NUCLEAR MEDICINE

Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study

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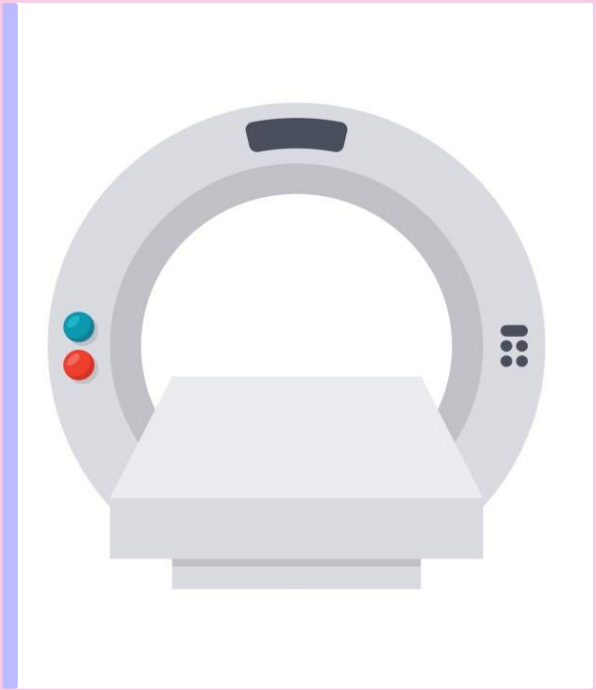

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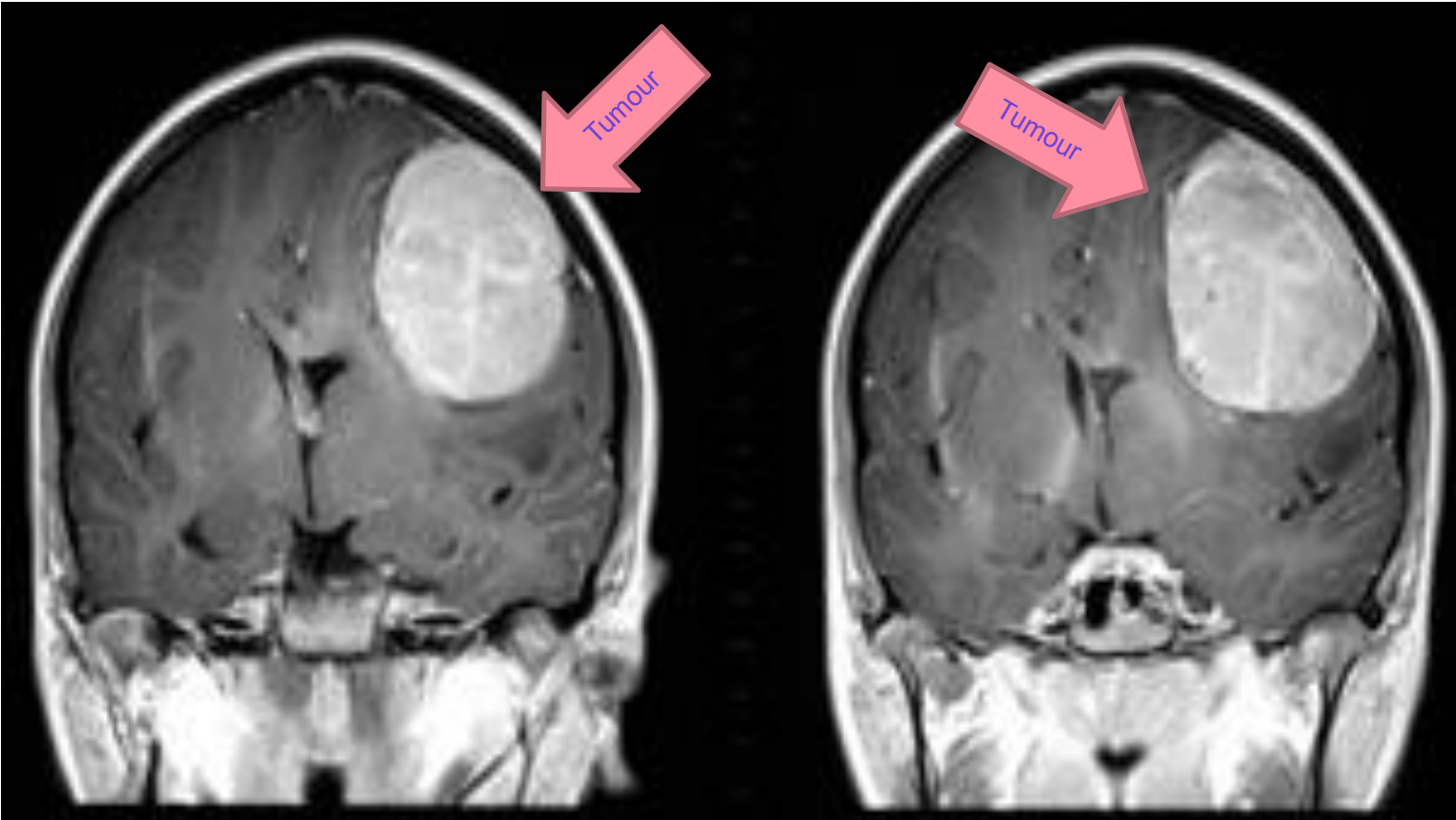
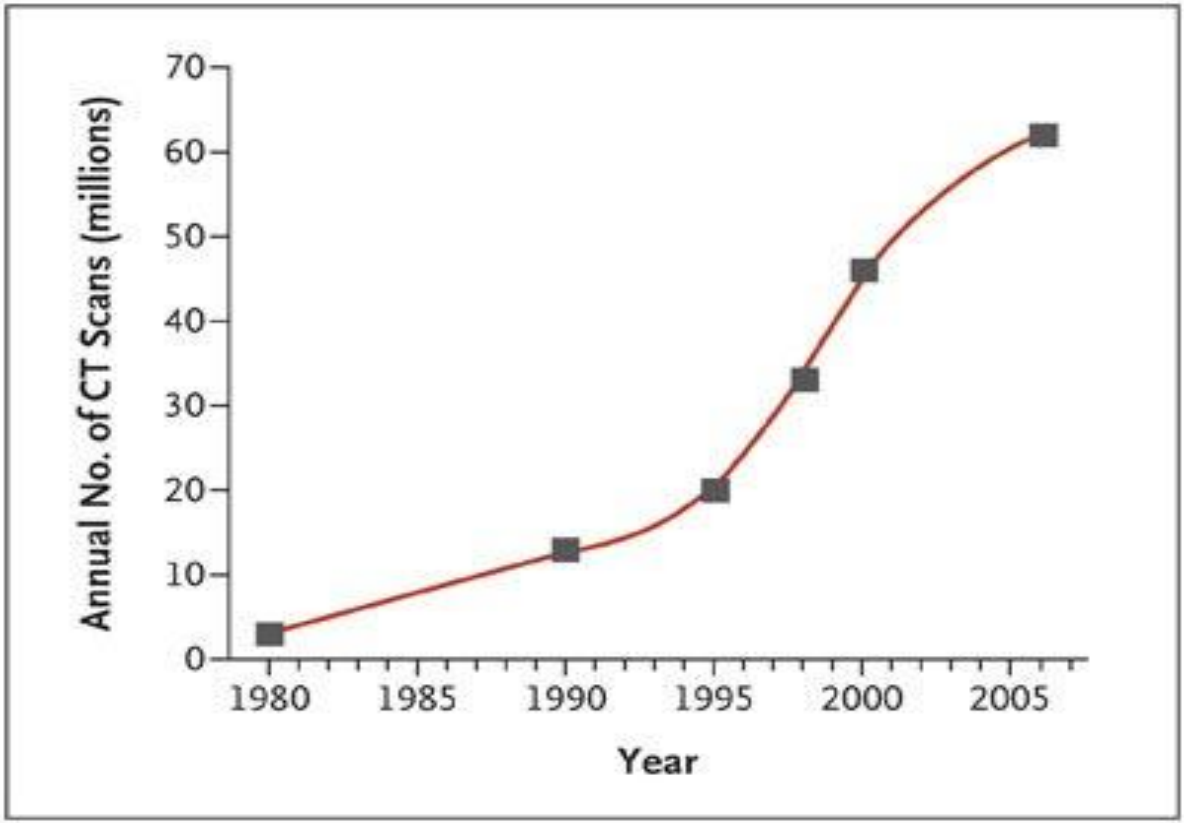

Tumour
Tumour

What are CT Scans?

A procedure that uses a computer linked to an x-ray machine to make a series of detailed pictures of areas inside the body. The pictures are taken from different angles and are used to create 3-dimensional (3-D) views of tissues and organs.

The CT machine was invented by Godfrey Hounsfield in 1972. Silver lining: he got a Nobel Peace Prize.

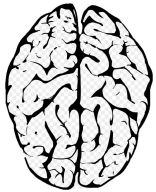

Annual No. of CT Scans (millions)
70
60
50
40
30
20
10
0
1980
1985
1990
1995
2000
2005
Year

Literature Review

Patients receiving other diagnostic radiographs

Japan Life Span Study

Nuclear Workers



Development of a database of organ doses for pediatric and young adult CT scans in the United Kingdom

These studies might be subject to recall bias whereby patients are more likely to recall previous medical radiation exposures than are unaffected controls, and also high levels of reporting error. We avoided such bias by taking a cohort approach and assessing more accurate exposure histories from medical records (panel).

In view of the increasing trend in use of CT scans, it is essential to investigate its potential risks.

Goal

We did a study to directly assess the question of whether cancer risks are increased after CT scans in children and young adult.

Retro spective cohort study

Scope

Great Britain

(England, Wales and Scotland)

Jan 1, 1985
to
Dec 31, 2008

Data obtained from participating hospitals within 81 NHS regional services in Great Britain

How do you operationalise increase in cancer risk due to CT scans?

$$Incidence\ rate = \frac{Number\ of\ Cancer\ cases\ over\ a\ period\ of\ time}{Total\ Person - Years}$$

$$RR_{dose|base} = \frac{Incidence_{dose}}{Incidence_{base(<5\ mGy)}}$$

$$ERR = RR_{dose|base} - 1$$

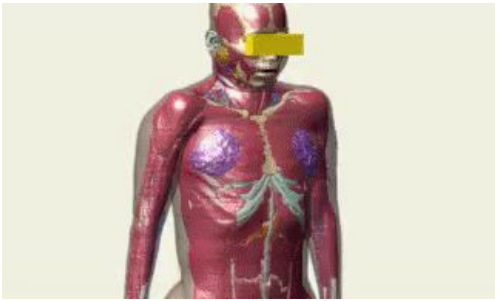
$$ERR\ per\ mGy = \frac{ERR}{Total\ Estimtaed\ Dose\ per\ person}$$

Data needed to accomplish the goal ?

	Cases at age X	Cases at age Y	Person Years*
Dose Base	???	???	???
Dose D1	???	???	???

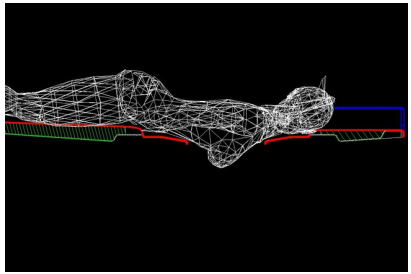
Reason for exclusion year of 2 and 5 year for brain cancer and leukaemia respectively

Calculation of dose in mGy



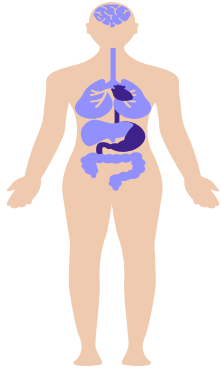
Phantoms

+



Monte Carlo radiation transport

=



Estimation of Organ Doses

Obtaining Sample from Population

Total number of children in Great Britain

Sample

Exclusion

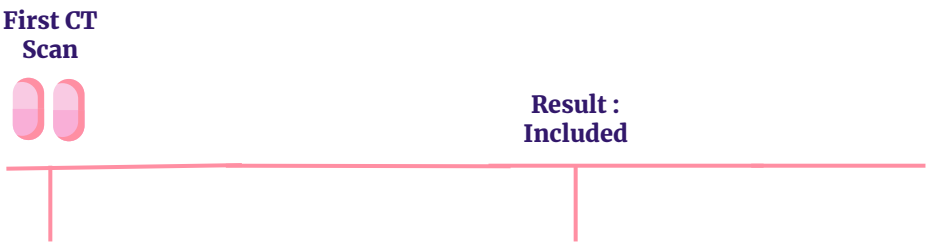
No prior CT scan or cancer diagnosis

Not in Sample

Missing / Inaccurate information
OR
Exited within exclusion period

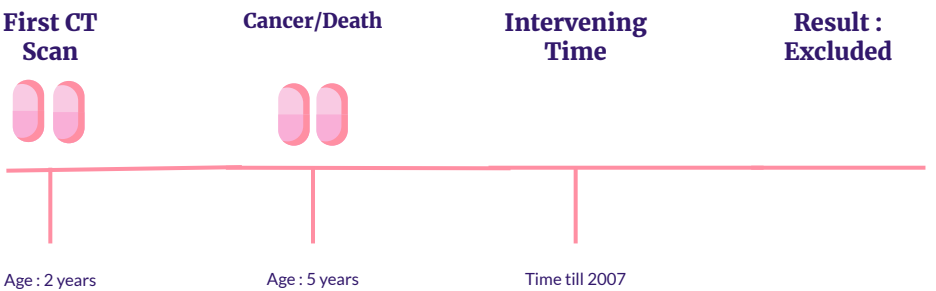
We need this to calculate person-years accurately!

Case Timeline : 1



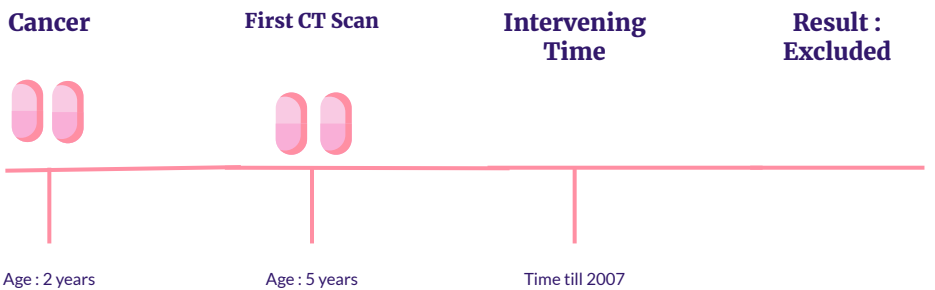
$$Person\ Years\ =\ 16$$

Case Timeline : 2



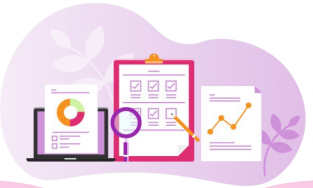
$$Person\ Years = 0$$

Case Timeline : 3



$$Person\ years = 0$$

Data Collected



Qualitative Variables

- Date of Birth
- Gender
- Year of CT Scan and body part scanned
- Postal code

Quantitative Variables

- Number of cancer cases
- Number of fatalities and age at death
- Year of exit of study

Procedure

- Modelling: Poisson Relative Risk Model
  - Poisson Regression
  - Linear relative risk model
- Sensitivity Analysis
  - Change in lag period, follow-up period, age
- Significance test: 2-tailed likelihood-ratio test
- Confidence Intervals on profile likelihood
  - Based on EPICURE program (DATAB & AMFIT modules)
  - Wald-based (Fisher information based) when above software failed to produce a convergent bound

Poisson Regression

Main Equations:

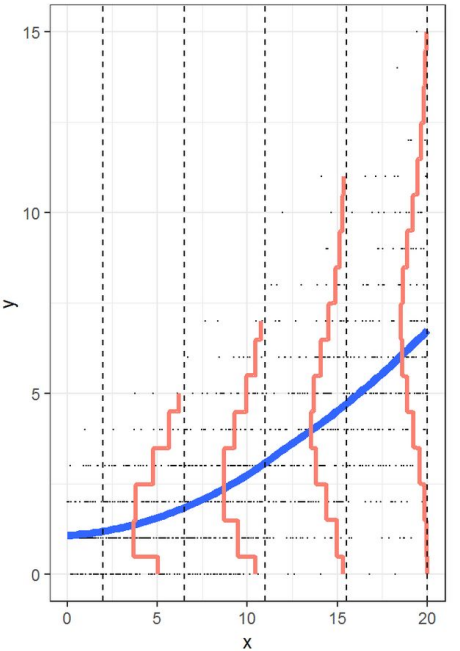
$$\log\big(E(Y|D)\big) = \beta_0 + \beta_1 D$$

$$\log(\mu_i) = \beta_0 + \beta_1 d_i$$

$$Y_i \sim Po(\mu_i)$$

- Y_i is the number of cancer cases in stratum i, based on the dose
- d_i is the dose in stratum i
- μ_i represents the expected number of cancer outcomes in stratum i

Right diagram shows an example of Poisson Regression



Dose–Response Model

$$Expected\ Number\ of\ Cases\ (\mu_i) = PY_i \times Incidence_{dose}$$

$$\downarrow$$

$$Incidence_{dose} = Incidence_{base} \times (1 + \beta z)$$

$$\downarrow$$

$$RR = \frac{Incidence_{dose}}{Incidence_{base}}$$

$$\downarrow$$

$$RR = 1 + \beta z$$

Results

The rise of the p-value, β and ERR – and hypothesis testing!

Hypothesis

Association between covariates and type of cancer

H_0: The risk of cancer in children and young adults is **independent** of the covariate (e.g. years since first exposure).

H_a: The risk of cancer in children and young adults is **associated** with covariate.

Results (Potential Covariates and Type of Cancer)

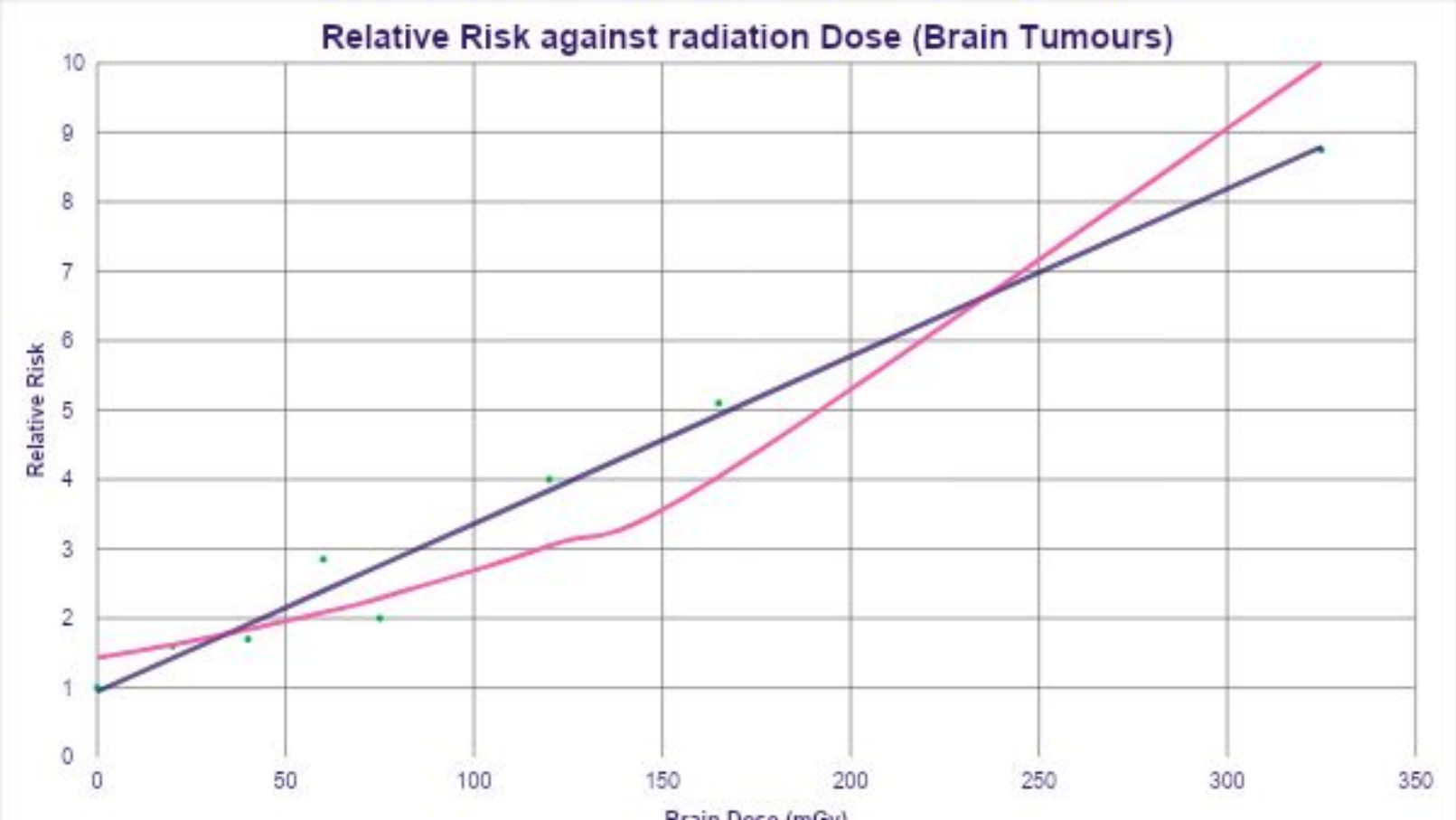
Potential Covariate/ Type of Cancer	Leukaemia	Brain Tumour
	P-value	P-value
Sex	0.63	0.085
Year Since First Exposure	0.8061	0.6468
Year Since Last Exposure	0.3004	0.1976
Number of CT Scans	0.8013	0.1213
Age of Exposure (Years)	0.5381	**0.0003**
Years since Exposure	0.033 (0.002 to 0.439)	0.0195

Hypothesis

Non-linearity of the dose-response model

H_0: The dose-response model is **linear**

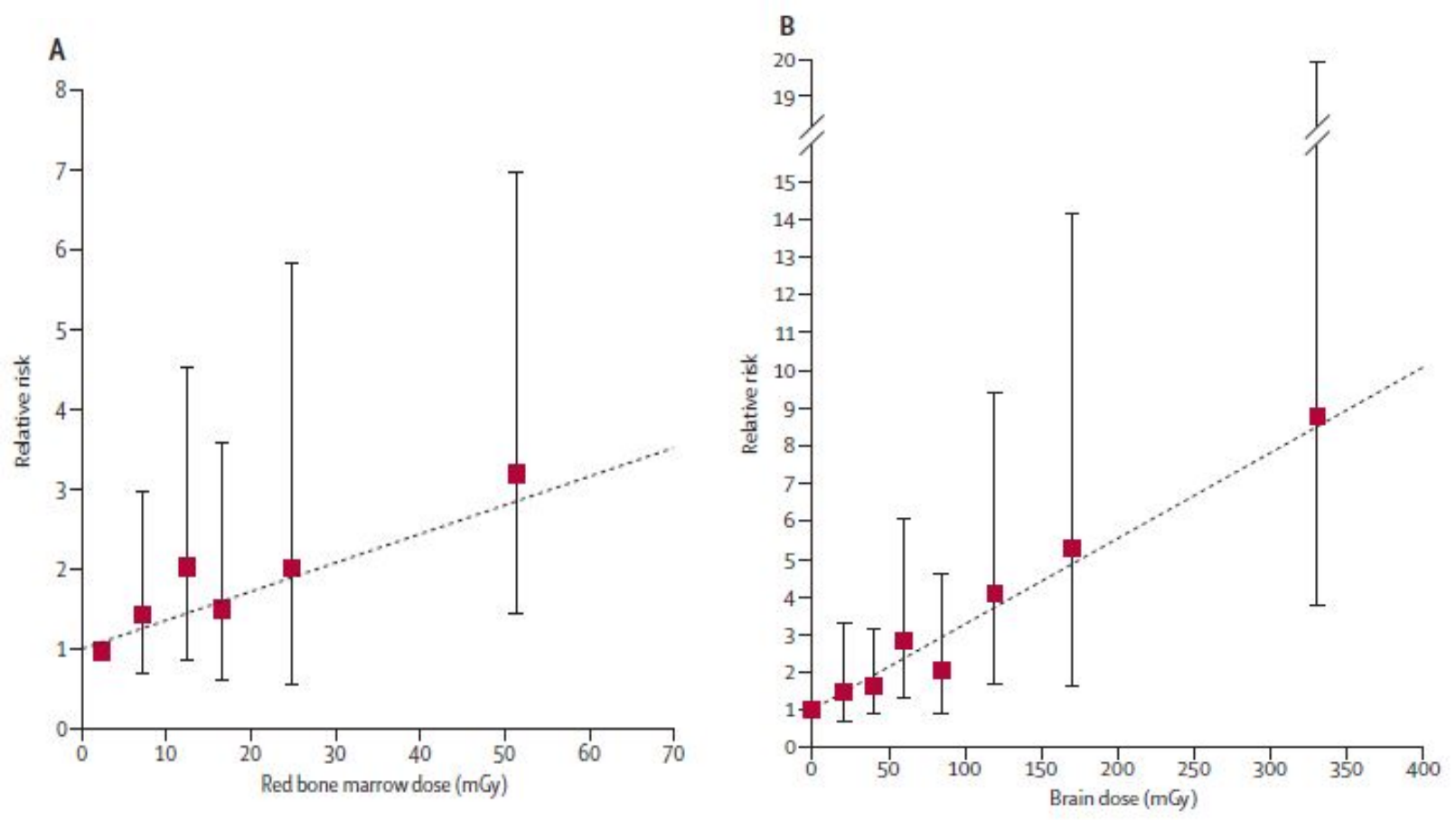
H_a: The dose-response model is **non-linear**


Relative Risk against radiation Dose (Brain Tumours)
Relative Risk
0
1
2
3
4
5
6
7
8
9
10
0
50
100
150
200
250
300
350

Results (Non-linearity of the dose-response model)

	Leukaemia	Brain Tumour
	P-value	P-value
Linear Quadratic	0.4683	0.8993
Linear Exponential	0.2673	0.9203

Bold values indicate that the null hypothesis was rejected for the corresponding scenarios

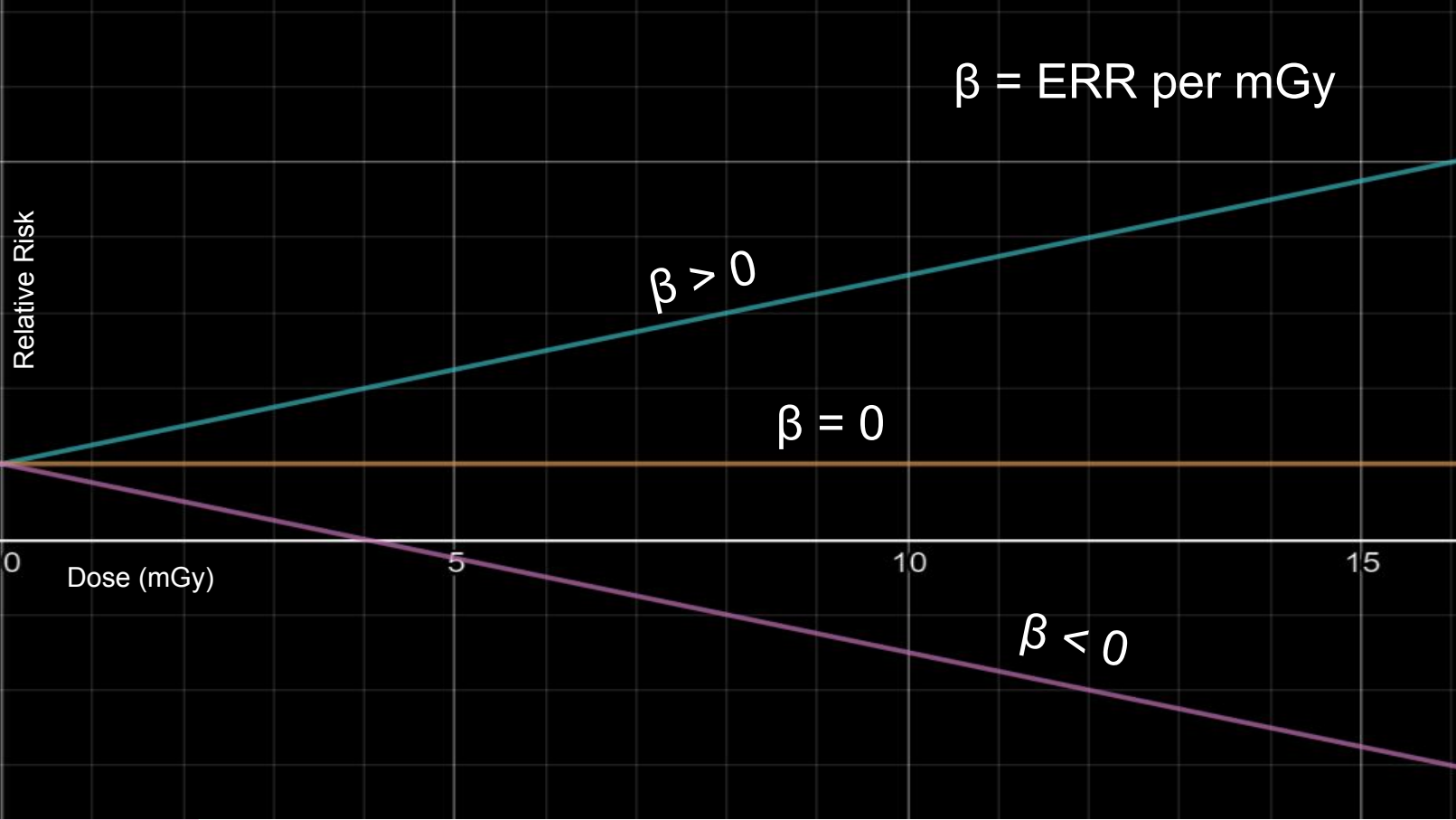

A
Relative risk
0
1
2
3
4
5
6
7
8
0
10
20
30
40
50
60
70
Red bone marrow dose (mGy)
B
Relative risk
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
19
20
0
50
100
150
200
250
300
350
400
Brain dose (mGy)

Hypothesis

Association between risk of cancer and radiation doses from CT scans

H_0: The risk of cancer in children and young adults is **independent** of radiation doses from CT scans. ($\beta = 0$)

H_a: The risk of cancer in children and young adults is **associated** with radiation doses from CT scans. ($\beta \neq 0$)


β = ERR per mGy
Relative Risk
β > 0
β = 0
β < 0
0
5
10
15
Dose (mGy)

Results (Cancer Risk and Radiation Doses)

Red Bone Marrow Dose	ERR per mGy (95% CI)	P-value
All leukaemia (including myelodysplastic syndromes)	0.036 (0.005 to 0.120)	0.0097
Acute lymphoblastic leukaemia	1.719* (>0 to 17.73^)	0.0053
Acute myeloid leukaemia	0.021* (-0.042^ to 0.155)	**0.2653**
Myelodysplastic syndromes	6.098*(>0 to 145.4^)	0.0032
Leukaemia excluding Myelodysplastic syndromes	0.019 (0.012^ to 0.079)	**0.1436**

* Denotes cases where the software failed to produce a convergent bound
^ Denotes Wald-based Confidence Intervals
Bold values indicate that the null hypothesis was not rejected for the corresponding scenarios

Results (Cancer Risk and Radiation Doses)

Brain Dose	ERR per mGy (95% CI)	P-value
All Brain	0.023 (0.010 to 0.049)	<0.0001
Glioma	0.019 (0.003 to 0.070)	0.0033
Schwannoma and meningioma	0.033 (0.002 to 0.439)	0.0195

ALS

Assumptions, Limitations & Strengths -
because we need a break from numbers
(and apply plain logic!)

Assumptions

The cancer was caught in the first CT scan i.e. no misdiagnosis was done.

Assumptions

Other sources of radiation from other scans like radiographs were considered to have negligible impacts on cancer risk.

Assumptions

The ‘typical’ settings were assumed to hold for all patients across sex, organ, and age.

Strengths

Pioneering study which directly measures the impact of low dose radiation on children and young adults.

No extrapolation from high dose responses to low doses

Strengths

No recall bias since all data from system is gathered

(no individual response taken)

Strengths

No selection bias since characteristics of excluded patients are reported to be similar to those included.

Strengths

Large sample size was considered

n =178604 and n = 176587

for leukaemia and brain tumour respectively

Strengths

Utilisation of lag period of 2 years for leukaemia and 5 years for brain cancer

Strengths

Sensitivity analysis of co-variates allowed us to surmise that confounding due to the co-variates analysed is unlikely

Limitations

Limited generalisation to adults who are exposed to radiation from CT scans.

The studies only considers patients who underwent CT scans when they were 22 years old or younger.

Limitations

Limited generalisability to all ethnic groups

80% of the patient assessed were of fair skin

Limitations

Deaths and incidence of only 2 types of cancer were evaluated, thus if a patient dies from other type of cancer it does no contribute to the ERR computed.

Limitations

The reason for conducting the CT scan is not considered:

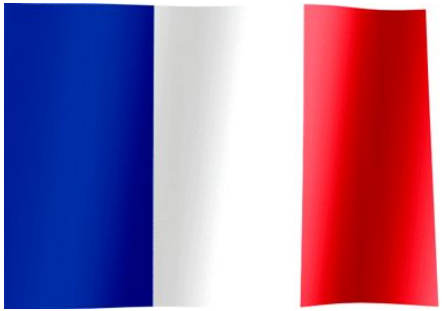
potential confounder

Beyond The Study

The French, the Australians,
and EPI-CT!

Journy et al.

(Motivation : solution to a limitation)

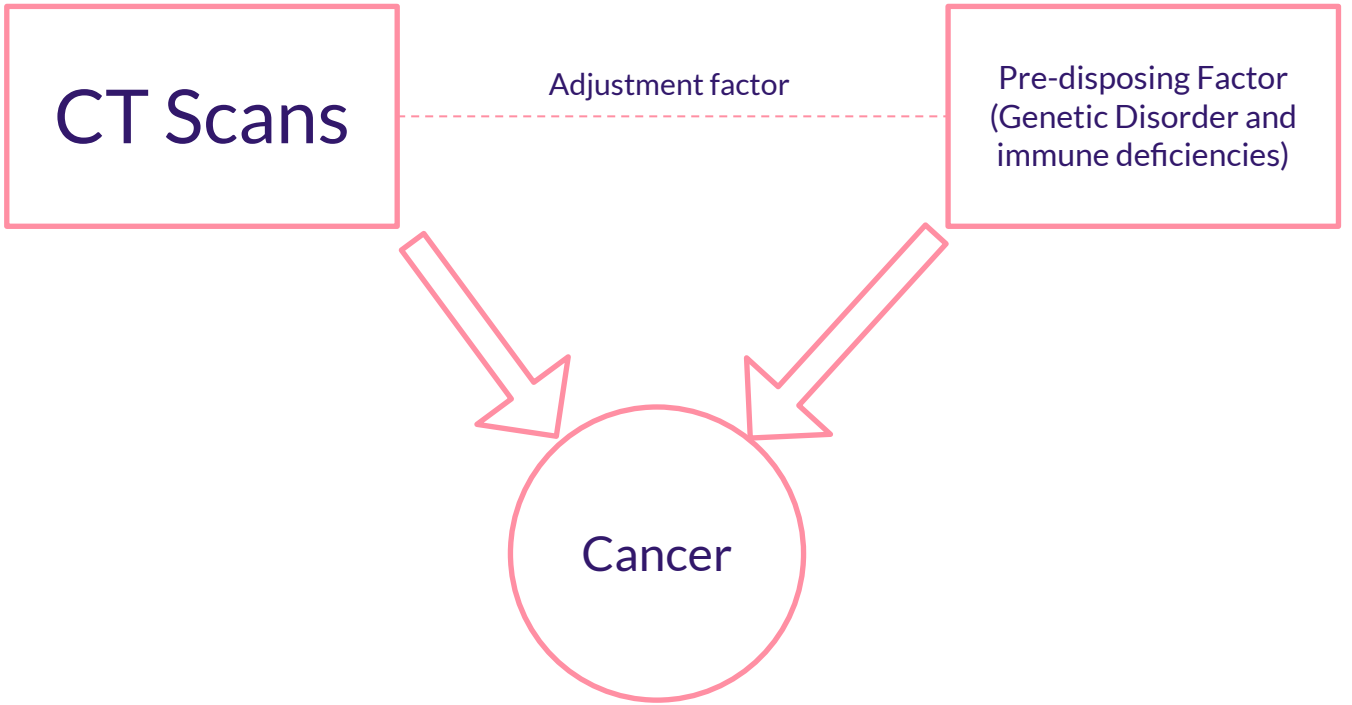


Also a retrospective cohort study!

#TBT : "Reasons for conducting CT Scan not considered"

Where they Differ

- This study includes pre-disposed factors such as genetic disorder and immune deficiencies.
- Reduces the uncertainty by considering individual CT scan data
- Considers a larger variety of cancer types:
  1. Brain tumours
  2. Leukaemia
  3. Lymphomas
- They conducted a sensitivity analysis to determine the exclusion period.


CT Scans
Adjustment factor
Pre-disposing Factor (Genetic Disorder and immune deficiencies)
Cancer

Adjustment for PF

Consider 2 Patients:

1 with PF at first Scan (P1)

1 without at first Scan (P2)

Calculation for P1

$$ERR = RR_{dose|base\ PF} - 1$$

Calculation for P2

$$ERR = RR_{dose|base\ without\ PF} - 1$$

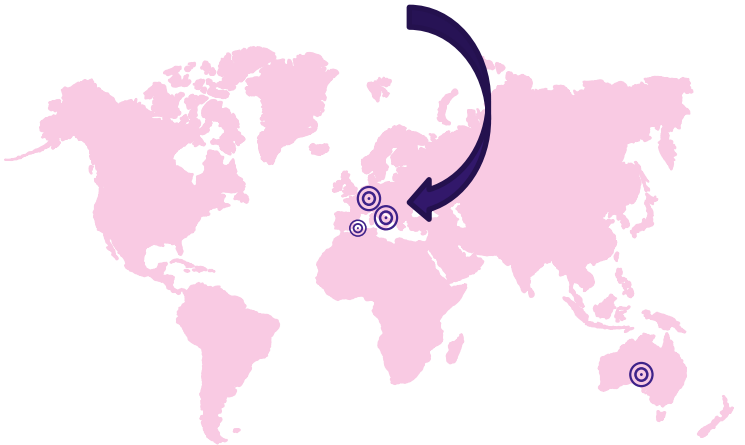
$$Risk_{base\ PF} > Risk_{base\ without\ PF}$$

Results

	Journy *et al.*		Pearce *et al.*	
	ERR	(95% CI)	ERR	(95% CI)
Brain	**0.0012**	**-0.013 to 0.037**	0·023	0·010 to 0·049
Leukaemia	**0.027**	**-0.065 to 0.159**	0·036	0·005 to 0·120
Lymphoma	**0.008**	**-0.057 to 0.073**	-	-

More Findings

French Study (Journy et al)



EPI-CT Mega Cohort Study in Europe

1.04M

Cohort Size of the study (3x the size of the British study)

9

Number of European countries, with both childhood and adult cancer incidences observed

Conclusion