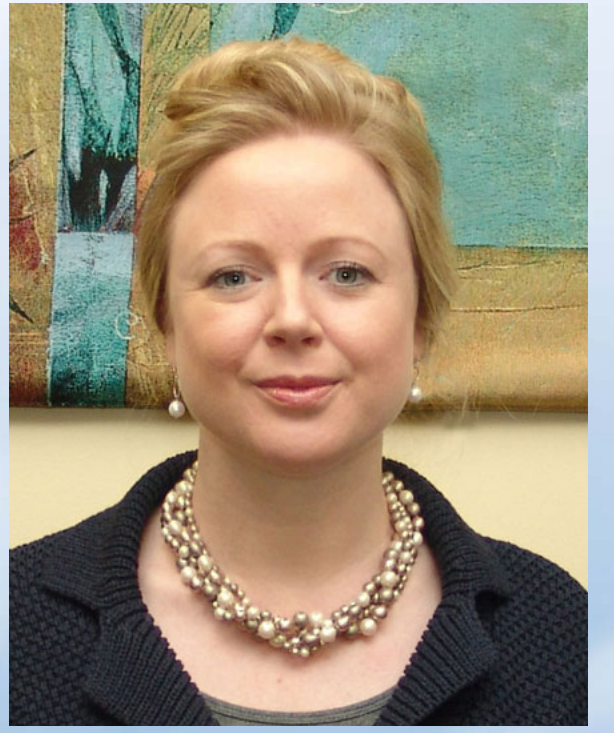
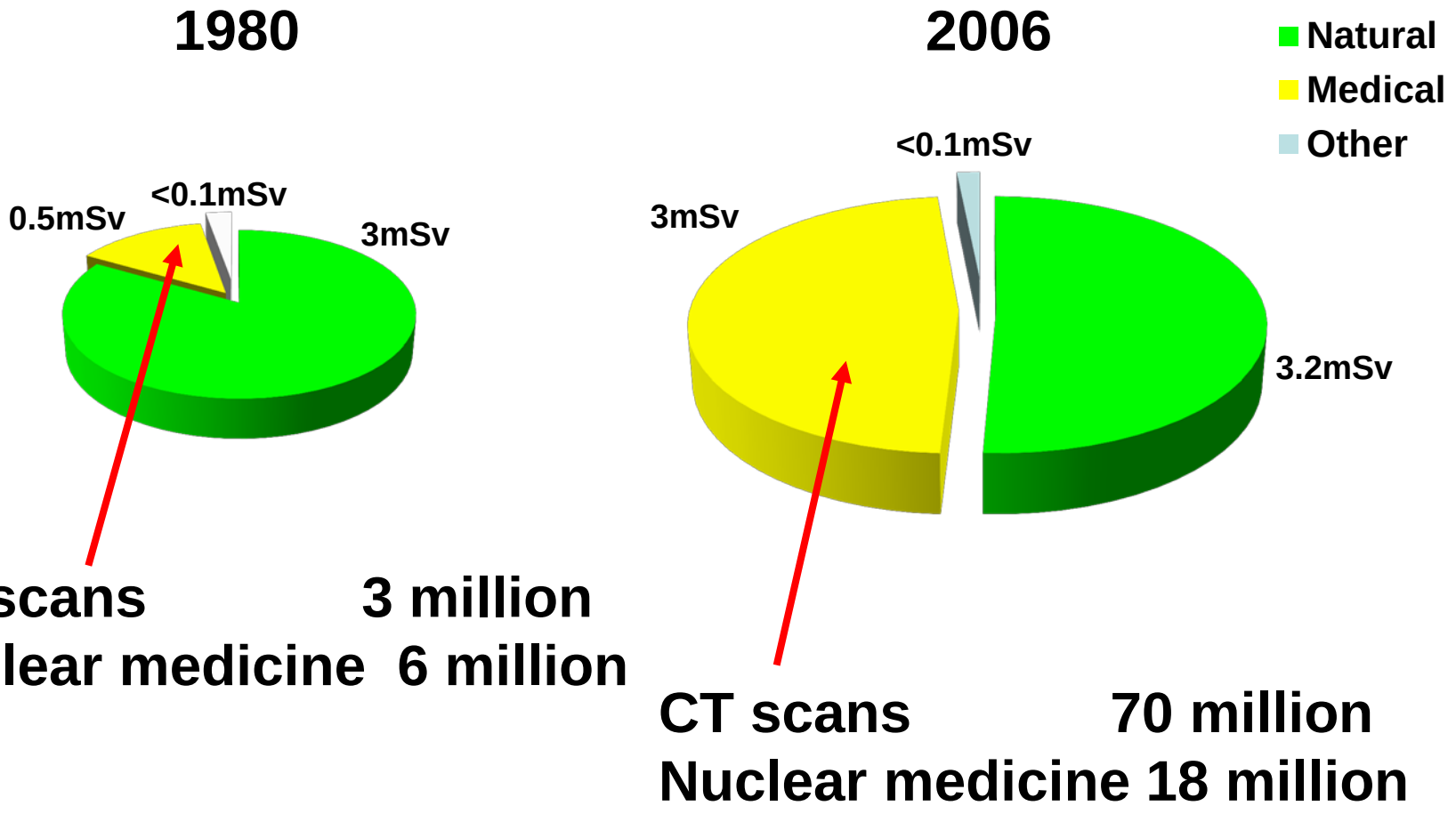
Amy Berrington de González, D.Phil.
Chief, Radiation Epidemiology Branch
and Senior Investigator



Diagnostic Imaging, Screening and Cancer Risk

Radiation Epidemiology & Dosimetry Course

Dramatic Increase in Medical Exposures in the U.S.

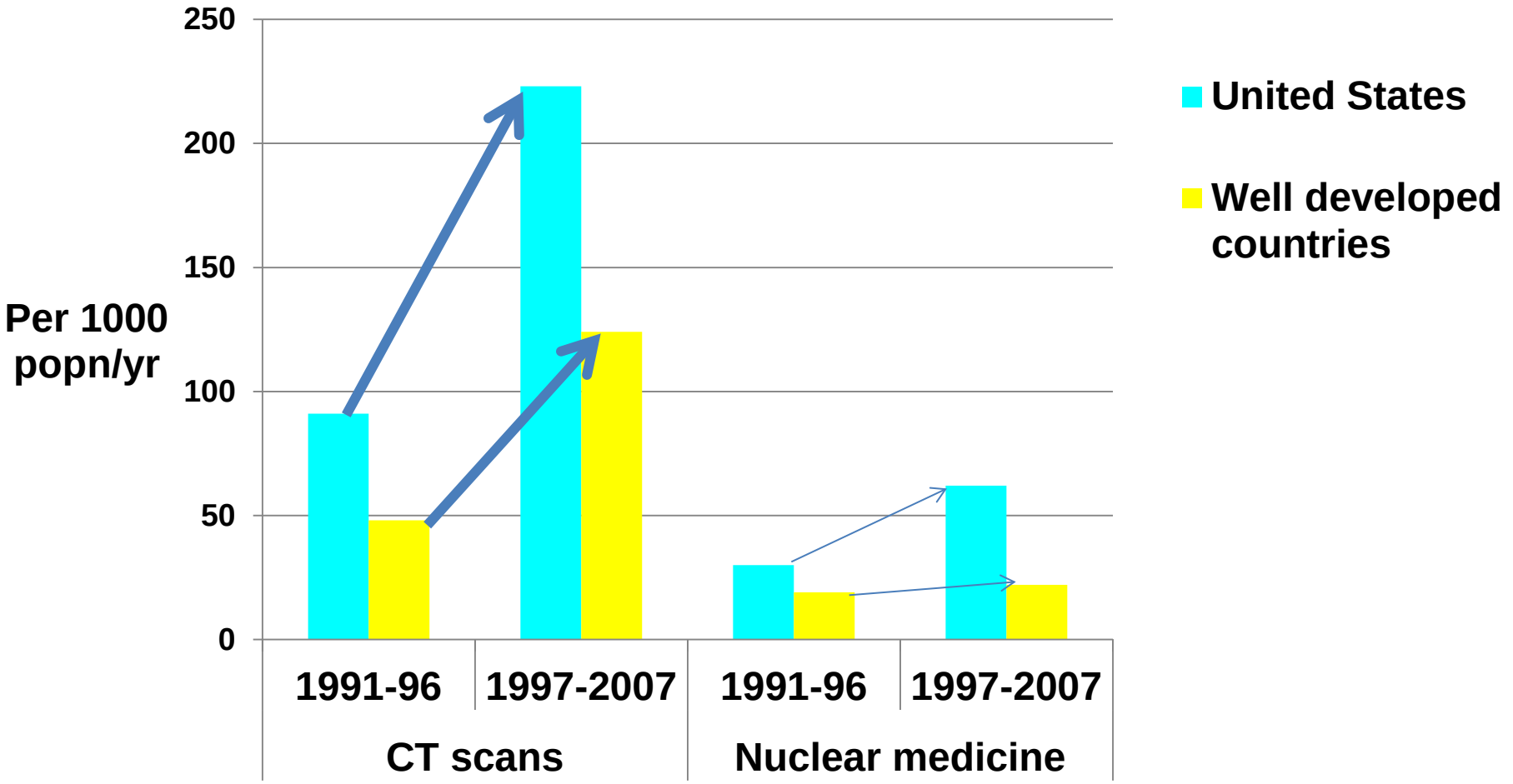


CT scans 3 million
Nuclear medicine 6 million

CT scans 70 million
Nuclear medicine 18 million

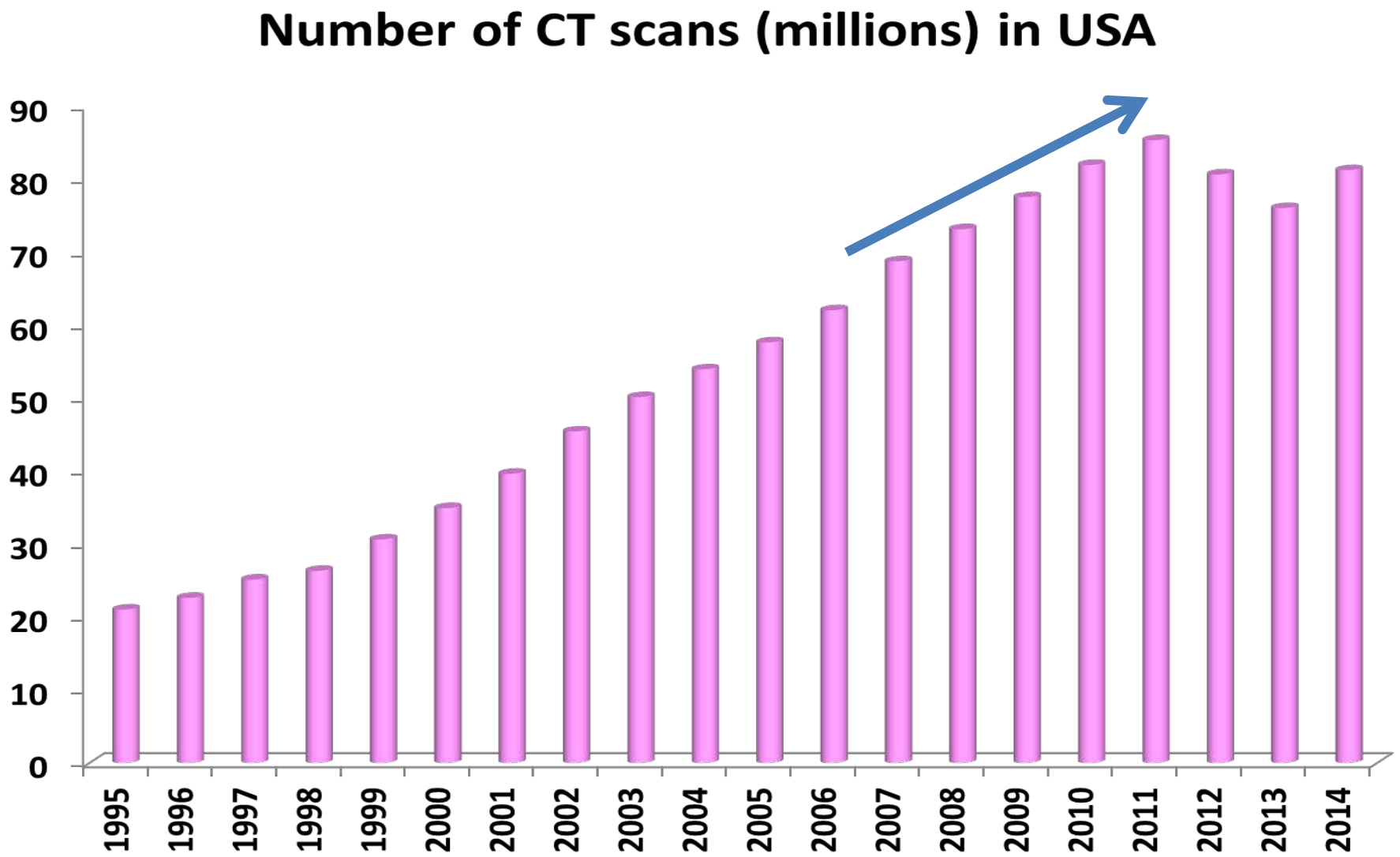
NCRP report 160 (2009)

International Trends in Diagnostic Imaging



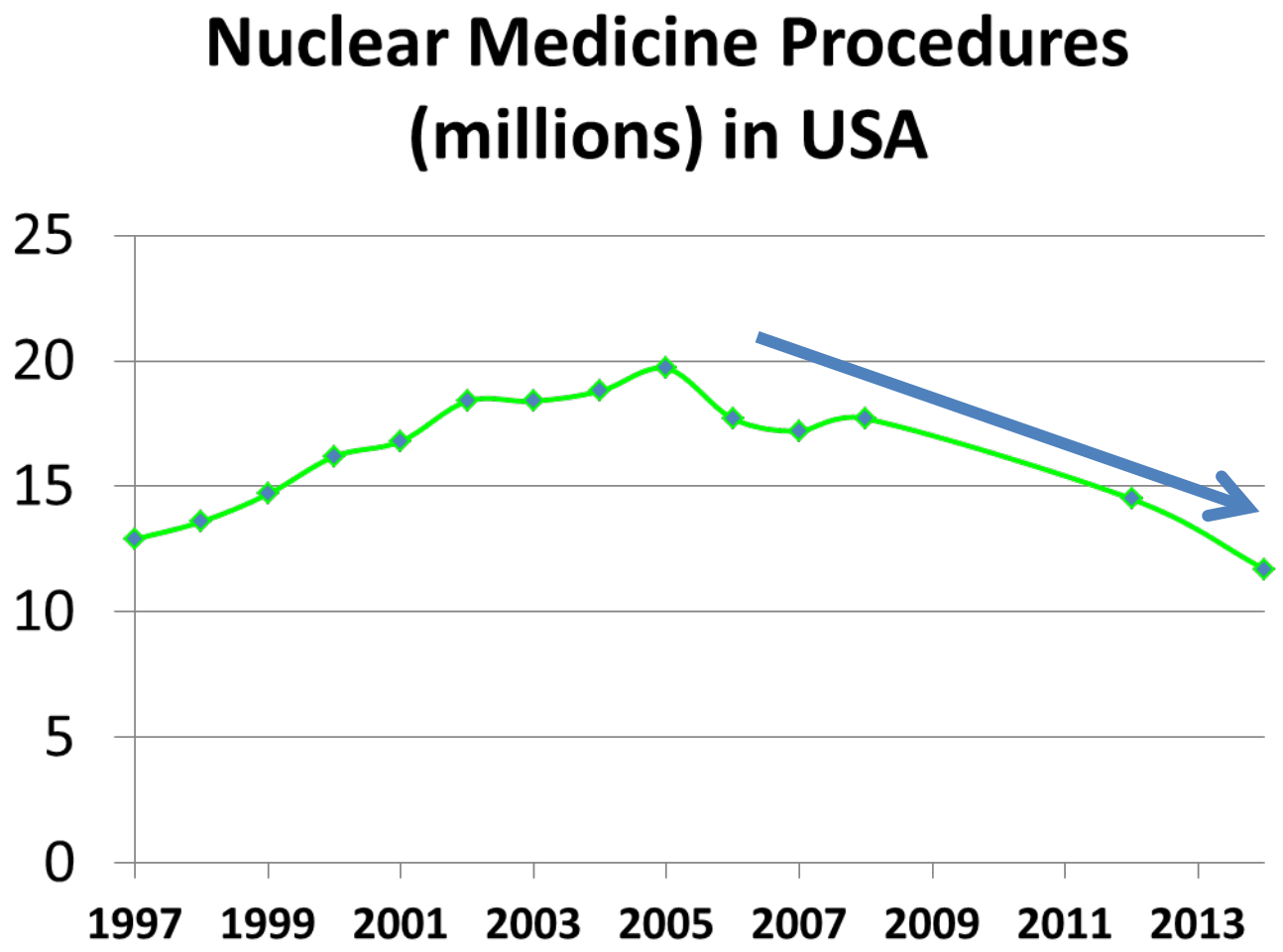
Mettler et al (Radiology 2009)

Recent Trends in CT use in the USA



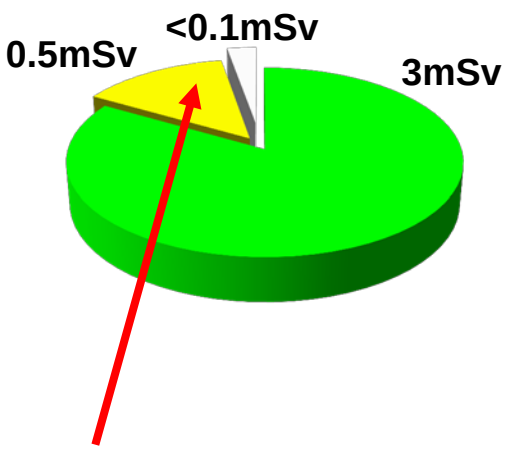
IMV 2014

Recent Decline of 10%/year in Nuclear Medicine



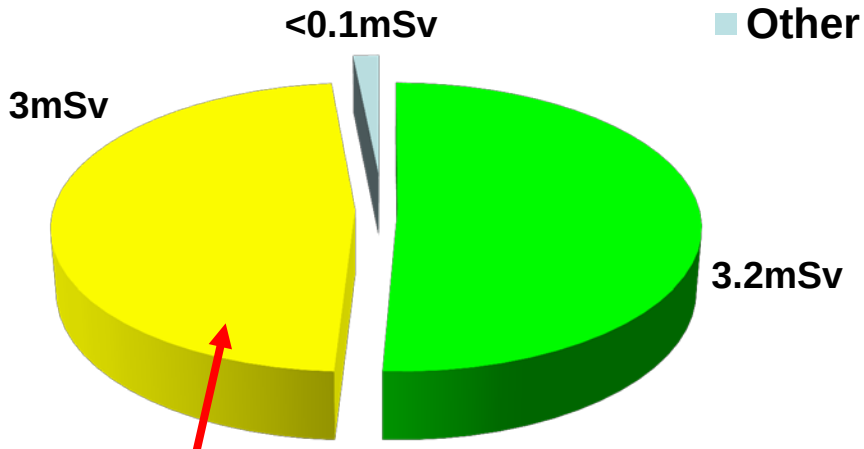
Radiation Exposure in the U.S. (updated)

1980



CT scans 3 million
Nuclear medicine 6 million

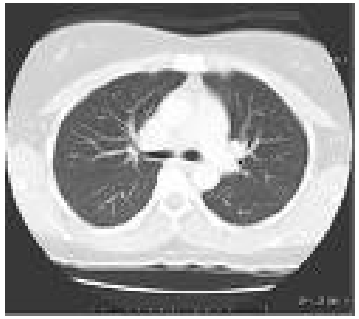
2015?



CT scans 80 million (+10)
Nuclear medicine 12 million (-6)

Diagnostic Imaging - Effective & Organ Doses

Procedure	X-ray	CT scan
Skull	0.1 mSv	2 mSv
Chest	0.1 mSv	7 mSv
Abdomen	0.7 mSv	8 mSv



CT scan	Brain	Lung	Stomach
Skull	40 mGy	0 mGy	0 mGy
Chest	0 mGy	20 mGy	6 mGy
Abdomen	0 mGy	3 mGy	20 mGy

Mettler et al (Radiology 2009)

Why Study Diagnostic Radiation & Cancer Risk?

- Public health concern & Clinical decision making
- Radiation carcinogenesis
  - Low-dose fractionated exposures
  - Medical records – exposure history
  - Any organ & exposure age

Methodological Issues

- Case-control vs cohort
- Sample size
- Exposure assessment
  - Medical records
  - Self-reported
  - Dose reconstruction
  - Organ doses
- Timing of exposure
  - Age at exposure
  - Latency period
- Confounding by indication (underlying conditions)

Pediatric CT Scans & Cancer Risk

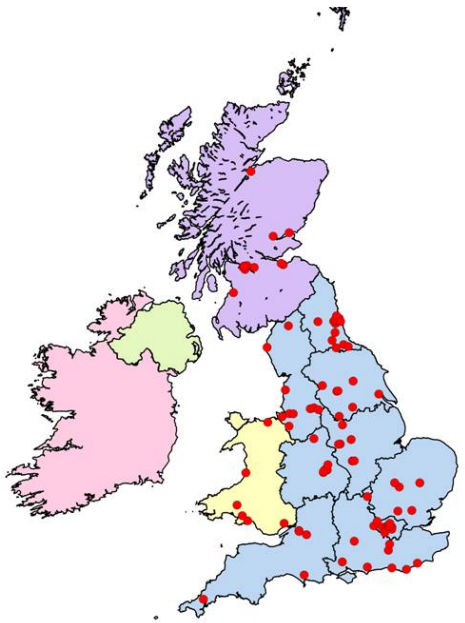
- Higher doses & risks for children
  - Patient size
  - Adult settings in past (<2000)
  - Head CT 60 mGy brain
  - Chest CT 30 mGy breast

Retrospective, record linkage studies of 2+ million children

- NCI-UK Cohort – 200k
- European Study EPI-CT – 1 million
- Canada (n=400k), Israel (n=70k) and Australia (n=680k)

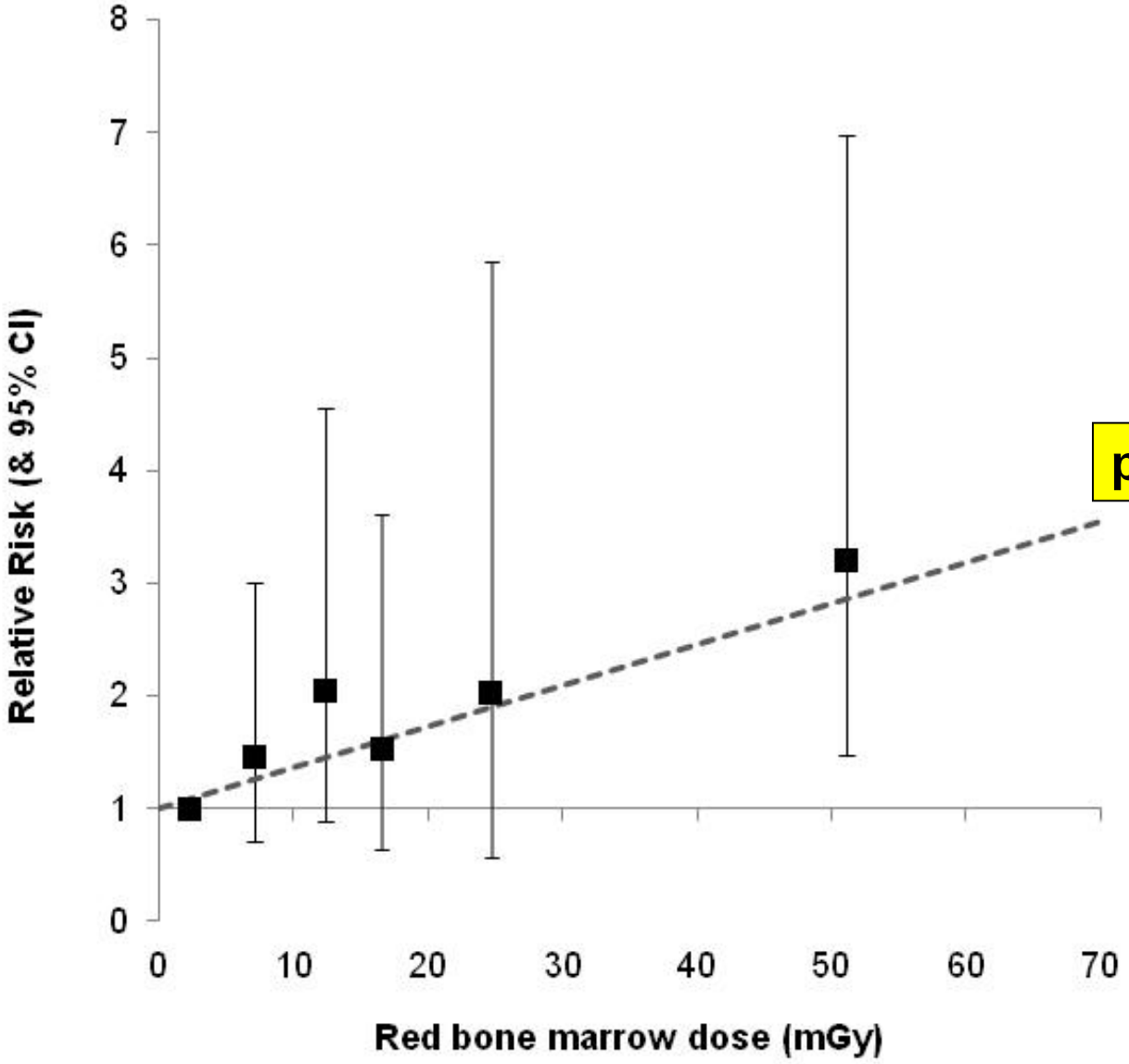
NCI-UK Pediatric CT scan Cohort

- **1990-2002 CT scans aged 0-21 yrs**
- **Link to cancer registrations, vital status**
- **Organ dose estimates – generic dosimetry**
- **Leukemia & brain tumors dose-response**



Pearce et al (Lancet 2012); Kim et al (Radiat Prot Dosimetry 2012)

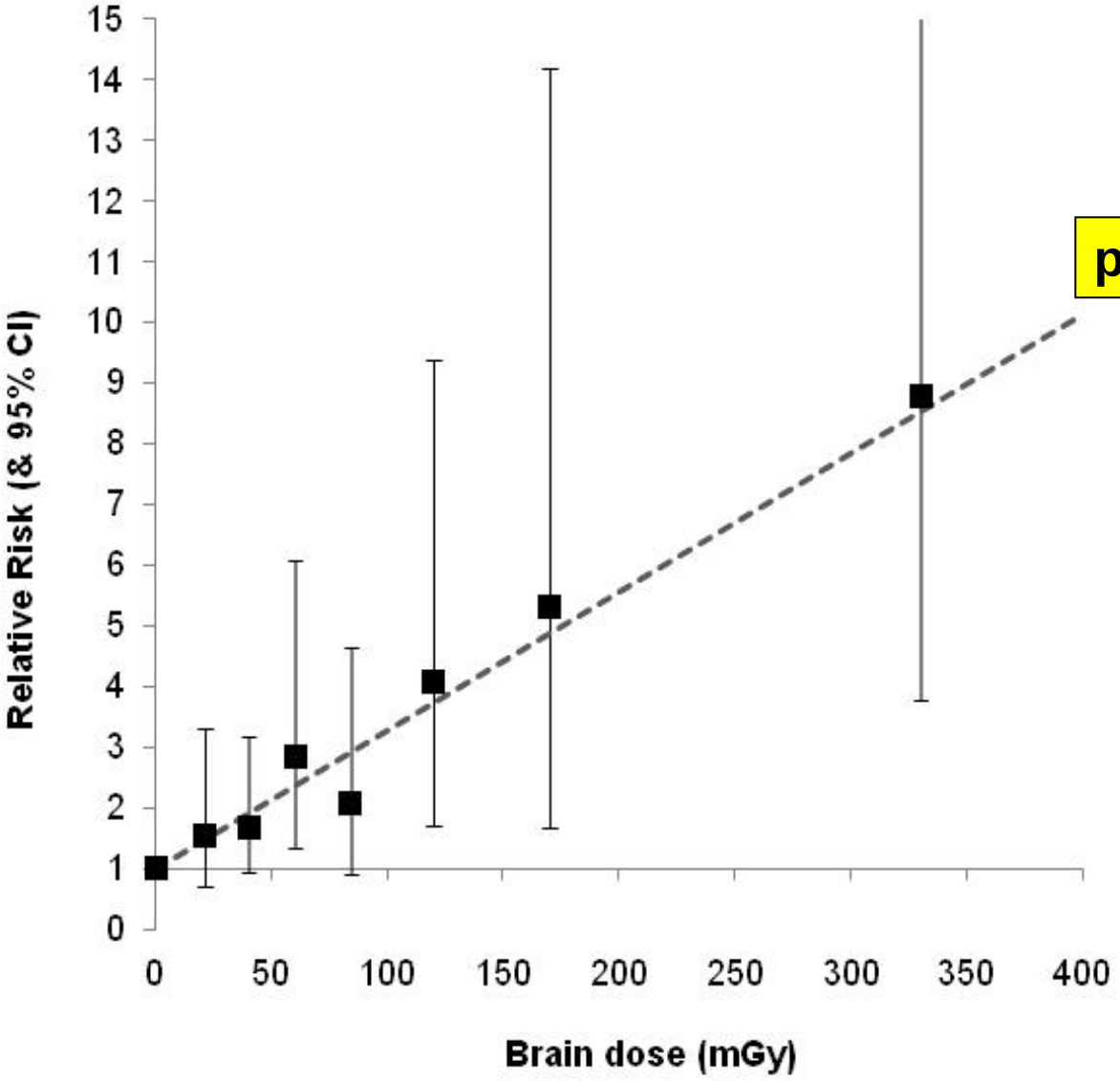
Leukemia/MDS and Radiation Dose to Red Bone Marrow



p-trend=0.010

Pearce, Salotti, Little, McHugh, Lee …, Berrington de Gonzalez (Lancet 2012)

Brain Tumors and Radiation Dose to Brain

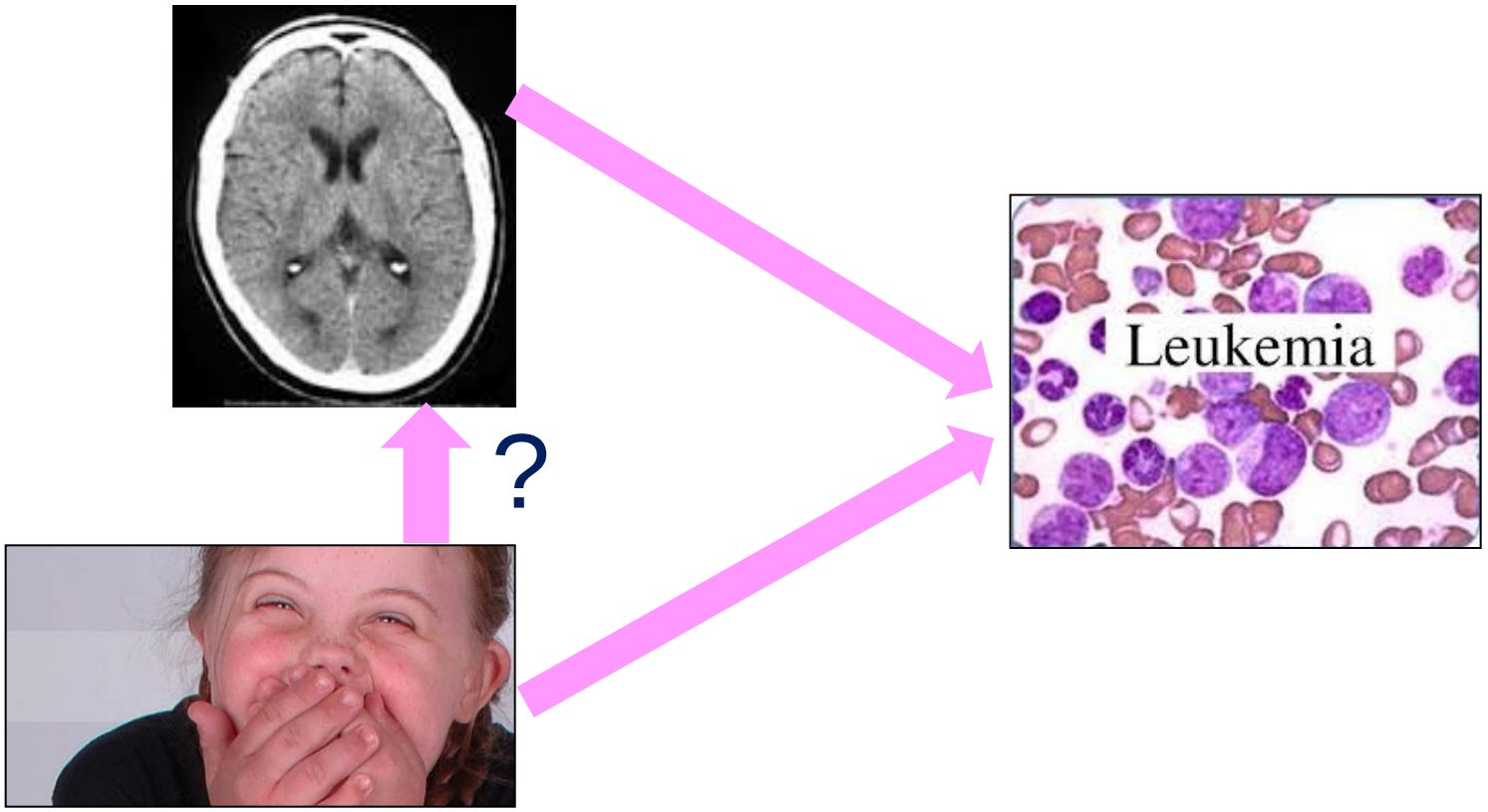


p-trend<0.0001

Pearce, Salotti, Little, McHugh, Lee …, Berrington de Gonzalez (Lancet 2012)

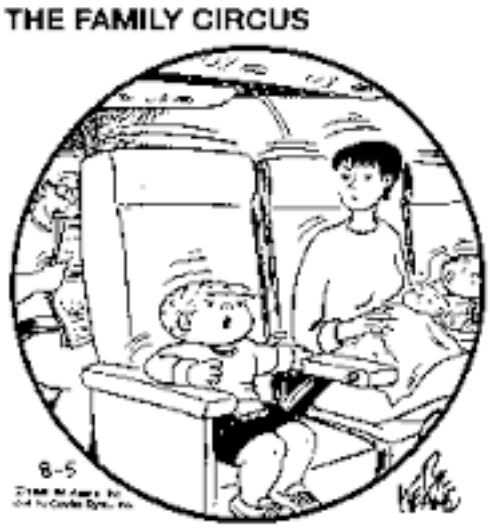
Leukemia - Confounding by Indication?

Underlying condition related to cancer & the condition related to CT scan frequency



Reproduced from DOWN'S SYNDROME ASSOCIATION Website (www.downs-syndrome.org.uk)

Reverse Causation – Brain Tumors?



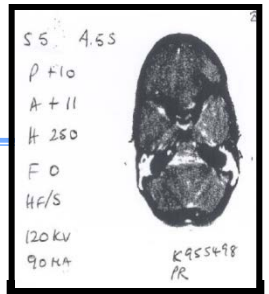
"I wish they didn't turn on that seatbelt sign so much! Every time they do, it gets bumpy."

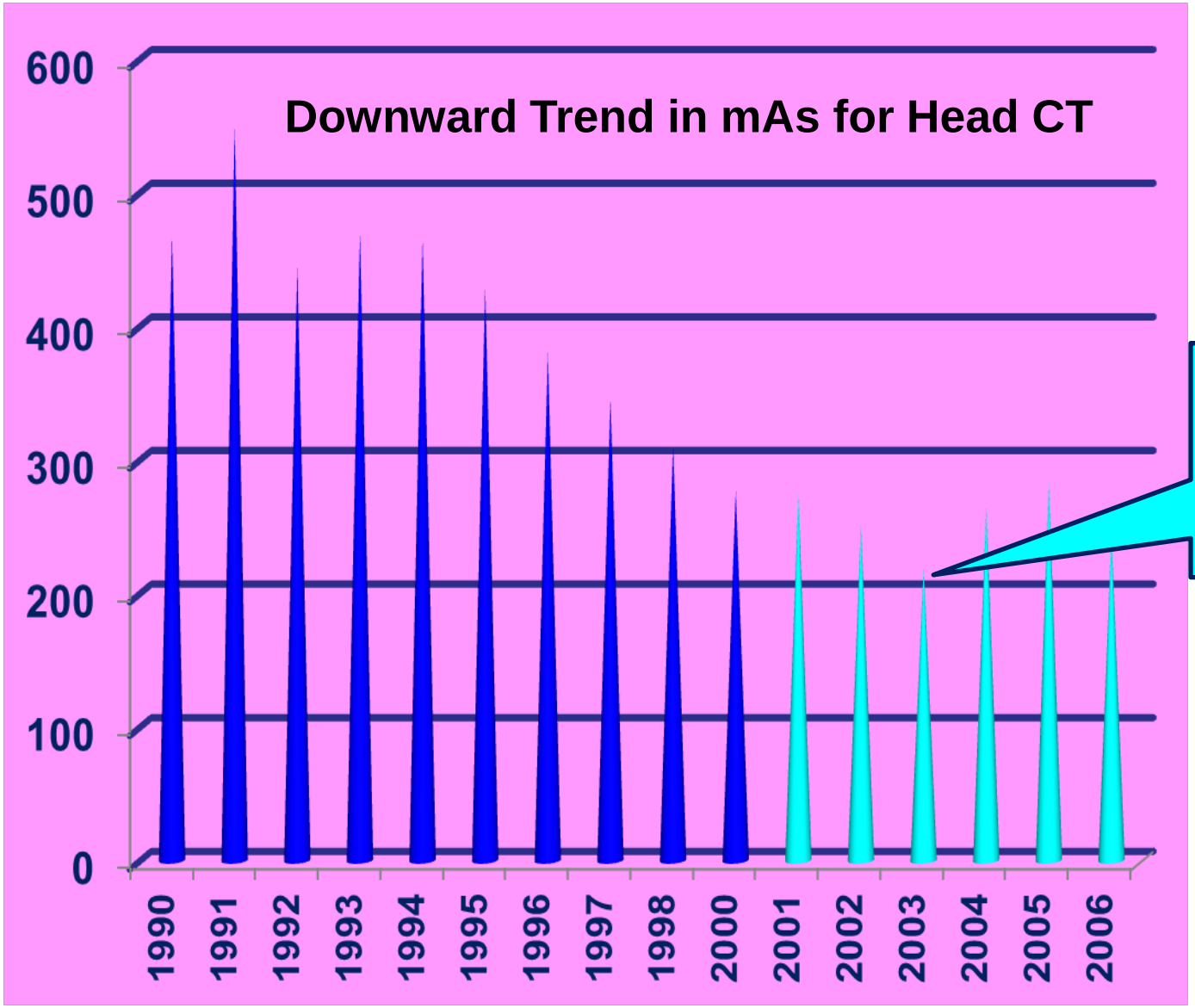
Impact of Excluding Underlying Conditions

ERR/mGy	UK CT Study	UK CT Study (after exclusions)	Life Span Study
Leukemia	0.036 (0.005-0.12) (n=74)	0.031 (0.003, 0.109) (n=70)	0.045 (0.016-0.188)
Brain tumors	0.023 (0.010-0.049) (n=135)	0.012 (0.004, 0.031) (n=112)	0.006 (0.0001-0.063)

Berrington de Gonzalez et al

Collection of CT Films to Improve Dosimetry/Uncertainty





0-4 yrs	195
5-9 yrs	240
10-14 yrs	280

Ongoing Pediatric CT Scans Cohorts

Australian Cohort

- **680k exposed children, 11m unexposed**
- **RR=1.16 per CT (1.13-1.19)**
- **Excesses of leukemia, MDS, brain, thyroid, melanoma, lymphomas… but only 1 year exclusion period**
- **Dosimetry ongoing**

French Cohort

- **67k exposed children (2000-2010)**
- **Mean follow-up 4 years (n=27 brain, 25 leukemia, 21 lymphomas)**
- **32% cases had cancer pre-disposing syndromes**

German Cohort

- **45k exposed children (1980-2010)**
- **46 childhood cancers**
- **Exclusion 2 years but 7 cases excluded due to evidence of cancer on CT**

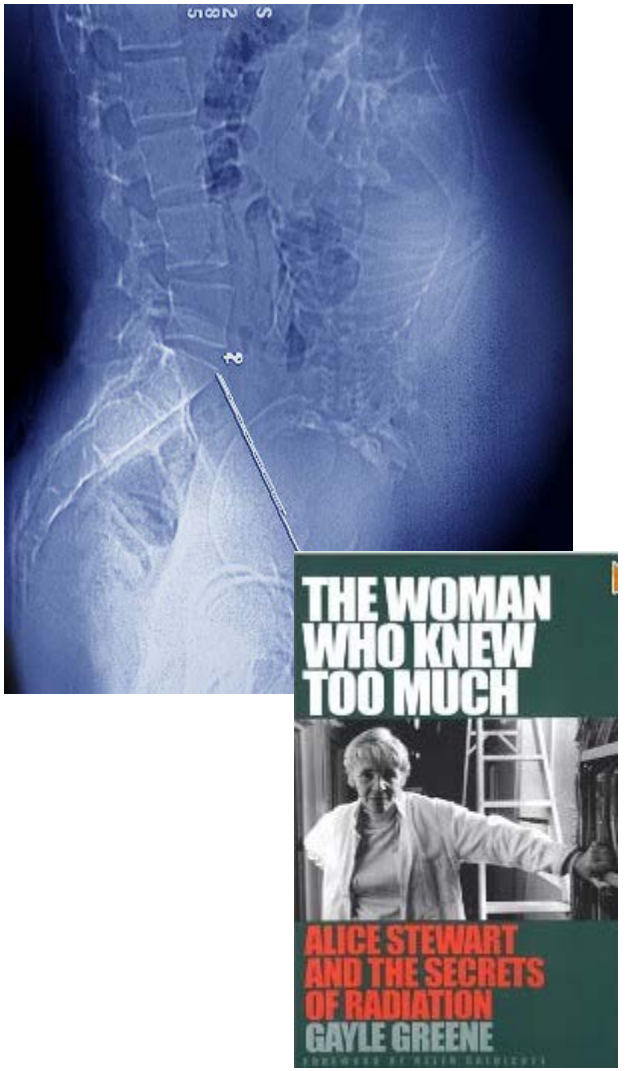
EPI-CT 1+million children: results due 2017

Mathews et al (BMJ 2013); Journy et al (Br J Cancer 2014); Krille et al (Radiat Environ Biophys 2015)

In Utero Exposures & Childhood Cancer

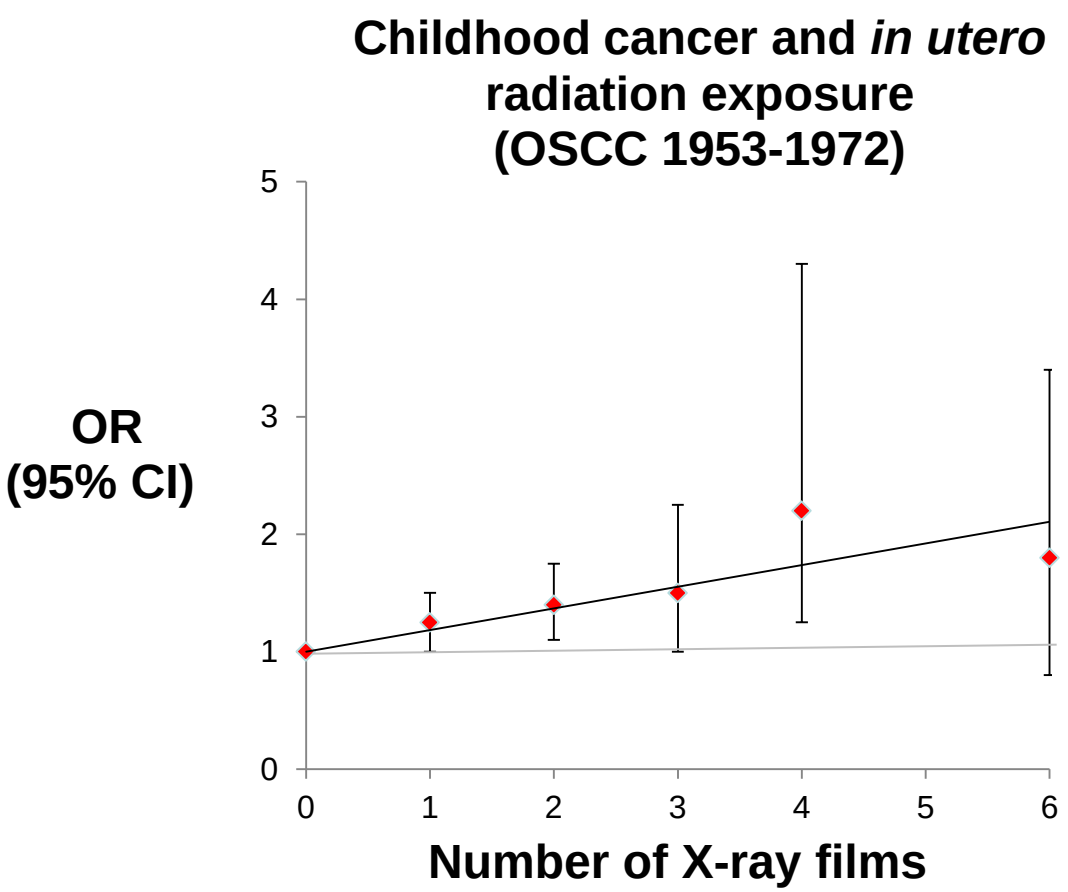
- **OSCC 15,300 case-control pairs**
  - **Self-reported exposures**
  - **OR=1.39 (1.30-1.49)**
- **US medical records**
  - **OR=1.47 (1.22-1.77)**
- **Meta-analysis RR=1.38 (1.31-1.47)**
  - **Similar for Leukemia & other cancers**

- **Cohort studies RR=1.13 (0.84-1.53)**
  - **25 cases**



Doll and Wakeford (Br J Radiology 1997); Wakeford (Radiat Prot Dosimetry 2008)

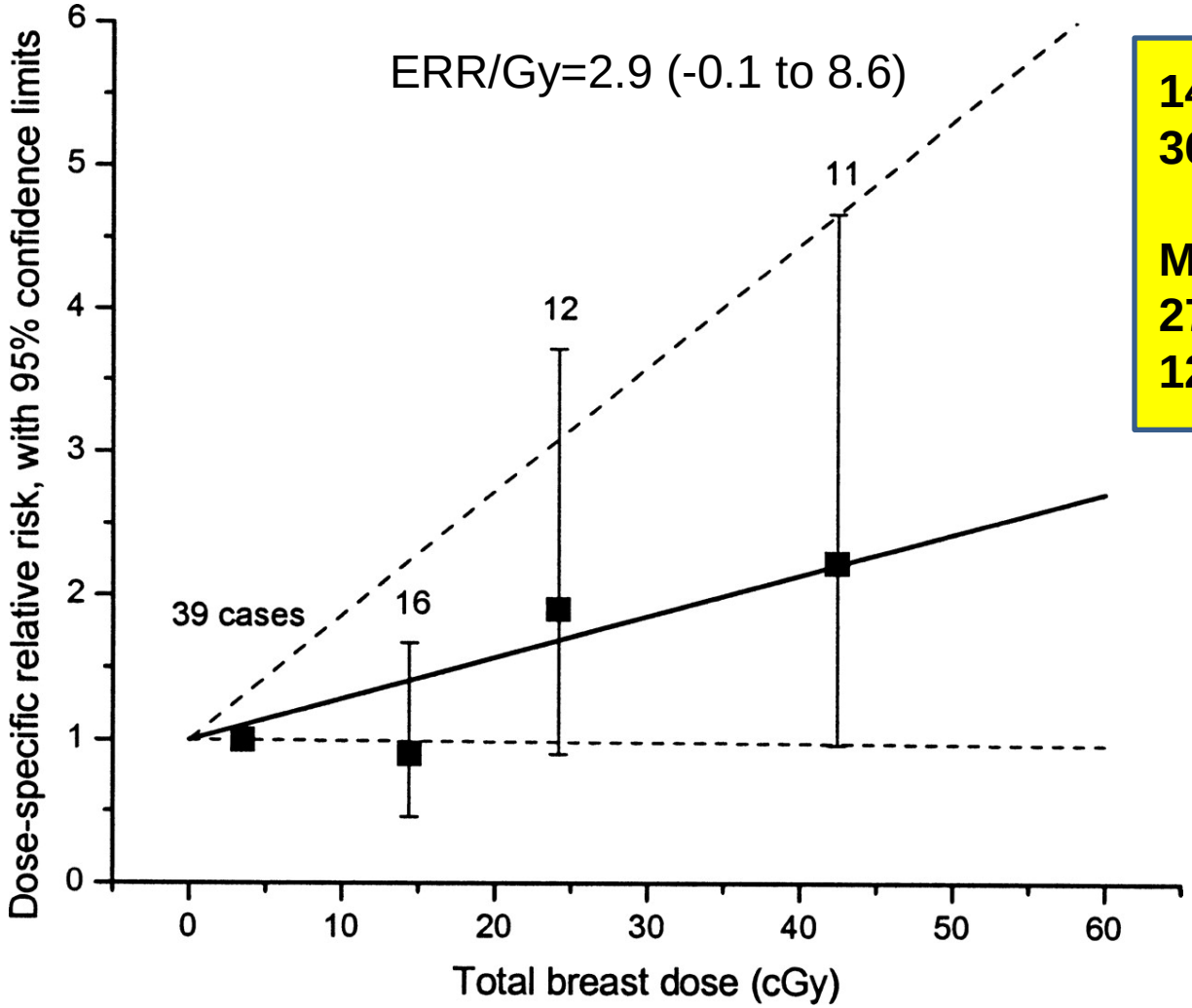
In Utero Exposures cont.



- Dose per film
  - 15mGy 1940s
  - 3mGy 1960s
- Decline in risk by birth cohort

Doll and Wakeford (Br J Radiology 1997)

Radiation Dose Response for Breast Cancer & Multiple Spine X-rays in 3,002 Scoliosis Patients



140,000 X-rays
36 years follow-up

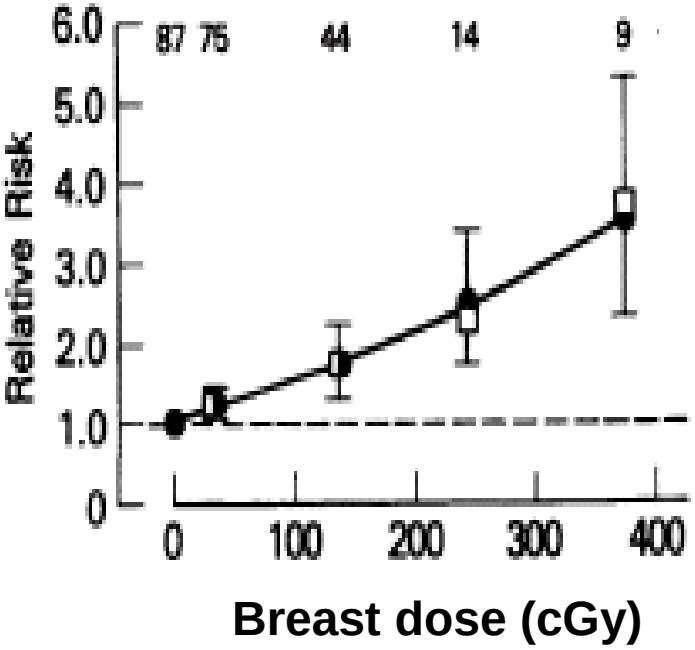
Mean (range):
27 (0-332) X-rays
120 (0-1110) mGy

Ronckers et al (Cancer Epidemiol Biomarkers Prev 2008)

Breast Cancer & Multiple Fluoroscopies in TB Patients

Massachusetts TB 4940 women (1925-54)

- **Mean dose 0.8Gy (88 exposures)**
- **234 breast cancers**
- **RR=1.61 at 1Gy**

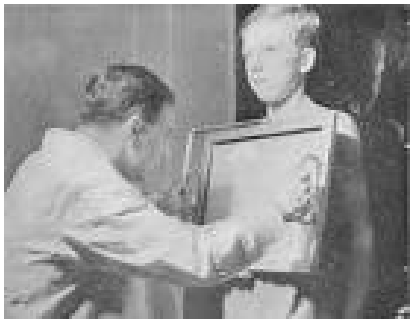


Canadian TB 31,710 women (1930-1952)

- **688 breast cancer deaths**
- **RR=1.36 (1.11-1.67) at 1Gy**

Boice et al (Radiat Res 1991); Howe and McLaughlin (Radiat Res 1996); Howe (Radiat Res 1995) ;

Lung Cancer & Multiple Fluoroscopies in TB Patients



Massachusetts 13,572 patients (Mean dose 0.8Gy)

- **357 lung cancer deaths by 2002**
- **ERR/Gy -0.04 (-0.11 to 0.14)**

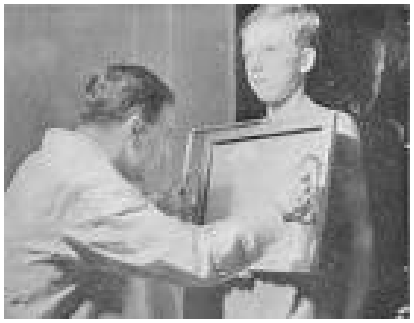
Canadian TB (Mean dose 1Gy)

- **1178 lung cancer deaths**
- **ERR/Gy -0.00 (-0.04 to 0.07)**

- **Confounding by indication?**
  - **TB risk factor for lung cancer**
  - **Misclassification of cause of death (dose-dependent)?**

Brenner (Conference Abstract Radiat Res 2010) ; Howe (Radiat Res 1995) ;

IHD Mortality & Multiple Fluoroscopies in TB Patients



Canadian TB

- **5818 Ischemic Heart Disease deaths (Mean dose 0.8 Gy)**
- **ERR/Gy = 0.18 (95% CI: 0.01-0.39)**
- **Decrease with time since exposure and age at exposure**

Zablotska et al (AJE 2014);

Breast cancer & Chest X-rays in BRCA carriers

Cohort n=1601 BRCA 1/2 mutation carriers

- **Retrospective questionnaire**
- **Any chest X-ray HR=1.54 p=0.007**
- **Exposure <age 20 HR=4.64 p<0.001**
- **Gene-radiation interaction?**
- **Recall bias?**

Case-control n=1600 pairs BRCA 1/2

- **Any mammograms OR=1.03 (0.85-1.25)**
- **1+ yrs before diagnosis**
- **Could not evaluate number of exposures**

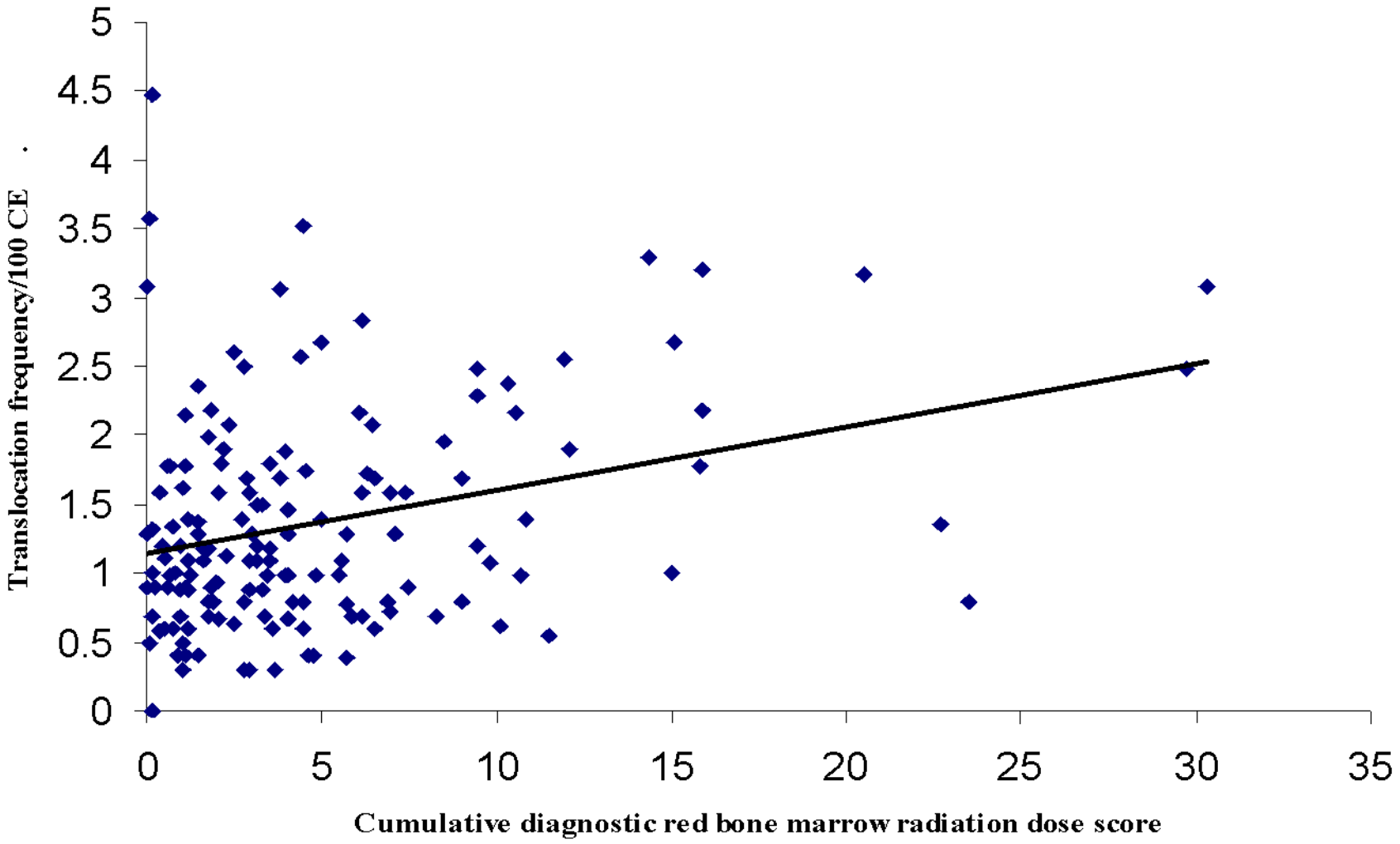
Andrieu et al (JCO 2006); Narod et al (Lancet Oncol 2006)

USRT Cohort – Personal Diagnostic X-rays

- **Self-reported diagnostic exposures by type and calendar period**
  - **Biodosimetry for 152 technologists**
  - **Dose scores for red bone marrow**
  - **FISH whole chromosome painting for translocations**
  - **Expressed per 100 cell equivalents (CE)**

Sigurdson et al (Cancer Res, 2008)

Translocation frequency versus personal diagnostic radiation red bone marrow dose "score"



0.04 excess translocations/100 CE/dose score, P = 0.003

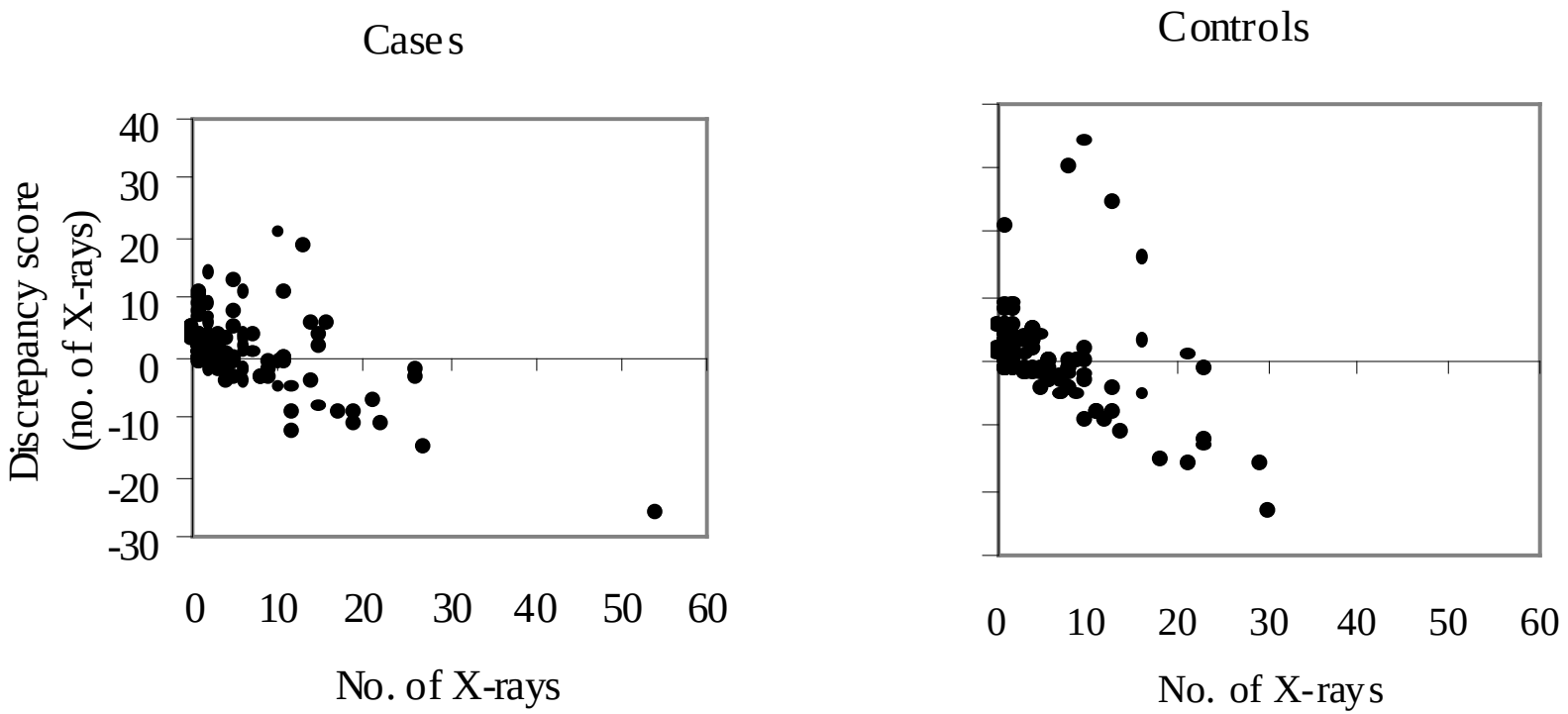
Thyroid Cancer & Diagnostic X-rays

- 3 questionnaire based studies suggested associations
- Swedish medical records study
- 484 cases and matched popn controls
- Radiology records from hospitals
- 6148 X-rays 5+ yrs before diagnosis
- Generic thyroid dose estimates
- No risk associated with past X-rays
  - Dose 7-75 mGy OR=1.05 (0.7-1.5) P-trend=0.8
  - Similar results <age 20 exposure

Inskip et al (JNCI 1995)

Poor Recall of Diagnostic X-rays

- **123 cases & controls Sweden**
- **50 cases & controls US**
- **Medical records vs Telephone interview**



Berrington de Gonzalez et al (AJE 2003)

Leukemia, NHL & Multiple Myeloma Case-Control Study

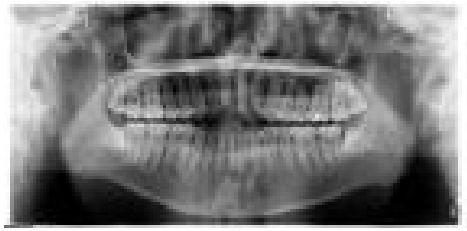
Kaiser NW and Kaiser NC Health Plans – Record Linkage

- **565 Leuk, 318 NHL and 208 MM cases & 1390 controls**
- **Matched on age, sex, years in plan, year entered plan**
- **25,000+ X-rays from medical records**
- **Bone marrow dose score**
- **52% exposures were chest X-ray (0.1mGy)**
- **No clear evidence of association**
  - **Especially with 2+ years lag period**

Lag	1	2	3	4	p-trend
3 mths	1.3	1.3	2.0	1.8	0.06
2 yrs	1.0	0.9	1.6	1.2	0.32

Boice et al (JAMA 1991)

Dental X-rays & Cancer Risk



Thyroid cancer in USRT cohort (n=251)

- **HR=1.13 (1.01-1.26) per 10 dental X-rays <1970**

Parotid gland tumors

- **269 benign & 139 malignant tumors**
- **408 neighbourhood controls**
- **OR=3.4 (1.02-11.5) for 50 rad vs 0 (p-trend<0.05)**

Glioma (202 pairs) and meningioma (70 pairs)

- **OR=1.5-3.0 for full-mouth dental x-rays**

Meningioma (1443 pairs)

- **OR=2.0 (1.4-2.9) for ever/never bite-wings**

Neta et al (AJE 2013); Preston-Martin et al (JNCI 1988); Preston-Martin et al (Cancer Res 1989); Claus et al (Cancer 2012)

Dental X-rays cont

Australian case-control study
- **Glioma OR 0.42 (0.24-0.76)**
- **Meningioma adult males – possible association**

Swedish case-control study
- **Meningioma OR 2.1 (1.0-4.3) for annual age 25+**
- **Other CNS - no association**

Australian case-control study
- **Childhood brain tumors – no association**

- **Recall similar for cases and controls**
- **Confounding by indication? (pain?)**

Ryan et al (Eur J Cancer B Oral Oncol 1992); Rodvall et al (Oral Oncol 1998); McCredie et al (Int J Cancer 1994)

Why Do We Study Screening Tests & Cancer Risk?

- **Doses lower than diagnostic**

  Eg 1mSv vs 10mSv for chest CT
- **Older populations (eg 50+)**
- **Screening exposes large numbers of healthy individuals**
- **Benefits > Risks?**
- **Risk projection rather than direct studies**

- **2 mammograms at age 35 (10mGy)**
- **20 years follow-up**
- **60 million women for 50% power (Land, 1981)**

Screening Examinations: Risk Projection

- **Younger screening ages**
  - **Higher radiation risks & lower absolute mortality reduction**
- **Benefits > radiation risks**
  - **Mammography BRCA carriers > age 35**
  - **Lung CT smokers > age 50**
  - **CT colonography > age 50**

Berrington de González et al (J Natl Can Inst 2009) Berrington de González (J Med Screen 2007)
Berrington de González et al (J Med Screen 2009)

Summary I

Fractionated low-dose diagnostic exposures can cause cancer

- **Fluoroscopy TB studies**
- **Scoliosis cohort**
- **In utero**
- **Pediatric CT?**
- **Dental X-rays uncertain**
- **Effect of fractionation uncertain**

Basis for conclusion

- **Established carcinogen**
- **Dose-response**
- **Consistency with LSS data**
- **But… limited power <50mGy**

Summary II

Attributes of key studies

- Relatively high exposure levels
- Or high risk sub-group (eg children, radio-sensitive?)
- Medical records for dose reconstruction to avoid recall bias
- Dose uncertainty complex, but << environmental exposures

Risk projection

- Alternative for timely assessment of potential risks

Questions and Answers

U.S. Department of Health and Human Services
National Institutes of Health | National Cancer Institute
www.dceg.cancer.gov/RadEpiCourse
1-800-4-CANCER
Produced May 2015