How much risk from CT exams of children?

Radiation risks at a level of few CT scans: How real? Science and practice

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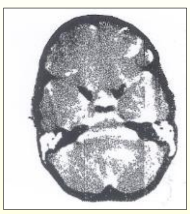
Dramatic Increase in CT Scan Usage in the US



1980 - 3 million scans

2011 - 85 million scans

(Courtesy of A Berrington de Gonzalez, NCI)

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Low, but Potentially Significant, CT Exposures Have Become Very Common

- **About 25 million patients in the USA received CT exams in 2007**
- **Sodickson study – large representative sample of 31,000 U.S. patients receiving CT exams in 2007**
- **The distribution of cumulative effective doses from CT over the previous 20 years showed:**
  - **15% with ≥ 100 mSv → (~3.8 million)**
  - **4% with ≥ 250 mSv → (~1 million)**
- **Mean dose to A-bomb survivors: ~200 mSv**

(Sodickson et al, *Radiol*, 251:175, 2009; adapted from slide by D Brenner)

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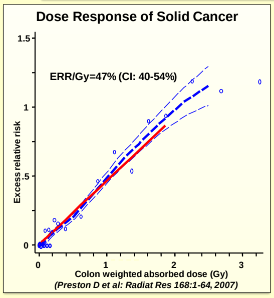
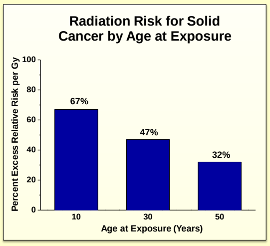
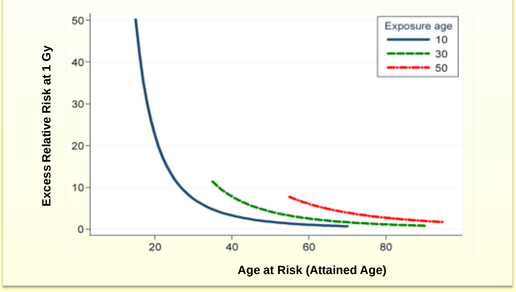
A-bomb LSS Radiation and Solid-Cancer Risk: Dose and Age

- Significant dose response even below 150 mGy
- Those exposed when young are at highest risk





A-bomb LSS Radiation and Leukemia Risk by Age at Exposure and Age at Risk



(Hsu, *Radiat Res*, 179:361-82, 2013)

Main Pediatric CT Studies that Directly Estimate Risks

Outline of Pediatric CT Cohort Studies

# Persons Exposed to CT Exams (Unexposed)	Years of CT in Study (Last Follow-up)	CT Ages Included	Exposed: # Leukemias // # Brain Tumors
Pearce[A] 178,600 (UK cancer registry data)	1985-2002 (2008)	0-21	65 // 135
Mathews[B] 680,000 (10,260,000)	1985-2005 (2007)	0-19	211 // 283
Huang[C] 24,400 (~98,000)	1998-2006 (2008)	0-17	8 // 19

[A] Pearce, *Lancet*, 380:499-505, 2012
[B] Mathews, *Br Med J*, DOI:10.1136/bmj.f2360, 2013
[C] Huang, *Br J Cancer*, 110:2354-60, 2014

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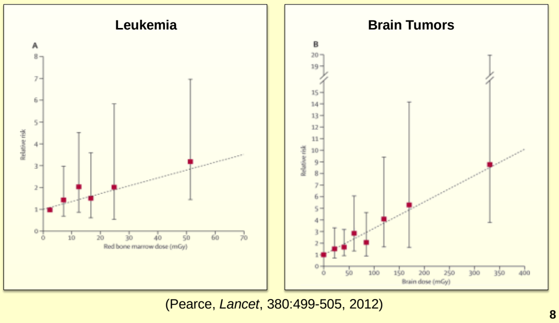
Relative Risks of Leukemia and Brain Tumors by Estimated Radiation Dose (Pearce, 2012)



(Pearce, *Lancet*, 380:499-505, 2012)

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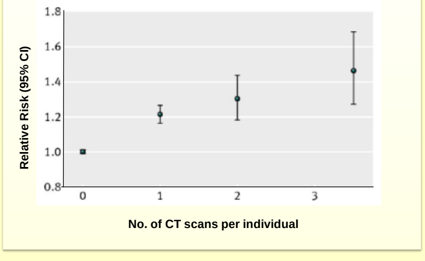
Relative Risk of All Cancers by Number of Pediatric CT Scans (Mathews, 2013)



(Mathews, *Br Med J*, DOI:10.1136/bmj.f2360, 2013)

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Estimated Relative Risks from Pediatric CT Scans, for Dose Groups (Dose to Target Organ; Pearce, 2012)

	# tumors	Dose Group (mean dose, mGy)	Relative Risk (95% CI)
Leukemia			
Total # leukemias + MDS	74		
Leukemia, including MDS (myelodysplastic syndromes)	(15)	≥ 30 (51.1)[B]	3.2 (1.5, 6.9)[A]
Brain tumors (malignant + benign)			
Total # brain tumors	135		
Doses ≥ 50 mGy	(53)	≥ 50 (104)	3.3 (1.8, 6.4)

[A] Risk estimates for 2+ years after first CT examination for leukemia and MDS, and 5+ years for solid cancers.
[B] They reported that after 2001 for CTs at ages <15y: 5-10 head CTs gave 50 mGy RBM dose, & 4-5 gave 100 mGy brain dose.

(From: Pearce, *Lancet*, 380:499-505, 2012)

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Relative Risks (RR) in the CT Exposed v. Unexposed Group by Type of Cancer (Mathews, 2013 & Huang, 2014)

Cancer type	RR (95% CI)[A]
All solid cancers (M)[B]	1.25 (1.20–1.31)
Brain cancer after brain CT (M)	2.44 (2.12–2.81)
Leukemias (M)	1.19 (1.03–1.37)
All brain tumors (H)	2.56 (1.44–4.54)

[A] Based on 1+ Years after First Exposure (2+ for Huang). [B] M= Mathews, H=Huang

(Mathews, *Br Med J*, DOI:10.1136/bmj.f2360, 2013; Huang, *Br J Cancer*, 110:2354-, 2014)

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Comparison of Radiation Risk Estimates in the Pediatric CT Studies and the A-bomb Study

Outcome and Study	No. of Malignancies	Relative Risk at 1 Gy (95% CI)
Brain tumors (Pearce '12)	135	24 (11-50)
Brain cancers after brain CT (Mathews '13)	210	30 (24-38)
Nervous system tumors, A-bomb survivors, exposed ages 0-19 (Preston '07)	114	1.9 (1.3-2.8)[A]
Leukemia/Myelodysplastic Syndromes & pediatric CT (Pearce '12)	74	37 (6-121)
Leukemia/Myelodysplastic Syndromes & pediatric CT (Mathews '13)	246	40 (15-71)
Leukemia, A-bomb survivors, exposed ages 0-19 (Hsu '13)	106	7.5 (5.0-11)

[A] 90% CI

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Dosimetry Uncertainties and Potential Bias

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CT Dose Reconstruction – Pearce, 2012

- Used age, sex, anatomic site and year of scan (1985-2000, 2001-02), but hospital or individual CT settings (e.g., millampere seconds, kVp etc) not available.
- Used CT dose information on young people from UK-wide dose surveys undertaken in 1989 & 2003; then used age-specific phantoms and Monte Carlo techniques to estimate CT doses.
- Found that dose estimates before 2001 were generally 2-3 times higher than after, because age-specific technical settings were rarely used in earlier years.

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CT Dose Reconstruction – Mathews, 2013

- Estimated average effective doses (mSv) per scan by anatomic site, year of scan (1985-2000, 2001-05) and age based on information from the literature (no information for specific hospitals or individuals).
- Modeled average effective doses for 1985-2000 & 2001-2005.
- Since little information on pediatric doses before 2001, they applied a scaling factor to reported adult effective doses before 2001.
- Applied further scaling factors to convert the estimated effective doses to red bone marrow & brain doses.
- Estimated a mean effective dose of 4.5 mSv per CT exam.

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Sources of CT "Missing Dose"

- No CT exposure information outside of the time and age bounds of the study design
  - E.g., no information on CT scans before 1985, or after age 21 (Pearce) or 19 (Mathews), but cancer incidence was included for ages up to the early 40's
- Long scan times in the 1980's and 1990's (>10 minutes) → sometimes blurred images due to child movement → retakes → retake information not recorded.
- "Overexposures"? – especially in the early days.

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Issues and Indications of Possible Bias

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Relative Risk (RR) Estimates Suggesting Possible Biases

Cancer type	RR [A] (exposed *v* unexposed)	95% CI
Brain after brain CT	2.44	(2.12, 2.81)
Brain, after non-brain CT	**1.51**	**(1.19, 1.91)**
Melanoma	**1.12**	**(1.04, 1.20)**
Hodgkin lymphoma	**1.15**	**(1.01, 1.32)**
Myelodysplastic syndromes	1.60	(1.13, 2.27)
Leukemia, excluding MDS	1.19	(1.03, 1.37)

[A] **Data for one or more years after first CT exposure**
(Mathews, *Br Med J*, DOI:10.1136/bmj.f2360, 2013)

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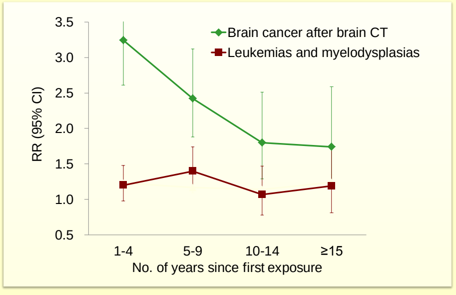
Concept of "Reverse Causation"

- **Reverse Causation: Cancer symptoms or prodromal stages of cancer caused the CT exam to be performed.**
  - **I.e., early signs/symptoms of undetected cancer may be the reason for a CT scan, and these undetected cancers, rather than the radiation dose *per se,* may cause the apparent subsequent excess risk of diagnosed cancer**
  - **If so, the cancer would likely be diagnosed within a few years, rather than >10y later (i.e., the reverse causation bias would be greatest soon after the CT exam).**

Relative Risks (RR) for the Exposed Group by years since first CT exposure (Mathews, 2013)



(Mathews, *Br Med J*, DOI:10.1136/bmj.f2360, 2013)

Steps Ahead

Individualize CT dose estimates – by each hospital's CT equipment & practices over time or, if possible, from individual CT records.

Reverse causation issue: Get information on reasons for CT referrals; if some reasons lead to high subsequent cancer risk, it implies reverse causation.

Forthcoming Pediatric CT Studies	Projected Numbers with CT Exams
EPI-CT (9 European countries, pooled)	1,045,000
Ontario, Canada	370,000
Israel	42,000

Summary of Results to Date

- Data of Pearce and Mathews **agree on risks for brain tumors and leukemia** from pediatric CT scans – large potential impact on public and medical communities
- Both studies had good study designs and mostly good methodology, and showed **dose-response** associations.
  - But substantial uncertainties in imputed doses, and missing dose information
- Especially the Mathews study probably reported biased overestimates for brain tumor risk due to "reverse causation"
  - But even for >10 years after CT scans, when little reverse causation is expected, brain tumors were still associated with CT

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Status and Conclusions

Status: coherent results suggest risk from pediatric CT exams, but the available studies are not yet definitive

- One should be **careful in interpreting the magnitude of the putative risks** because of limited dosimetry, inconsistencies in risks of other cancers, and possible biases.
- Refinements in methodology are needed (e.g., regarding **"reverse causation"**).
- Large-scale studies with more **individualized dose** estimates and **additional clinical information** are underway to (dis)confirm these results.

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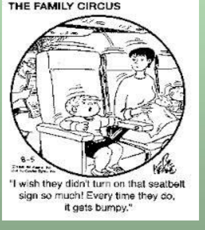
Missing CT Doses by Age and Temporal Period

Earliest Birthdate	Years of CT in Study (Last Follow-up)	CT Ages Included	Maximum Follow-up Age
1964 (Pearce) [A]	1985-2002 (2008)	0-21	45
1966 (Mathews) [B]	1985-2005 (2007)	0-19	42

[A] Pearce, *Lancet*, 380:499-505, 2012; [B] Mathews, *Br Med J*, DOI:10.1136/bmj.f2360, 2013

"Reverse Causation"



(Courtesy of A Berrington de Gonzalez, NCI)