47th Annual Aubrey O. Hampton Lecture

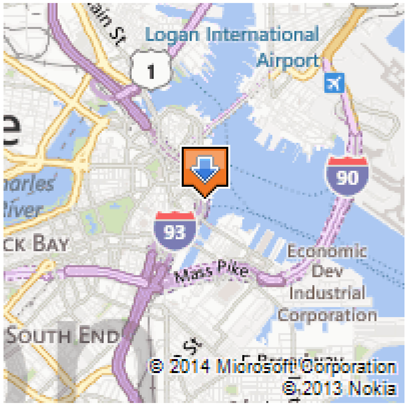
When
Friday March 21, 2014 from 5:30 PM to 11:00 PM EDT
Add to Calendar

Where
Boston Harbor Hotel
70 Rowes Wharf
Boston, MA

Dear John,

Thank you for registering for the MGH Department of Radiology's ***47th Annual Aubrey O. Hampton Lecture.*** *Following is some helpful information for planning your evening:*

Friday, March 21, 2014
5:30 pm Cocktails & Hors d'Oeuvres
6:30 pm Program Begins
7:30 pm Dinner Service & Dancing



Driving Directions

Place: Boston Harbor Hotel, the Wharf Room

Hotel Staff will be available to guide you to the beautiful Wharf Room, with a panoramic view of Boston Harbor.

Our distinguished Hampton Lecturer this year is:

John Boice, Sc.D.

President, National Council on Radiation Protection and Measurements*
Professor of Medicine, Vanderbilt University School of Medicine

"Cumulative Diagnostic Radiation and Cancer Risk"

*National Council on Radiation Protection and Measurements (NCRP). NCRP, located in Bethesda, Maryland, is a Congressionally-chartered not for profit organization that supports the scientific and public aspects of radiation protection through independent analyses by leading scientists throughout the United States.

Please click here for complete speaker profile.

Please contact Catherine Colt, Administrative Assistant, at ccolt@partners.org or 617-726-3403 if you have any questions.

Sincerely,

James A. Brink, MD
Radiologist-in-Chief

The 47th Aubrey O. Hampton Lecture at the Massachusetts General Hospital was presented on March 21, 2014 by Dr. John Boice, President of the National Council on Radiation Protection and Measurements (NCRP) and Professor of Medicine at Vanderbilt University. The title of Dr. Boice's lecture was "Cumulative Diagnostic Radiation and Cancer Risk."

Aubrey O. Hampton (1900–1955) was born in Copeville, Texas and received his medical degree from Baylor University in 1925. His association with the Massachusetts General Hospital (MGH) began in 1926 as a resident in radiology. He was also a member of the faculty of Harvard Medical School. Dr. Hampton then became the radiologist-in-chief in 1941, but he was granted a leave of absence in 1942 for military service. As a member of the medical corps, Dr. Hampton held the rank of major and served as the chief of radiology at Walter Reed Hospital in Washington, D.C. After the war, Dr. Hampton resigned from his position at the MGH to become the chief radiological consultant for the Veterans Administration and the chief of the radiological department at Garfield Hospital.

Dr. Hampton was a fellow of the American College of Radiology and the Radiological Society of North America. He was also a past president of the New England Roentgen Ray Society. The Aubrey O. Hampton Lecture at MGH was created in his honor. Dr. James A. Brink, Radiologist-In-Chief at the MGH introduced Dr. Boice.

Dr. Boice was the first chief of the Radiation Epidemiology Branch at the National Cancer Institute. His seminal discoveries and over 460 publications have been used to formulate public health measures to prevent radiation-associated diseases. Previous honors include the Harvard School of Public Health Alumni Award of Merit; the E.O. Lawrence Award from the U.S. Department of Energy; the Gorgas Medal from the Association of Military Surgeons of the United States; the outstanding alumnus award from the University of Texas at El Paso (UTEP); and the Distinguished Service Medal from the U.S. Public Health Service. His current studies include atomic veterans who participated in nuclear weapons tests and over a million radiation workers in the United States to examine the lifetime risk of cancer. He studies the children of cancer survivors to assess possible genetic risks from curative radiation treatments.

Cumulative Diagnostic Radiation and Cancer Risk

John D. Boice, Jr.
Vanderbilt University Medical Center
National Council on Radiation Protection and Measurements
john.boice@vanderbilt.edu
March 21, 2014

National Council on Radiation Protection & Measurements

"And it was so typically brilliant of you to have invited an epidemiologist."

The New Yorker, Nov 26, 2001, Wm Hamilton

Views of a Radiation Epidemiologist

Personal views are presented and not necessarily those of the:

NCRP (Report No.171, 2012)
UNSCEAR (Annex B, 2013)
ICRP
Vanderbilt University
et al.

Outline

Introduction – Boston Heros

TB Fluoroscopy for Pneumothorax

Scoliosis – Spinal X-Rays

CT Epidemiologic Studies

Examples of Reverse Causation

Vanderbilt-Ingram Cancer Center

Aubrey Otis Hampton

Copeville, Texas
Population ~ ???

Aubrey Otis Hampton, famous radiologist

Medical Physics and Imaging

Edward (Ted) Webster

Teacher, friend, and UNSCEAR delegate.
Webster Center for Advanced Research
and Education in Radiation

Thanks – Fred Mettler

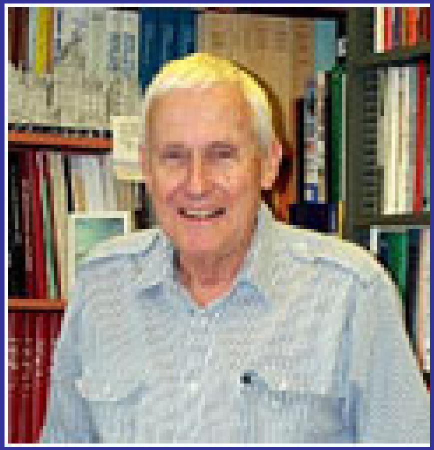
Professors at Harvard School of Public Health

Brian MacMahon

Head of Epidemiology

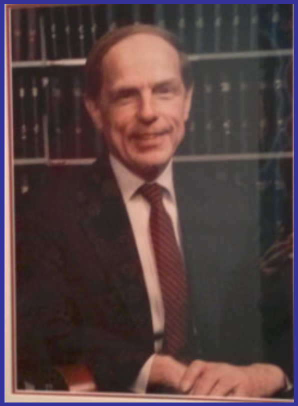
Richard Monson

Professor of Epidemiology
Advisor



Jack Little

Professor of Radiobiology
Thesis Committee, ICRP, NCRP



George Hutchison
Professor of Epidemiology
Thesis Committee

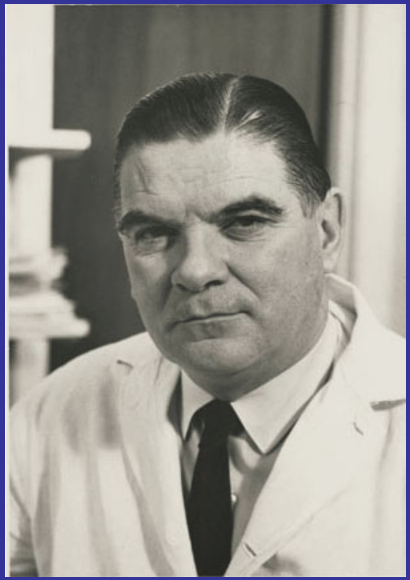
Mentor

Shields Warren

Pathologist, HMS, Deacones. First director of biology and medicine, AEC. Examined atomic-bomb survivors. Warren and Gates – 2nd Cancer

He recommended that I study children with Tuberculosis treated at the North Reading State Sanatorium – doctoral thesis.

Scientific Mentors and Collaborators



Hermann Lisco

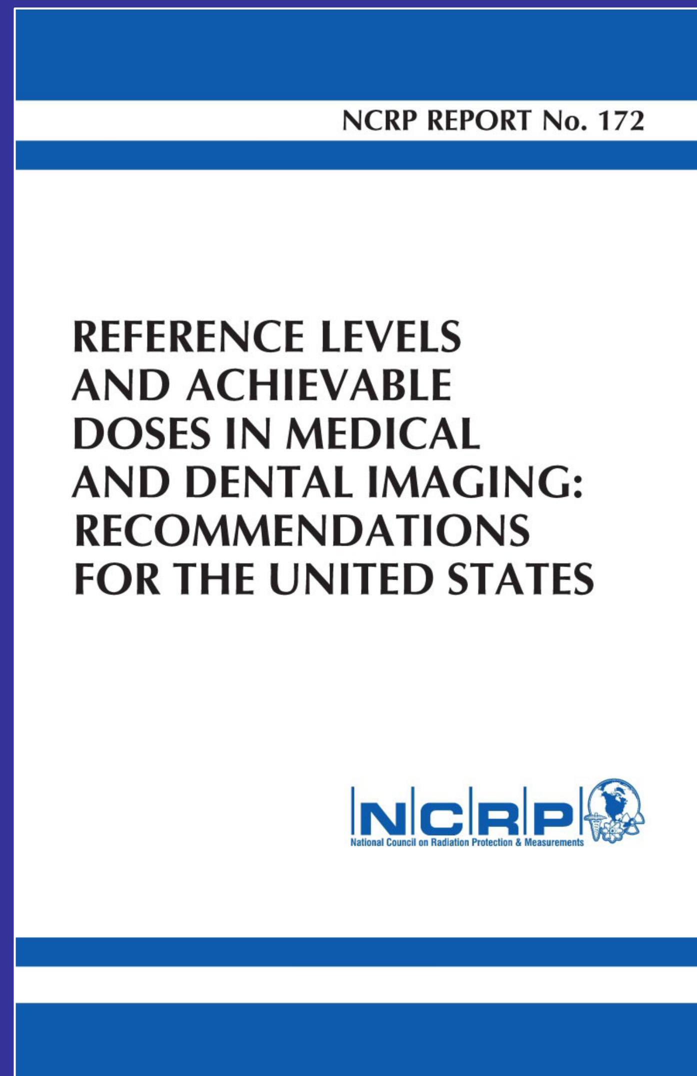
Professor, Harvard Medical School,
Dean Student Affairs
Radiation Pathologist

William (Bill) Moloney

Chief, Hematology, Professor of Medicine at Harvard Medical School and served as Chief of Hematology, 1966 - 1976

National Council on Radiation Protection and Measurements

Jim Brink, Chair of NCRP Committee on Medicine

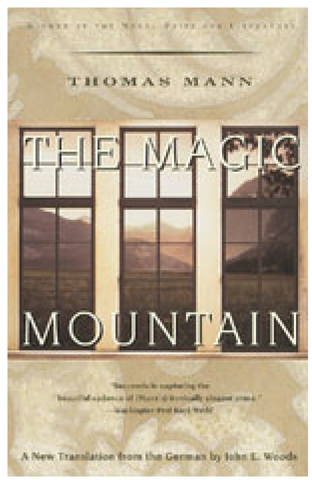


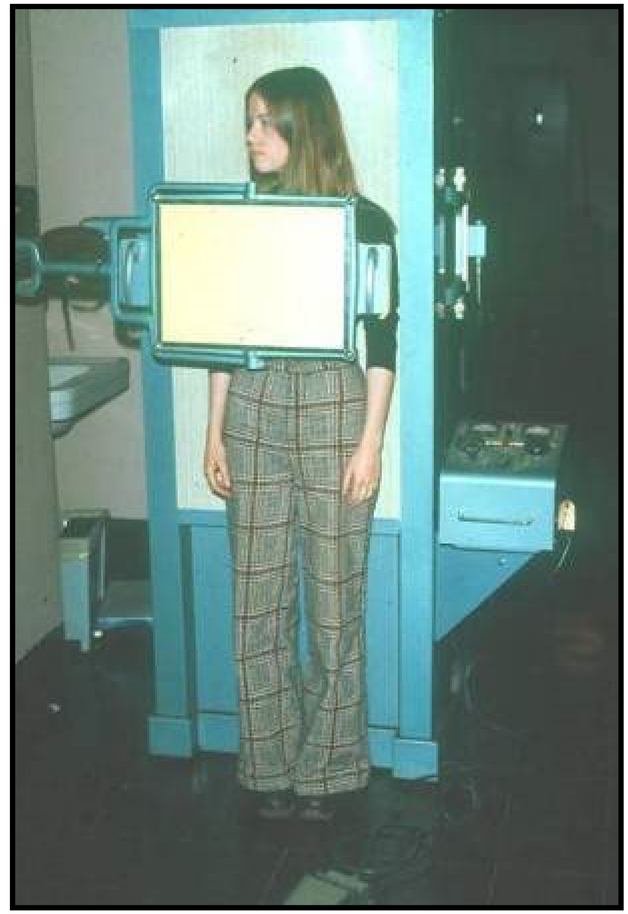
No frills, volunteer organization, boots on the ground, even the Boston heros pump their own gas …

Thanks – Fred Mettler

Studies of Low-Dose Exposures Accumulating to High Dose

Lung collapse therapy for tuberculosis and associated multiple chest fluoroscopic x rays (1930 - 1954)





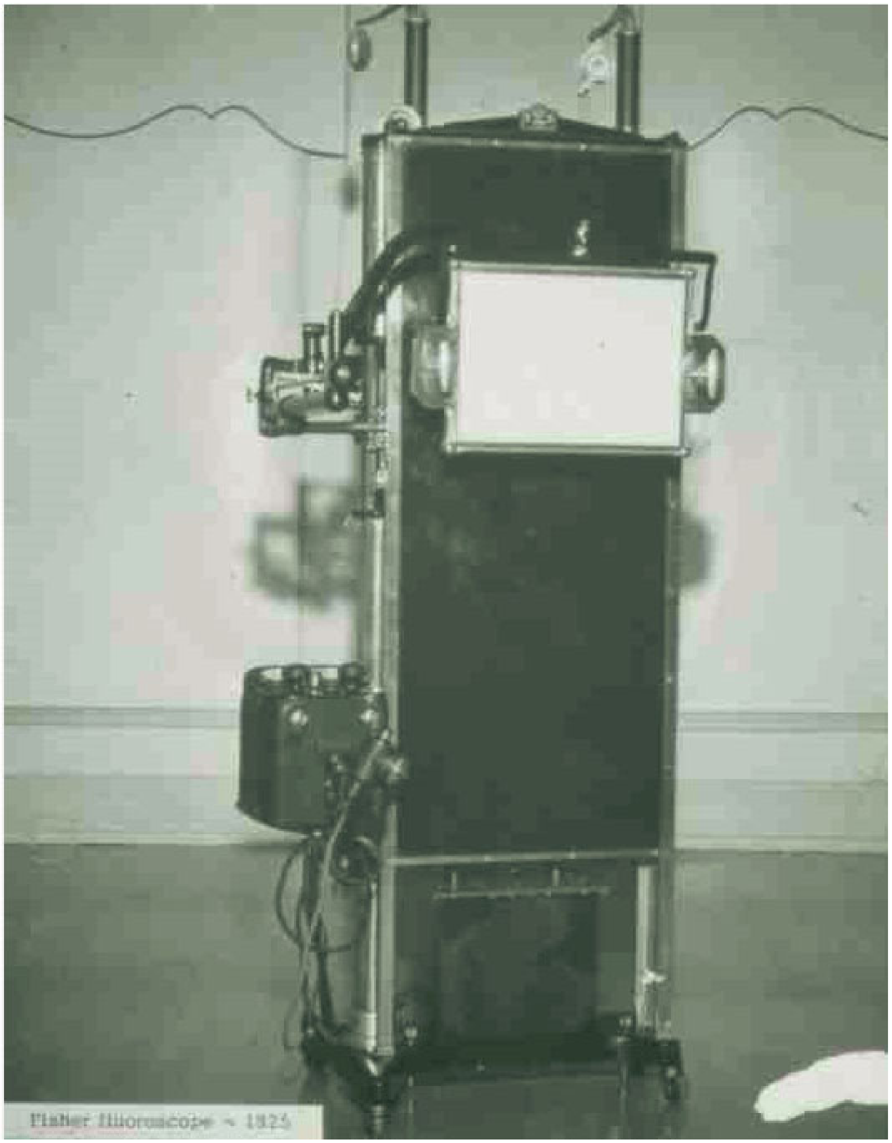
Breast Cancer
TB - Fluoroscopy, Massachusetts

	Exposed	Nonexposed
No. of women	2,573	2,367
No. chest fluoroscopies, ave	**88**	—
Dose (ave) [*Dale Trout*]	790 mGy	—
Breast cancers		
Observed (O)	147	87
Expected (E)	114	101
O/E	**1.29**	0.86

29% Excess

Boice *et al.*, *Radiat Res* 126:214, 1991
Boice and Monson, *J Natl Cancer Inst* 59:823 1977

1925 Fluoroscope

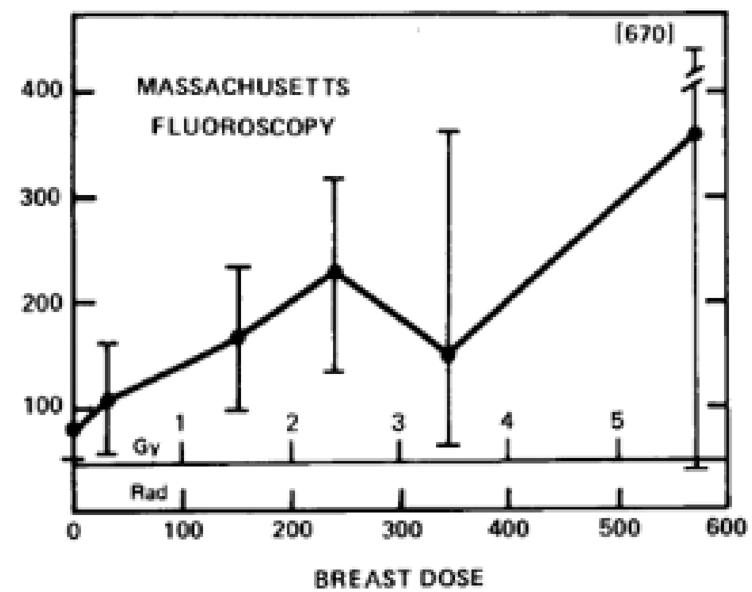


Estimation of Breast Doses and Breast Cancer Risk Associated with Repeated Fluoroscopic Chest Examinations of Women with Tuberculosis[1]

John D. Boice, Jr.,[2] Marvin Rosenstein,[3] and E. Dale Trout[4]

Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts 02115

Boice, J. D., Rosenstein, M., and Trout, E. D. Estimation of Breast Doses and Breast Cancer Risk Associated with Repeated Fluoroscopic Chest Examinations of Women with Tuberculosis. *Radiat. Res.* **73**, 373–390 (1978).



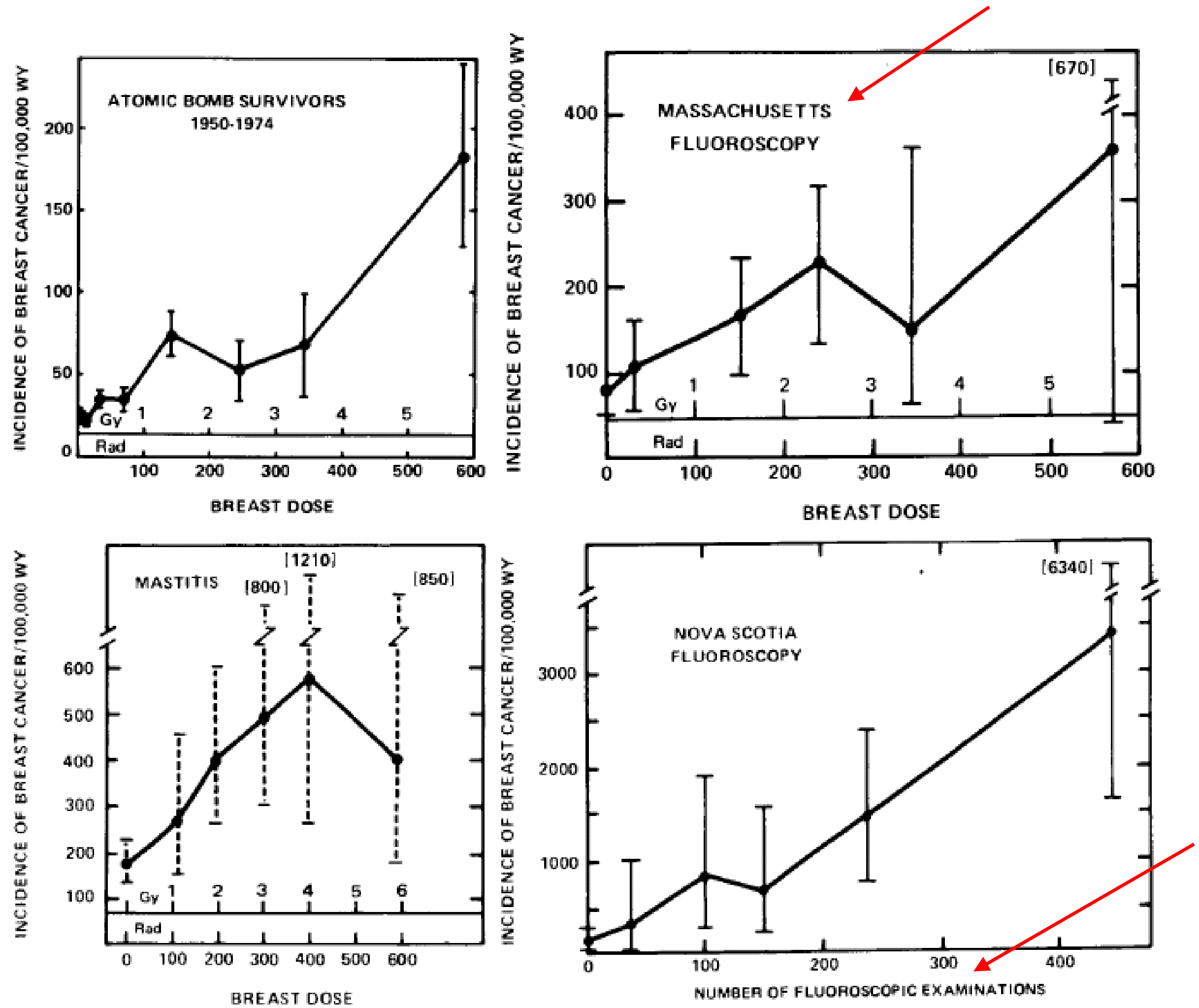
Breast Cancer After Exposure to External Radiation: A Pooled Analysis of Seven Studies

Dose Response – Pooled Analysis of Breast Cancer Studies

Breast Cancer

Consistent with linearity

Boice, Radiology 131:589, 1979



Lung and Leukemia
TB - Fluoroscopy, Massachusetts

	Lung	Leukemia
No. exposed	6,285	6,285
No. unexposed	7,100	7,100
No. chest fluoroscopies (ave)	77	77
Dose to lung or marrow	840 mGy	90 mGy
Observed (O)	69	17
Expected (E)	86	19
RR (95% CI)	**0.8** (0.6-1.0)	**0.9** (0.5-1.8)

Davis *et al.*, Cancer Res 49:6130, 1989

No excess lung or leukemia

Not all tissues respond similarly to fractionation.

Lung
TB - Fluoroscopy, Canada
Compared with Japanese LSS

	Multiple Fluoroscopy		Atomic Bomb	
Lung Dose (mGy)	# Lung Cancers	RR (95% CI:)	# Lung Cancers	RR (95% CI:)
<10	723	1.0	248	1.0
10 -	180	0.87 (0.7-1.0)	290	1.26 (1.1-1.5)
500 -	92	0.82 (0.7-1.0)	38	1.45 (1.0-2.1)
1,000 -	114	0.94 (0.8-1.2)	30	1.93 (1.3-2.9)
2,000 -	41	1.09 (0.8-1.5)	10	2.65 (1.5-4.7)
3,000+	28	1.04 (0.7-1.5)	3	—

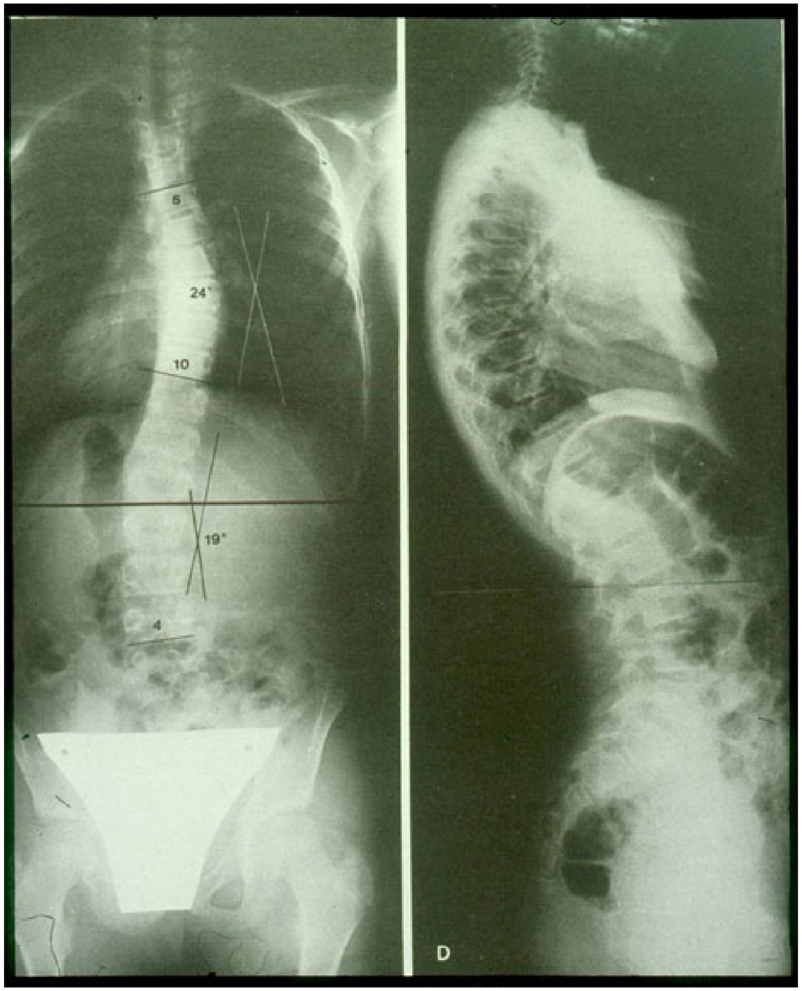
ERR/Gy (95% CI)	0.00 (-0.06–0.07)	0.60 (0.27–0.99)

Howe G, Radiat. Res. 1995; 142:295

Summary - Cumulative Dose and Risk
TB Fluoroscopy

- Low-dose fractions over many years increase breast cancer risk
- Age at exposure modifies effect
- Linearity fits the breast cancer data
- Low-dose fractions NOT found to increase
  - lung cancer
- Be cautious when generalizing

Spinal X Rays for Scoliosis During Growth Spurt



Breast Cancer
Scoliosis – Spinal Dx X Rays

No. Female Patients	**5,573**
Years Treated	**1912 - 1965**
Age, Mean (y)	**10.6**
No. X-rays	
Range	**0 - 618**
Mean	**24.7**
Breast Dose (cGy)	
Range	**0 - 170**
Mean	**11**
Breast Cancer Deaths	
Observed	**77**
Expected	**45.6**
O/E (95% CI)	**1.69 (1.3-2.1)**

Hoffman *et al.*. JNCI 81:1307, 1989

Doody *et al.*. Spine 25:2052, 2000

Sensitivity of immature breast

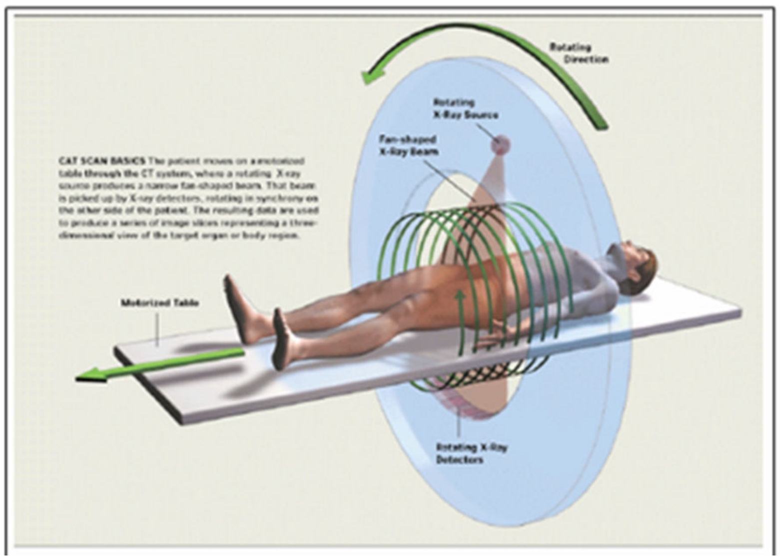
Breast Cancer Scoliosis

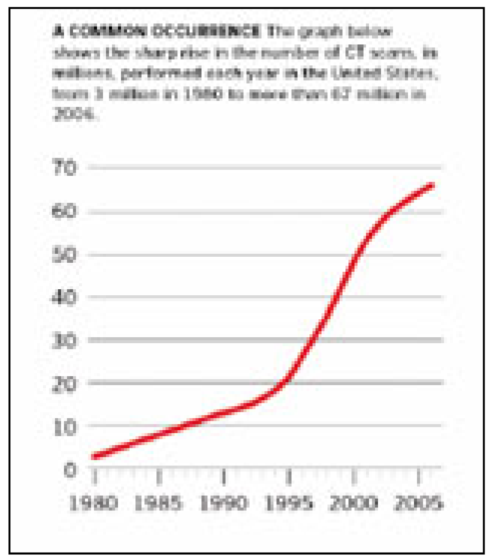
Breast Cancer Radiation Dose Response Among Women with Spinal Curvature, U.S. Scoliosis Cohort Study				
Cumulative Breast Dose (cGy)	Full Cohort (*N* = 5,512)			
	Number of Breast Cancer Deaths	Number of Comparison Subjects	RR	95 % CI
0 – 9	63	3,325	1.0	—
10 – 19	23	1,216	1.2	0.7 – 2.0
20 – 29	14	526	1.9	1.0 – 3.5
≥30	12	333	2.4	1.2 – 4.8
P trend			*0.001*	

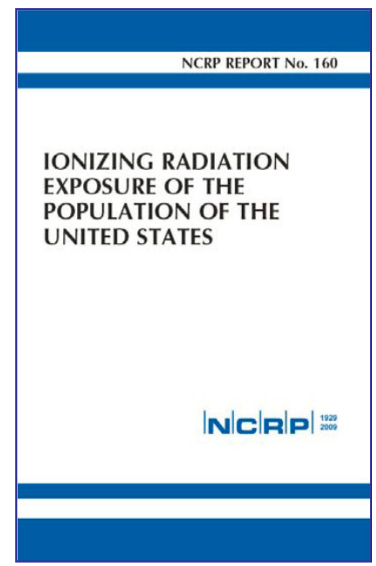
Ronckers *et al*., Radiat. Res. (2010)

CT Exams Are Increasing Each Year

- Over 85 million CT examinations were performed last year in the U.S. This is approximately one for every four U.S. citizens.







Charles Schultz, Peanuts

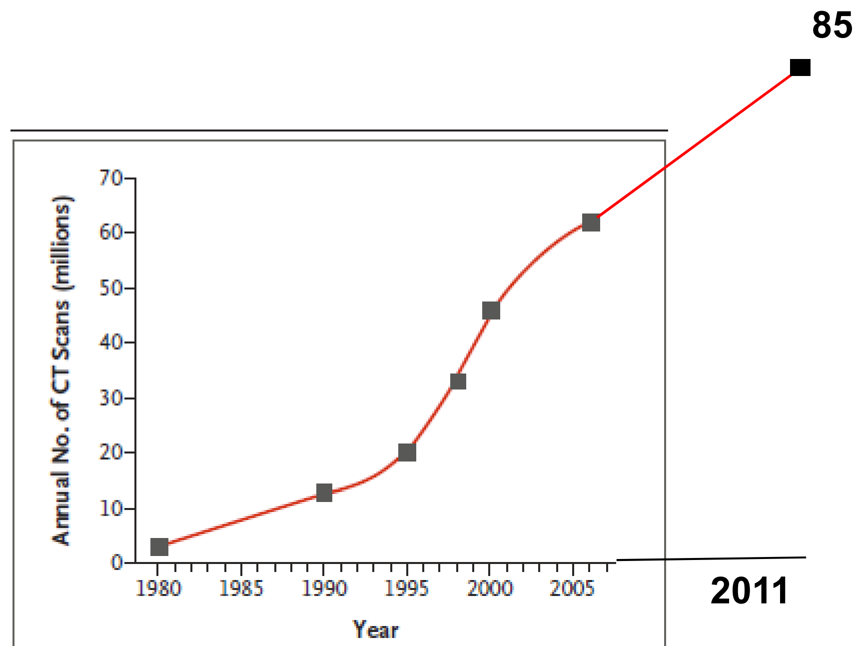


Figure 2. Estimated Number of CT Scans Performed Annually in the United States.

The most recent estimate of 62 million CT scans in 2006 is from an IMV CT Market Summary Report.[3]

Outline - Epidemiology and CT Studies

- Importance of CT Studies
- UK study (Pearce *et al.*, 2012)
- Reverse Causation
- Australian Study (Mathews *et al.*, 2013)
- Dosimetry Limitations
- Conclusions

NCRP (Report No. 171, 2012)
UNSCEAR (Annex B, 2013)
Walsh *et al*. (JRP 2014)

United Kingdom CT Study

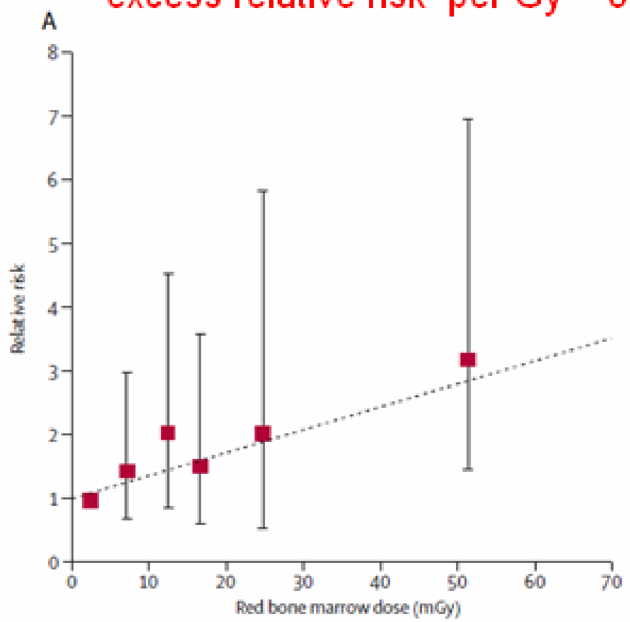
(Pearce *et al.*, Lancet 2012)

- Record linkage study of leukaemia and brain cancer incidence following CT scans to 178,000 persons at ages 0–21 y.
- Collection of scan data for individual patients was not possible. Average CT machine settings from two national surveys were used.
- Significant dose responses reported

Leukemia & MDS

excess relative risk per mGy = 0·036

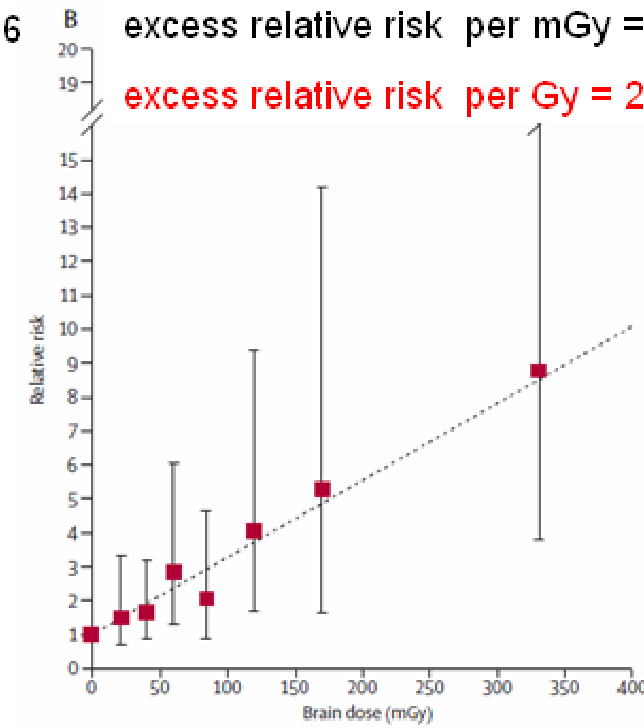
excess relative risk per Gy = 36.

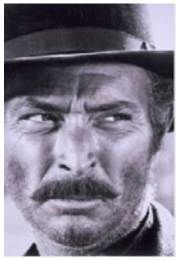


Brain

excess relative risk per mGy = 0·023

excess relative risk per Gy = 23.

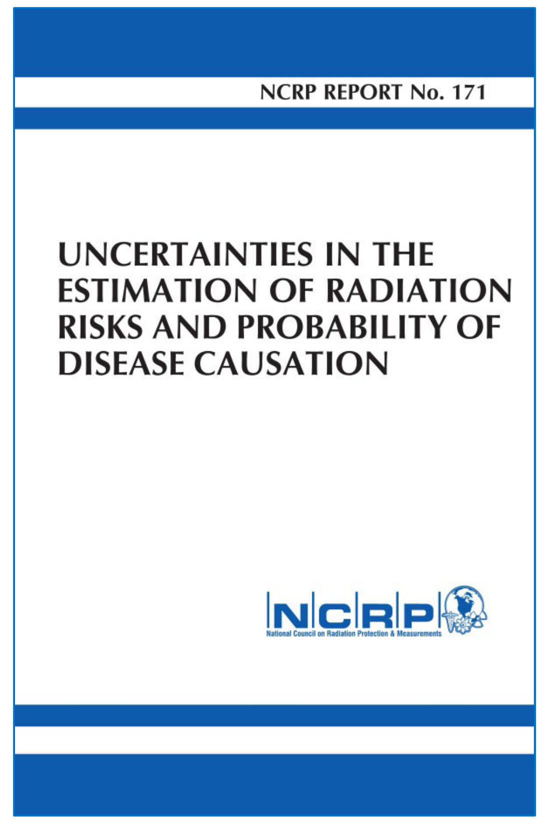




Major Epidemiology Limitation
No Information on Why Scans Performed

NCRP Report No. 171 (2012): UNCERTAINTIES IN THE ESTIMATION OF RADIATION RISKS (Chair: Julian Preston)

"**Children who receive frequent examinations** may have some underlying disability related to the outcome of interest. That is, a child who receives multiple CT exams of the head may have a central nervous system disorder that is prompting such examinations that eventually results in a cancer diagnosis." – Reverse Causation



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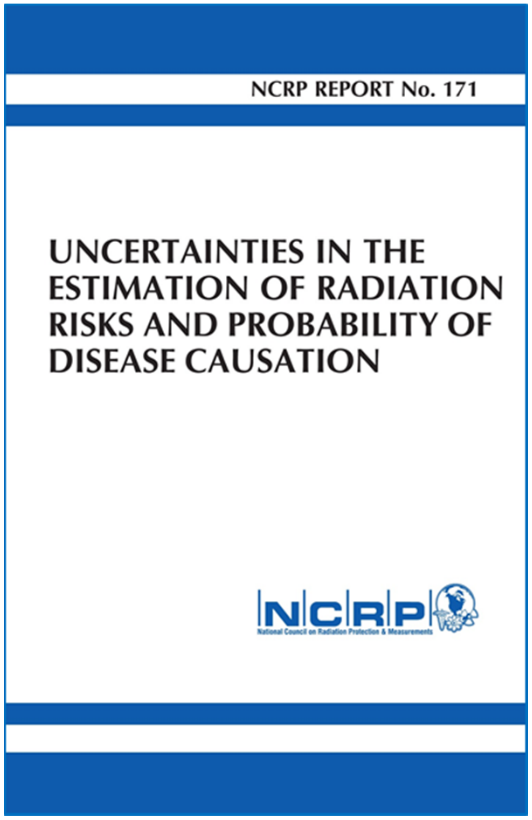

NCRP REPORT No. 171

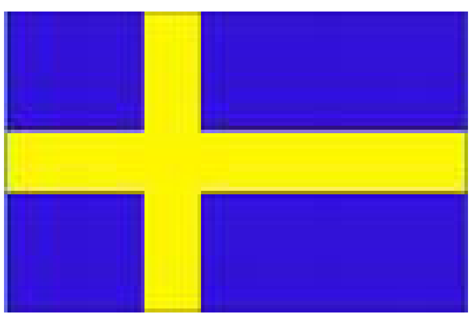
UNCERTAINTIES IN THE ESTIMATION OF RADIATION RISKS AND PROBABILITY OF DISEASE CAUSATION

NCRP

Example of Reverse Causation

- Thyroid cancer following I-131 scans for evaluation of suspected tumor in Sweden among 35,000 adults (ave thyroid dose 0.94 Gy)

Dickman PW, Holm LE, Lundell G, Boice JD Jr, Hall P. Thyroid cancer risk after thyroid examination with ^{131}I: A population-based cohort study in Sweden. Int J Cancer 106(4):580–587; 2003.



We abstracted clinical data for all 35,000 patients, including thyroid size, I-131 activity administered and the reason for the examination.
Holm *et al*., JNCI (1988)

Reason for I-131 Scan All Reasons

Reason for I-131 Scan (No. Cancers)	RR of Thyroid Cancer by Years After I-131 Scan				
	2-	5-	10-	>20	All
All Reasons (105)	3.1*	2.5*	1.2	1.7*	1.8*

- Significant thyroid cancer risk overall (RR 1.8*)

Note that the adult thyroid gland is not considered radiosensitive.

Reason for I-131 Suspicion of Tumour

Reason for I-131 Scan (No. Cancers)	RR of Thyroid Cancer by Years After I-131 Scan				
	2-	5-	10-	>20	All
All Reasons (105)	3.1*	2.5*	1.2	1.7*	1.8*
Suspicion of Tumour (69)	6.3*	4.8*	2.3*	3.5*	3.5*

- Risk very high when reason for scan was a suspicion of tumour (RR 3.5*)

Reason for I-131
Other Than Suspicion of Tumour

Reason for I-131 Scan (No. Cancers)	RR of Thyroid Cancer by Years After I-131 Scan				
	2-	5-	10-	>20	All
All Reasons (105)	3.1*	2.5*	1.2	1.7*	1.8*
Suspicion of Tumour (69)	6.3*	4.8*	2.3*	3.5*	3.5*
Other Reasons (36)	1.3	1.5	0.6	0.9	0.9

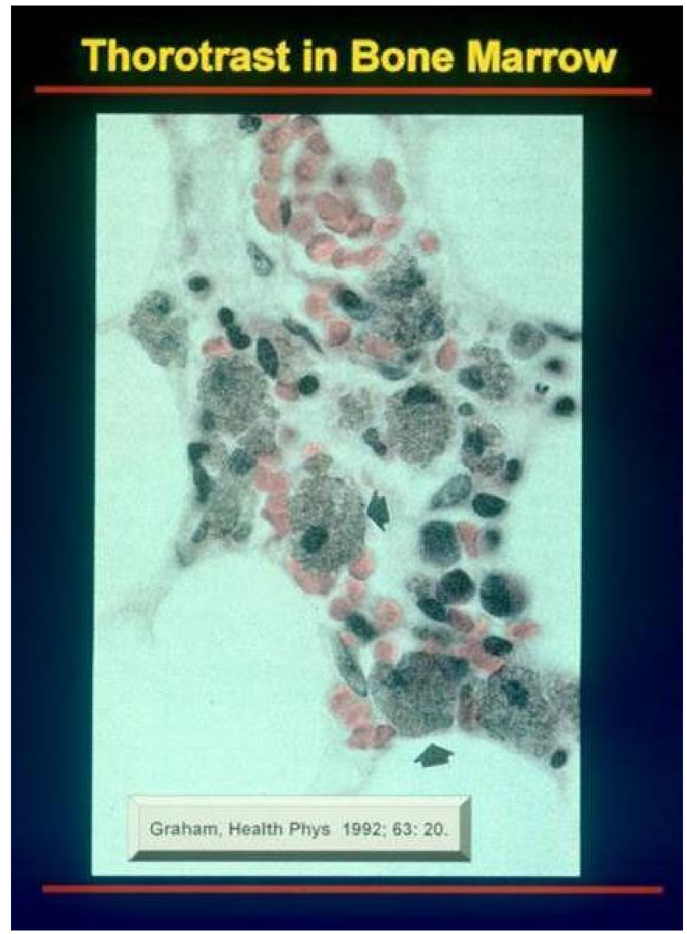
- No excess risk if scan performed for "other reasons" (RR 0.9), e.g., hyperthyroidism and hypothyroidism.

Reverse Causation Bias Lasted for More Than 20 y After 131-I Exam

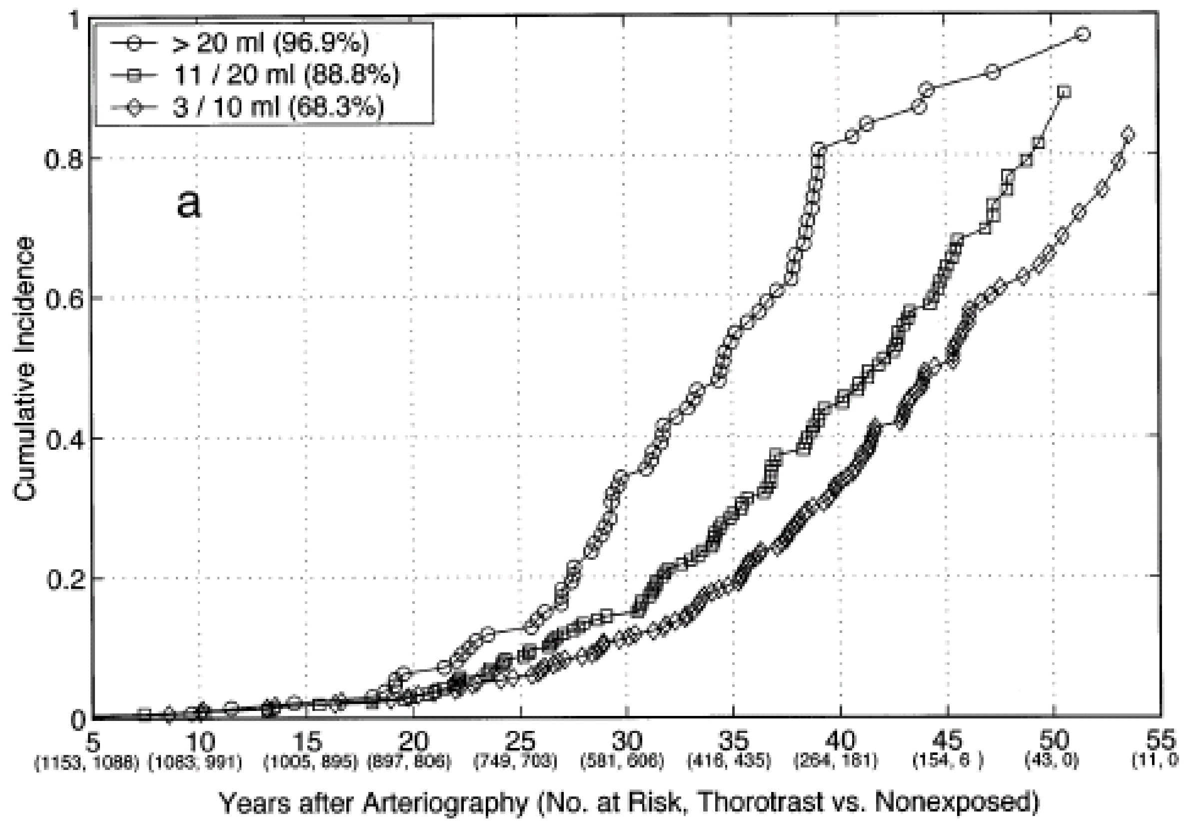
Reason for Scan (No. Cancers)	RR of Thyroid Cancer by Years After Scan 2-	5-	10-	>20	All
All Reasons (105)	3.1*	2.5*	1.2	1.7*	1.8*
Suspicion of Tumour (69)	6.3*	4.8*	2.3*	3.5*	3.5*
Other Reasons (36)	1.3	1.5	0.6	0.9	0.9

- The "suspicion of tumour" predicted future diagnoses of cancer even 20 y after examination

Thorotrast - Thorium Solution Contrast Agent



Cumulative Cancer Incidence After Thorotrast, Excluding Brain



The U.S. study population included patients exposed to Thorotrast during cerebral angiography at the Massachusetts General Hospital in Boston, MA and the Lahey Clinic in Burlington MA (Travis *et al*., 2001, 2004),

Thorotrast – Brain Cancer

(thorium dioxide solution)

Site-Specific Cancer Mortality Among Thorotrast-Exposed & Nonexposed Patients in the United States

Cancer	Thorotrast-Exposed		Comparison Group		Relative Risk	
	OBS	SMR	OBS	SMR	RR	95 % CI
Brain & other CNS	21	33.6	6	15.6	1.3	0.6 – 3.7

Patients who have examinations because of a suspicion of tumor usually are more likely to develop the tumor regardless to whether the exam included radiation or not. Travis *et al*. (2004) Reverse Causation.

Dental X-Rays and Risk of Meningioma
Reverse Causation

Association reported between dental x-rays and meningiomas (Claus *et al*., 2012) based on interviews. However:

- Meningiomas can cause referred pain to the orofacial region.
- A patient with such pain may receive dental x-rays during the course of their care.
- It may be that radiographs do not cause meningiomas but rather the presence of the tumors triggers the need for radiographs.

White *et al*., Cancer 2012

Radiation Exposure from CT Scans in "Childhood" . . . ‹22 y of age

Mother and 21 y old son

Radiation Exposure from CT Scans in "Childhood" . . . <22 y of age

Mother and 21 y old son

- A 21 y old is not a child

Age at Exposure Effect in UK Study Implausible - Risk Increased with Age

Age at Exam	ERR/Gy
0 -	5
5 -	28
10 -	37
15 -	41

Israeli tinea capitis [S5] – Malignant brain tumours		*Average ERR[a] at 1 Sv*
Age at exposure	0–4 years	3.6 (1.0, 9.9)
	5–9 years	2.2 (0.8, 5.5)
	10–15 years	0.5 (<0, n.a.)

UNSCEAR 2013: "The risk of glioma is highest at < 5 years at irradiation and seems to largely disappear at the age of 20 years or more at irradiation, suggesting that **susceptibility decreases as brain development nears completion**."

Australian CT Study

(Mathews *et al.*, BMJ 2013)

- Data Linkages study of 680,000 children (0-19 y) who received CT scans and 10,000,000 with no record of such exposures.
- Excesses reported for practically all cancers:
  - Digestive organs
  - Melanoma
  - Soft tissue
  - Female genital
  - Urinary tract
  - Brain
    - after brain CT scan
    - after other CT scan
  - Thyroid
  - Leukaemia (myeloid)
  - Hodgkins lymphoma

But not for:

- Breast Cancer
- Lymphoid Leukaemia

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Cancers not know to be increased after radiation — are increased

But not for:

- Breast Cancer
- Lymphoid Leukaemia

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  - Thyroid
  - Leukaemia (myeloid)
  - Hodgkins lymphoma

Brain cancers increased whether or not the brain was exposed.

But not for:
- Breast Cancer
- Lymphoid Leukaemia

UNSCEAR 2013 – Latency Too Short and Risks Too High

- The appearance within five years of first CT scan of a significant excess of solid cancers is implausibly early.

- The risk estimate for all cancers, excluding brain cancer after brain CT is statistically incompatible with the Japanese study on atomic-bomb survivors (ERR/Sv 27 vs 3)

UNSCEAR

Major Epidemiology Limitation
No Information on Why Scans Performed

UNSCEAR 2013: EFFECTS OF RADIATION EXPOSURE OF CHILDREN
(Consultant: Fred Mettler – Former C3 Chair)

"… there are concerns about the risk estimates because of lack of information about indications for the CT scans and the consequent potential for '**reverse causation**' (i.e. cancers may have been caused by the medical conditions prompting the CT scans rather than by the CT dose) and **lack of individual dosimetry**. "

UNSCEAR

Taiwan Head CT and Benign Brain Tumor

Huang *et al.*, Br J Cancer 2014

- 24,000 children with head CT with 4-1 match to nonexposed children. Excluded everyone with cancer or conditions predisposing to brain tumor. Significant association with benign, but not malignant, tumor reported.
- Apparently did not exclude those with benign tumors.
- Small numbers, only 5 malignant and 14 benign tumors
- Risk decreased with time since CT exam
- Youngest not at highest risk
- Reverse causation implies that it is the early symptoms of undetected tumor, or of factors that predispose to tumor, that are the indications for the CT scans, rather than the CT scans *per se* that are causing the apparent excess risk of cancer.

What To Do?

"Hopefully, CT studies that are now under way, such as the 'EPI-CT' study in Europe (see www.epi-ct.iarc.fr), will shed additional light on historical paediatric CT doses, have fewer 'missed doses', and be better able to address issues of possible risk factor confounding and reverse causation by, for example, establishing the reason(s) for an examination." (Walsh *et al*., JRP 2014).

Estimated size of cohorts

Summary

Cumulative exposure to high doses of diagnostic radiation may cause cancer later in life

We'll never detect cancer increases following a single CT. It may be tiny, it may be zero. But multiple CTs are a concern – thus medical benefit should be clear and dose ALADA (As Low As Diagnostically Acceptable)

Current studies of pediatric CT are not interpretable because of potential for confounding by indication and absence of individual dosimetry.

Good epidemiology could address the reasons for examination, provide individual dosimetry, and attempt to capture "missing doses".

Meanwhile, it would seem prudent to assume that the low doses of radiation received during a CT scan may produce a small additional risk of cancer, and clinical practice might be guided by this assumption.

Vanderbilt-Ingram Cancer Center


LUCY, AS YOUR MANAGER, I MUST INSIST THAT YOU SEE A DOCTOR ABOUT YOUR ARM
HE WON'T HURT YOU...ALL HE'LL DO IS TAKE A FEW X-RAYS...
ARE YOU CRAZY?!
THOSE X-RAYS DESECRATE YOUR BONES!
SCHULZ

Thank you!

Informative References on CT Studies

Critique of Both Studies

UNSCEAR 2013: *EFFECTS OF RADIATION EXPOSURE OF CHILDREN*

Walsh L, Shore R, Auvinen A, Jung T, Wakeford R. Risks from CT scans-what do recent studies tell us? J Radiol Prot. 34(1): Epub 2014 Mar 4.

Critique of UK Study

NCRP Report No. 171 (2012): *UNCERTAINTIES IN THE ESTIMATION OF RADIATION RISKS*

Critique of Australian Study

Walsh L, Shore R, Auvinen A, Jung T, Wakeford R. BMJ 4 June 2013 (http://www.bmj.com/content/346/bmj.f2360/rr/648506)

Boice J. Health Physics News July 2013.

Example of Reverse Causation (Confounding by Indication)

Dickman PW, Holm LE, Lundell G, Boice JD Jr, Hall P. Thyroid cancer risk after thyroid examination with 131I: A population-based cohort study in Sweden. Int J Cancer 106(4):580–587; 2003.