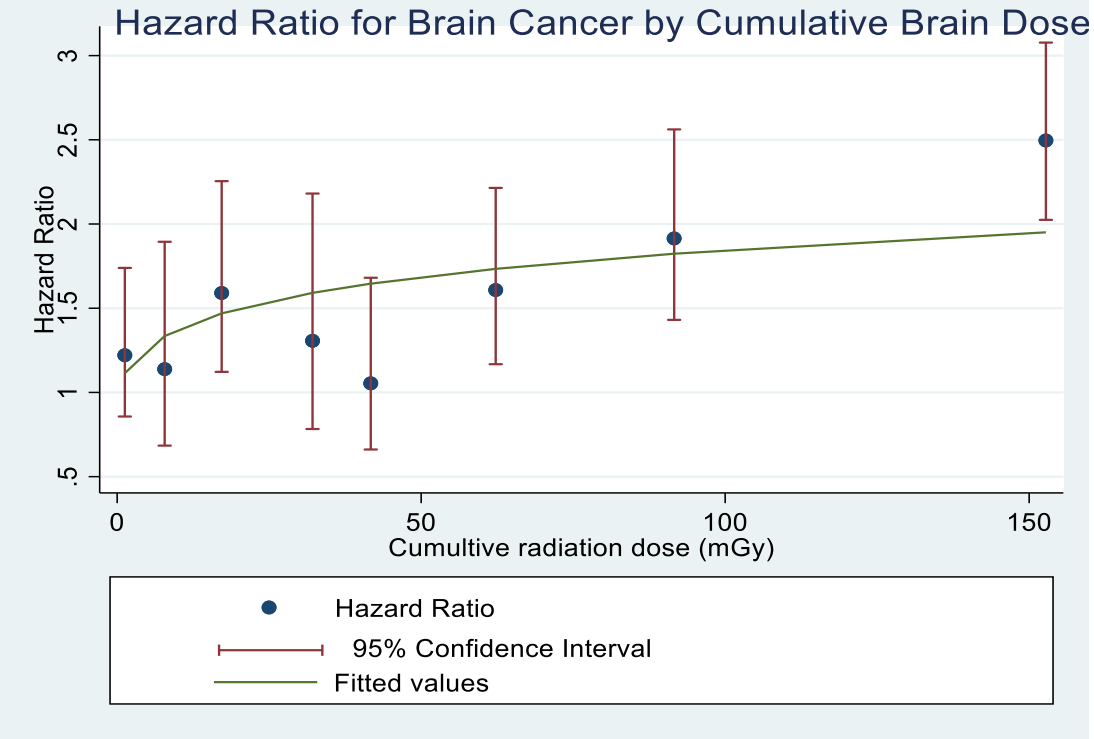
	Model 1 EP	Model 2 DOSE	Model 3 EP + DOSE	Model 4 DOSE
Brain Cancer	For the whole cohort			For the exposed cohort only
EP (Binary)	1.63 (1.43, 1.84)		1.28 (1.13, 1.46)	
DOSE (Linear)		1.0043 (1.0038, 1.0048)	1.0038 (1.003, 1.005)	1.0042 (1.0036, 1.0048)

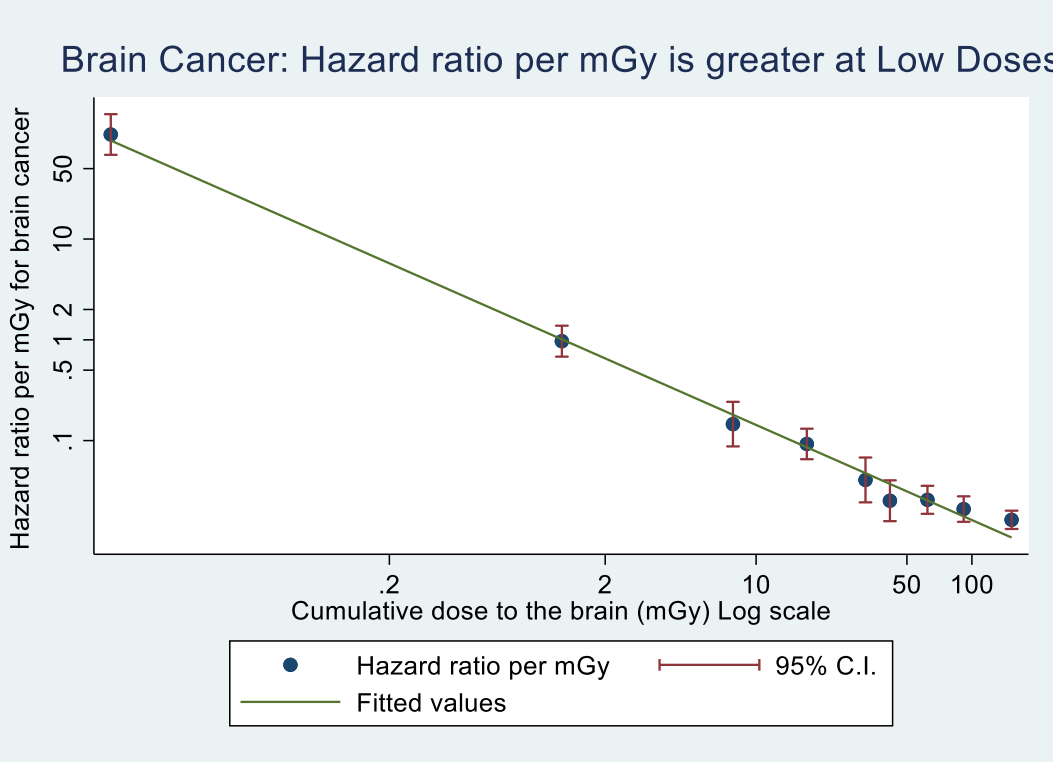
Non-Linear Dose Responses at Low Radiation Doses

MODEL		d.f.	Chisq	P-value	k	HR (A) per 100 mGy
Brain cancer						
Linear Dose	HR = A.DOSE	1	86.5	<<0.00001	1	1.47 (1.45-1.50)
Transformed dose	HR = A.DOSE^k	1	21.7	0.00001	0.75	*
Leukemia						
Linear Dose	HR = A.DOSE	1	15.7	0.0001	1	1.38 (1 .34-1.43)
Transformed dose	HR = A.DOSE^k	1	8.3	0.001	0.25	*

After exclusions for reverse causation and lagging of exposures by two years to allow for cancer latency, we used Cox regression to estimate the Hazard Ratio (HR) for cancer excess as a function of cumulative radiation doses to brain and active marrow doses for brain cancer and leukemia respectively. There were highly significant linear trends for cancer risks to increase with dose. However, for both brain cancer and leukemia, model fit was greatly improved by a power transformation of the dose (DOSE^k). In each case, the profile log likelihood was maximised for k less than 1, indicating that cancer risk per unit of dose was greater as low doses.

Dose responses at low radiation doses: We also categorised brain doses into nine quantiles, and calculated Hazard Ratios for brain cancer by dose category. The figure on left shows that the HR tends to increase with brain dose, while the figure on the right, based on the same data, confirms that the HR per unit of dose tends to increase at lower doses.



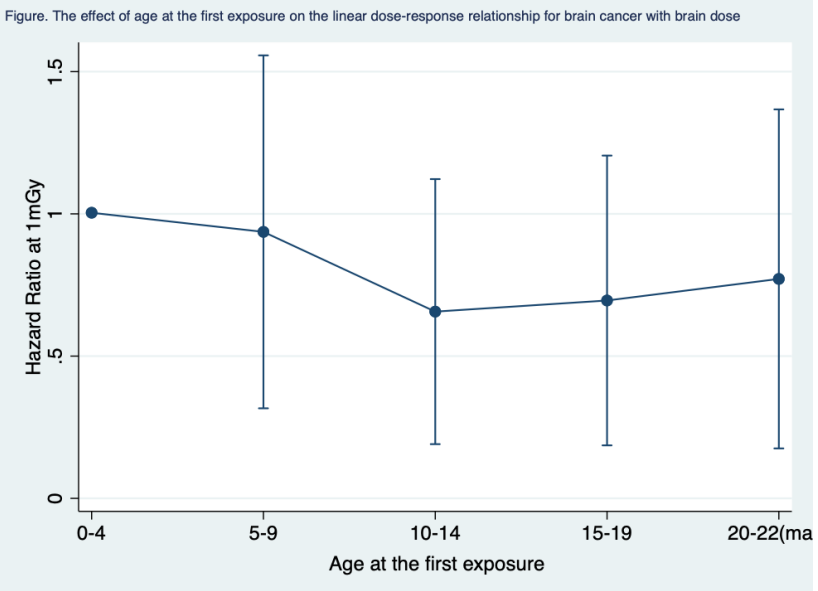


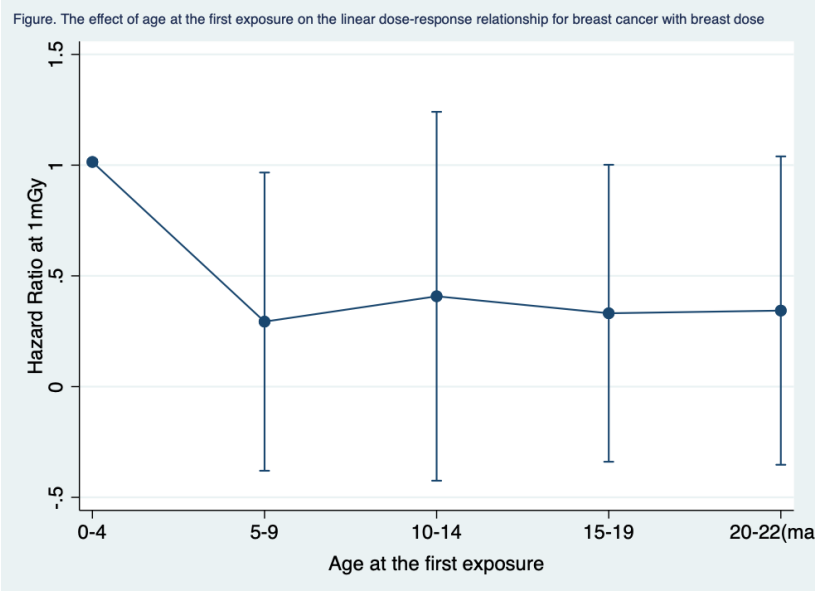
Mean hazard ratio per mGy = 1.00385 (1.0034-1.0043) by Cox regression

The HR per mGy was 0.021 at a dose of 90 mGy, but much larger (0.97) at a mean dose of 1 mGy. Some of this effect may arise from errors in dose estimation.

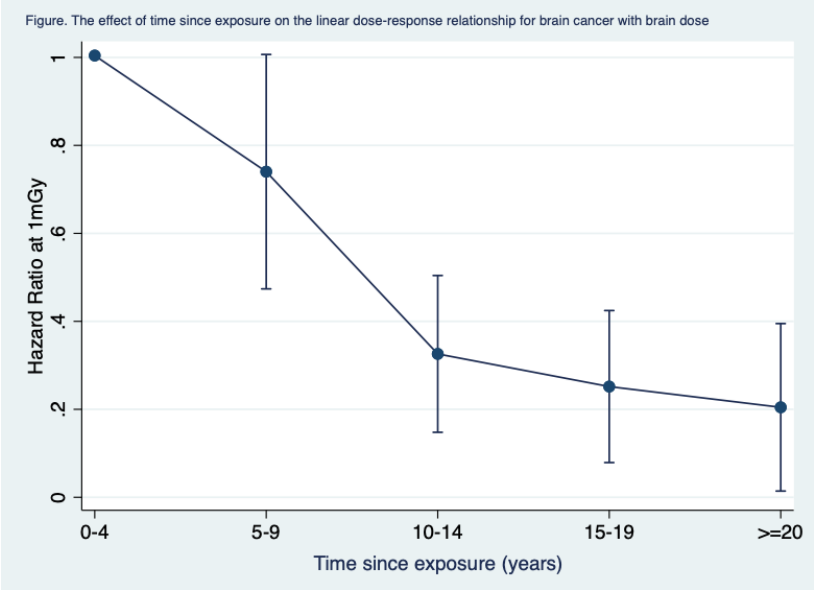
Effects of potential confounding factors

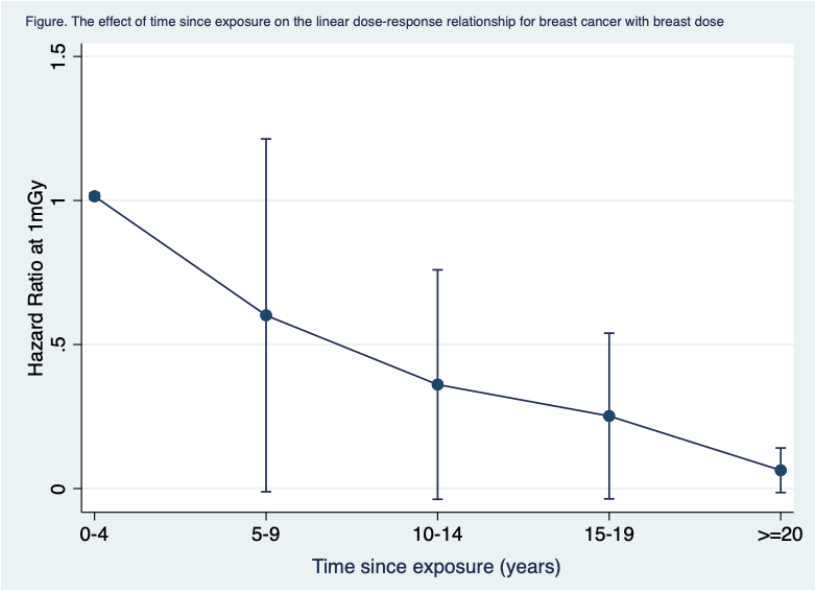
1. Age at the first exposure (Brain and breast cancer)



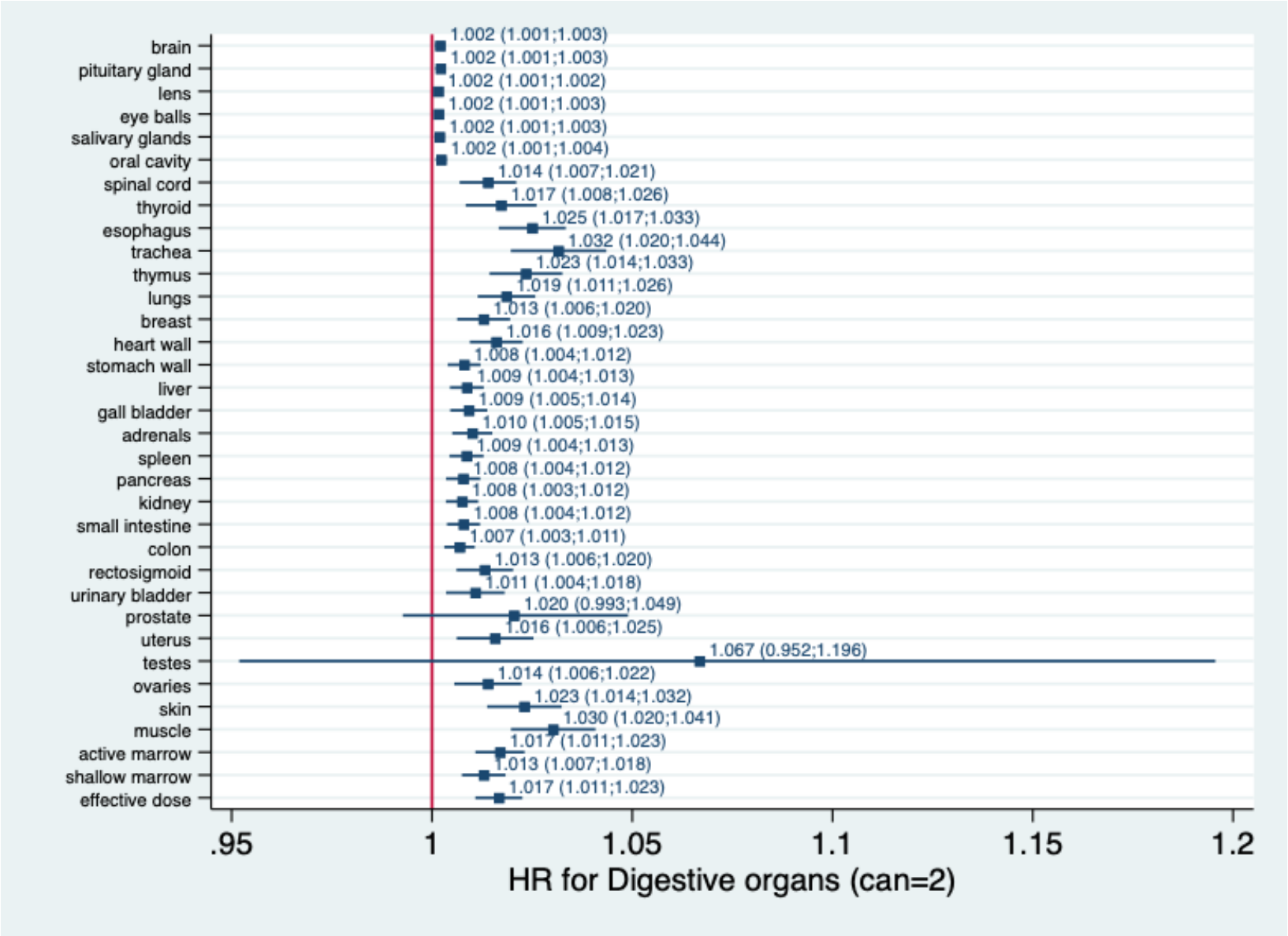


2. Time since first exposure (Brain and breast cancer)





Solid cancer risk by different estimated organ dose



Comparing dose response estimates

CANCER	Source of estimate	ERR per 100 mGy	HR-1 per 100 mGy
Leukemia	15 Country study	0.19	
	Inworks	0.30	
	Life Span Study	0.26	
	Other CT	3 (0.2-10)	
	Our Study		3.8 (3.3-4.3)
Solid Cancer	15 Country Study	0.087	
	Inworks	0.047	
	Life Span Study	0.025	
	Our Study		0.2-2
Brain cancer	Other CT	1.0 (0.4-2.5)	
	Our Study		0.43 (0.38-0.48)

Summary - 1

- Our cohort is the largest population-based study of diagnostic medical radiation exposures that has access to organ-specific radiation doses and cancer outcomes.
- Organ-specific radiation doses were estimated from de-identified Medicare records of diagnostic scans. Outcomes were assessed by linkage to national cancer records. Exposures at lags of less than two years were attributed to reverse causation and excluded.
- The risks of site-specific solid cancers and leukemias were increased following low dose radiation from CT scans.
- At lags of more than two years, cancer risks increased with radiation dose to the relevant target organ.
- Significantly, the Hazard Ratio per unit of dose was greater at low doses and greater than previously accepted estimates.
- Although effective dose has been designed to capture the overall detriment from radiation exposure, organ-specific doses are better able to capture cancer risks in specific target organs.

Summary – Looking Ahead

- Further work is needed to estimate the magnitude of any residual biases arising from reverse causation, potential confounders and measurement error.
- To explain radiation effects at low doses, we suggest that radiation can expedite the clinical onset of cancer in individuals with pre-existing mutations that predispose to cancer.
- In other words, external radiation can act as a promoter that shortens the latent period of cancer. This perspective avoids the implausible idea that low-dose radiation does not interact with other causes of cancer.
- In future, it may be useful to avoid the distinction between cancer initiation and cancer promotion, and to use “years of healthy life lost” as an overall measure of epidemiological outcome attributable to low-dose radiation.
- Our valuable cohort has already allowed us to model cancer risks to inform radiological practice and to help understand the biology of radiation effects at low doses. We are currently seeking new funding to extend cohort follow-up to 2022. This will document cancer risks at even longer latent periods after low dose radiation exposures.
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