Radiation exposures from CT scans in childhood and subsequent risk of leukaemia and brain tumours

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CT scan history and usage

- A very useful tool
- Introduced in the early 1970's for head scanning
- Available worldwide at over 30,000 centres (and continuing to increase)
- 4% of all medical imaging examinations in the UK
- >40% of total collective dose to UK population from medical x-ray examinations

Usage in children

- Estimated that 5-10% of all CT exams are in children
  - Though varies by country
- Use has grown rapidly over the past two decades as procedures have become much faster

Why study young people?

- With their smaller mass, children tend to receive higher doses to specific organs
  - Great variability of doses, as procedures are not always adapted for young patients
  - Paediatric parameters are dependent on age and weight
  - Historically these parameters were often ignored
- Children have a longer remaining life span

What is known so far?

Generally:

- Other low dose exposures suggest increased cancer risks at the level of several CT scans
  - E.g. Japanese A-bomb survivors, nuclear workers, patients with high numbers of X-rays

What is known so far?

Specific to CT:

- Mostly risk projection studies extrapolating ‘expected’ doses and ‘expected’ cancer risks
  - i.e. no empirical data

- Projections often limited to certain scans, mortality outcomes only and made assumptions regarding modern protocol adjustments that may not have been possible historically

The UK CT Scan Study

- Long-term sequelae of radiation exposure due to computed tomography in childhood and early adulthood

- Funders:
  - US National Cancer Institute
  - UK Department of Health

Why in the UK?

- National Health Service (NHS)
  - Free access to healthcare for all
  - CT scans performed primarily in public hospitals
- NHS Central Register
- National and regional cancer registries
- Ability to obtain ‘umbrella consent’ & ethics

Any drawbacks to doing it in the UK?

- Expensive matching processes compared to Scandinavian countries
  - But a much bigger country/patient group

- Lower usage of CT compared to countries such as the USA and Japan
  - But more difficult to do the data linkage in these countries

The Study

- Primary Objective
  - To assess the risk of subsequent cancers in individuals exposed via CT scanning during childhood or as young adults

Study protocol – phase 1

Cohort study

- Patients having one or more CT scans between 1985-2002
  - First scanned aged <22 years
  - Free from cancer at first CT

- Radiology departments with available electronic RIS data of sufficient quality
  - Film / paper records from small number of Trusts

Study protocol – phase 2

A nested case-control study to assess dose response more precisely

Cohort study dosimetry

- Date and type of scan, age and sex available from electronic RIS records
- Typical CT machine settings for young people taken from 2 UK-wide surveys (1989 and 2001)
- These data combined with those from hybrid computational phantoms and Monte Carlo radiation transport techniques to give estimated absorbed organ doses (e.g. red bone marrow)
- Cumulative doses where more than one CT scan

Outcome data

- RIS data linked with the NHSCR (1985-2008)
  - Cancer incidence
  - Mortality
  - Loss-to-follow-up (e.g. notified emigrations)

- Excluded patients with existing cancer and those diagnosed with leukaemia within 2 years of first CT scan (5 years for brain tumours)
  - Sensitivity analyses with greater years of exclusion

Statistical Methods

- Used Poisson relative risk models fitted by maximum likelihood methods.
- Accrual of person-time began 2 or 5 years after the initial CT scan
- Lag time of 2 or 5 years also included
  - Sensitivity with longer time periods

Results - descriptive

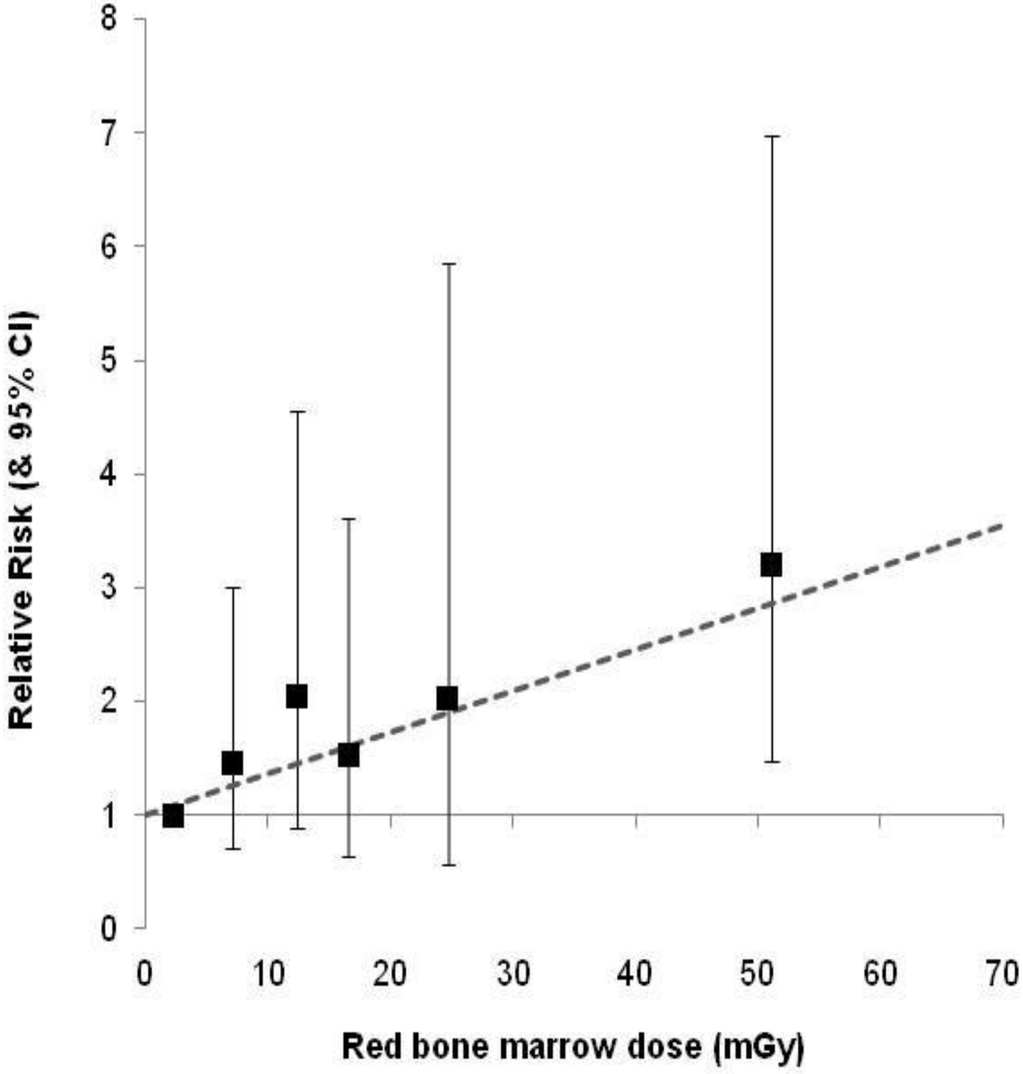
- Initial cohort, including cancer patients: 245,000
- Excluding those with cancer and those that could not be linked by NHSCR left 178,604 patients in the leukaemia analysis and 176,587 in the brain tumour analysis
- These patients had 280,000 CT scans, over 60% of which were of the head

Leukaemia - Excess relative risk per mGy organ-specific radiation doses received from CT scans

	Cases	ERR per mGy (95% CI)	p value (test for dose-response)
Red bone marrow dose			
All leukaemia, including myelodysplastic syndromes	74	0.0361 (0.0052 to 0.1198)	0.0097
Acute lymphoblastic leukaemia	26	1.719* (>0 to 17.73†)	0.0053
Acute myeloid leukaemia	18	0.0208 (-0.0415† to 0.1554)	0.2653
Myelodysplastic syndromes	9	6.098* (>0 to 145.4†)	0.0032
Leukaemia excluding myelodysplasmic syndromes	65	0.0187 (-0.0119† to 0.0794)	0.1436

*Iteratively reweighted least-squares algorithm failed to converge, so parameter estimates might be unreliable.
† Calculated using Wald-based CI.

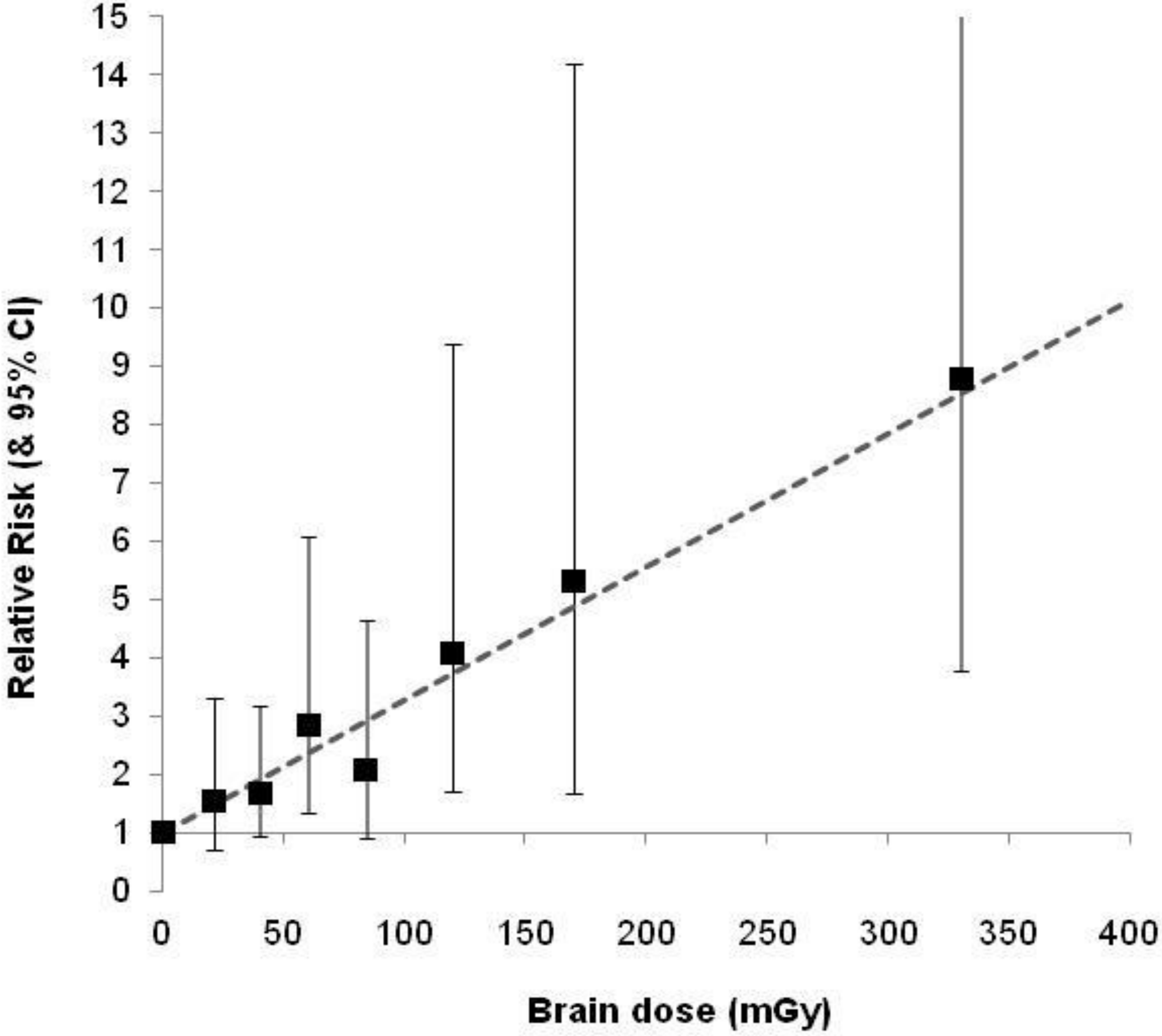
Leukaemia dose-response



Results for brain dose

	Cases	ERR per mGy (95% CI)	p value (test for dose-response)
All brain	135	0.0227 (0.0098 to 0.0494)	<0.0001
Glioma	65	0.0186 (0.0034 to 0.0703)	0.0033
Schwannoma meningioma	20	0.0331 (0.0019 to 0.4388)	0.0195

Brain dose-response



More on the results

- For leukaemia, dose-response did not vary between age at exposure, time since exposure, sex or any of the other covariates examined
- For brain tumours, the ERR increased with increasing age
- Little evidence of non-linearity of the dose-response for either outcome

Main findings

- Significant associations between the estimated radiation doses to red bone marrow and brain and subsequent incidence of leukaemia and brain tumours respectively

Critical appraisal of our study

- We used empirical data
- Cohort approach avoided recall bias (exposure data from medical records)
- The UK has free-to-access healthcare. Thus we should have a fairly representative sample.
- Nationwide cancer registration
  - Cancer ascertainment estimated at 97%

Critical appraisal

- Patients not linked to registry records had similar characteristics to those included
- Our results are based on exposures in childhood or early adulthood
  - Not clear if we can extrapolate the results to adults
- Used a careful approach to avoid those with existing cancers

Critical appraisal

- Dosimetry was improved on previous estimates
  - Provided organ doses, but unable to obtain individual-level parameter data for such a large and historical cohort
- Uncertainties still exist
  - Not expected to bias the findings

Comparisons with the Life Span Study

- Similar dose estimates with childhood exposure and similar follow-up time (<15 years)

- Life Span Study for leukaemia:
  - ERR= 0.045/mSv (95%CI 0.016-0.188)
- Our study:
  - ERR= 0.036/mGy (95%CI 0.005-0.120)

Interpretation

- Our results so far suggest that the risk of leukaemia is tripled with 5-10 head CTs in children aged under 15 years (based on 50mGy exposure)
    - And for brain tumours at 60mGy (2-3 head CTs)

- For every 10,000 head CTs in under 10s, expect one excess case of leukaemia and one excess brain tumour in the 1st decade after 1st CT

Interpretation

- The immediate benefits outweigh the (small) risks in most settings when CT is used appropriately

- Of utmost importance is that, where CT is used, it should only be used where fully justified from a clinical perspective

International collaboration

- Similar studies underway in:
  - Canada, Australia, Sweden, Israel and France
  - EU-funded collaborative study (EPI-CT) began in 2011
    - UK, France, Spain, Germany, Denmark, Sweden, Netherlands, Belgium, Norway and Luxembourg,
- All studies are using a similar study design and collaborations are underway re dosimetry

Acknowledgments

- **Newcastle University, UK**
  - Jane Salotti
  - Sir Alan Craft
  - Nicola Howe
  - Richard Hardy
  - Wenhua Metcalf
  - Claire-Louise Chapple
  - Katharine Kirton
- **NCI**
  - Amy Berrington de González
  - Choonsik Lee
  - Mark Little
  - Jay Lubin
  - Preetha Rajamaran
  - Elaine Ron
  - Cecile Ronckers
- **Dalhousie University, Canada**
  - Louise Parker
- **Great Ormond Street Hospital, London**
  - Kieran McHugh
- **Kyung-Hee University, Korea**
  - Kwang Pyo Kim