NCEH/EHSP/ Emergency Management, Radiation and Chemical Branch Presents:

Radiation Epidemiology: The Good, the Bad, and the Ugly

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Outline of Presentation

- What is Radiation Epidemiology?
- What Makes a Study Good (Reliable)?
- What Makes a Study Bad (Unreliable)?
- What Makes a Study Ugly (Flawed)?
- Summary and Recommendations

Radiation Epidemiology

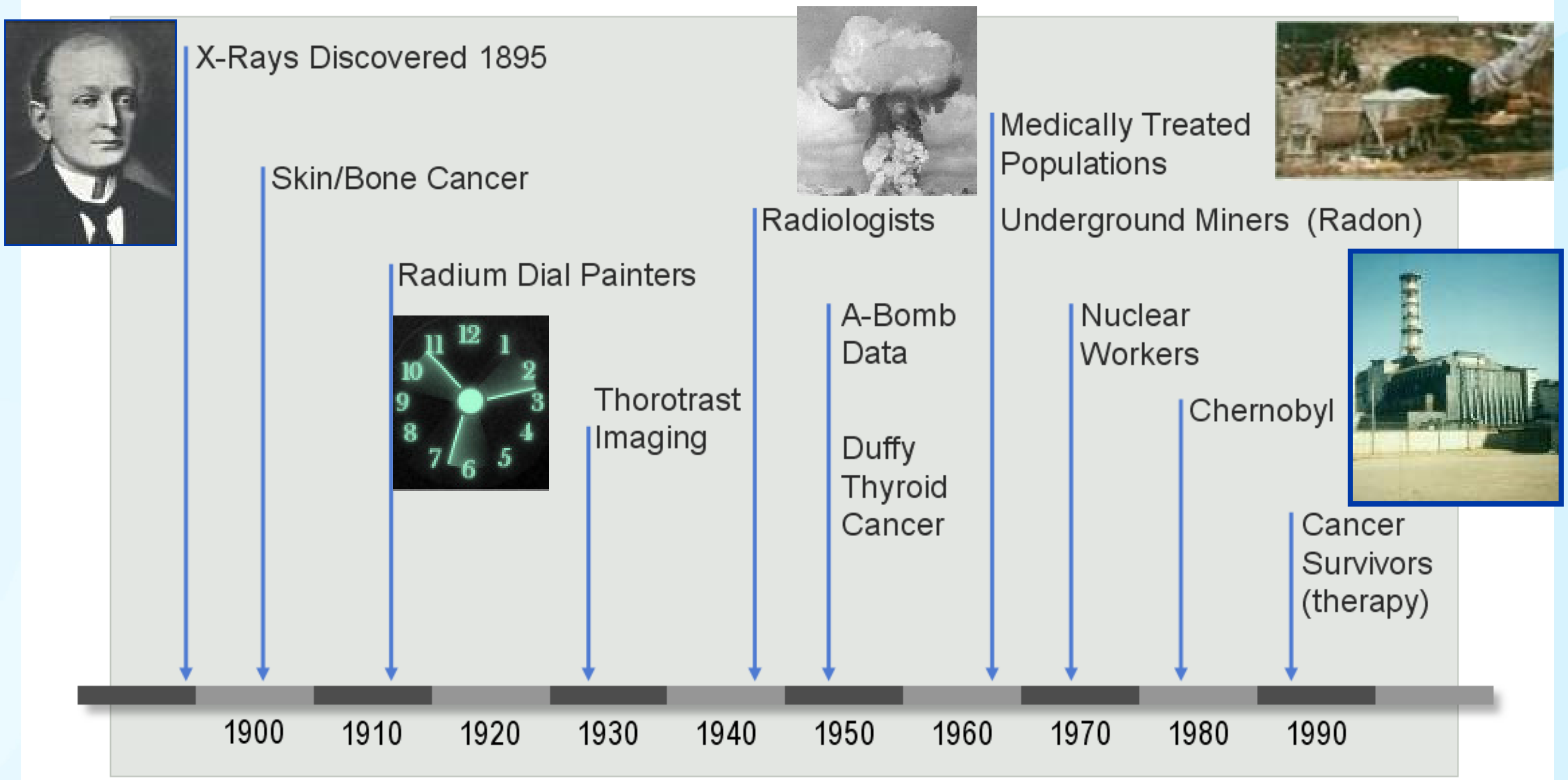
Radiation epidemiology is the study of ionizing radiation as a cause of disease in human populations

Radiation Epidemiology

- Radiation epidemiology is the basis for radiation protection standards and for compensation schemes.
- But the plethora of epidemiologic studies with conflicting results create confusion for the decision makers and general public. How do you separate the wheat from the chaff? What studies produce reliable estimates of radiation risk that can be used in making decisions?
- Good Study – reliable & could use in making decisions.
- Bad Study – unreliable, don't use for making decisions or estimating risks
- Ugly Study – flawed or inadequate design. Discount entirely for estimating radiation risks or making decisions.

Epidemiology is the study of the distribution and causes of disease in humans.

Radiation Epidemiology Dates Back 100 Years



Epidemiology changed the focus from genetic effects in offspring to somatic effects on the individuals exposed

Radiation epidemiology (United Nations 2008) tells us that:

- a single exposure to radiation increases cancer risk for life.
- the young are more susceptible than the old, with exceptions
- *in utero* susceptibility is no greater than early childhood
- females are more susceptible than males.
- risks differ by organ or tissue
- some cancers don't appear related to radiation, e.g., chronic lymphocytic leukemia, Hodgkin & non-Hodgkin lymphoma, melanoma; cancers of the cervix, prostate, pancreas, & some only at very high doses, e.g., sarcomas.

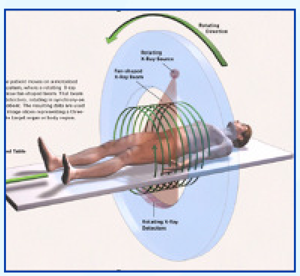
Why is Radiation Epidemiology Needed ?

Much is Known about Radiation Health Effects When Exposure is Received All at Once (Briefly)

The Major Gap is Understanding the Health Effects from Exposures Received Gradually Over Time

Needed to accurately access risks related to:

Medicine

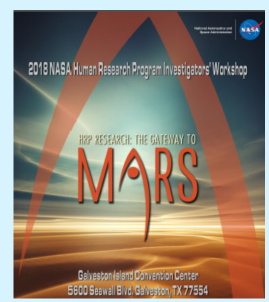


Accidents or Terrorism

Occupation

Environment

Space and High Altitude Travel

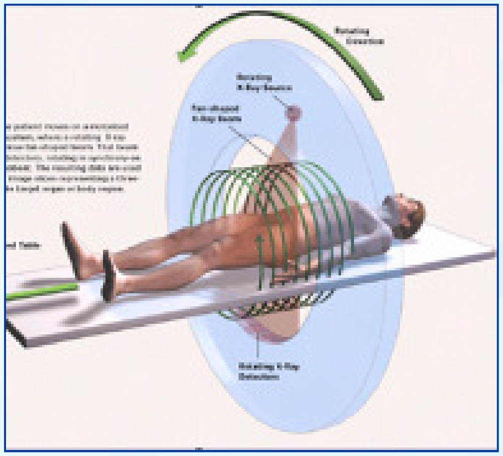


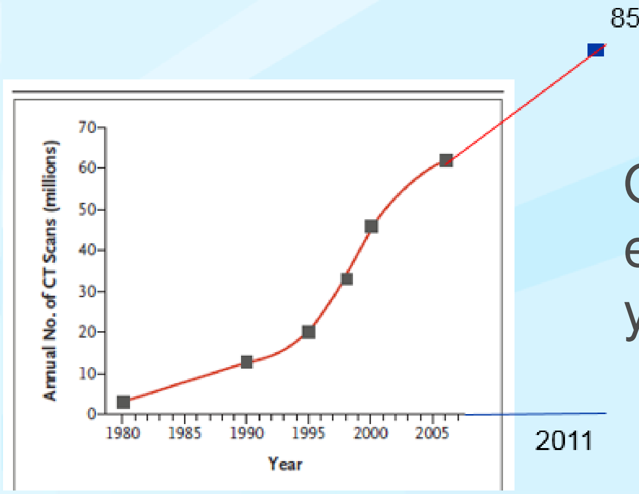
1- Why is Radiation Epidemiology Needed ?

Much is Known about Radiation Health Effects When Exposure is Received All at Once (Briefly)

The Major Gap is Understanding the Health Effects from Exposures Received Gradually Over Time

Needed to accurately assess risks related to medical exposures





Over 80 million CT examinations last year in the U.S.

2- Why is Radiation Epidemiology Needed ?

Much is Known about Radiation Health Effects When Exposure is Received All at Once (Briefly)

The Major Gap is Understanding the Health Effects from Exposures Received Gradually Over Time

Needed to **manage nuclear incidents and terrorism**

Fukushima Daiichi Reactor Accident

Radiation Poisoning - Litvinenko

Weapons of Mass Destruction - Aftermath

3- Why is Radiation Epidemiology Needed ?

Much is Known about Radiation Health Effects When Exposure is Received All at Once (Briefly)

The Major Gap is Understanding the Health Effects from Exposures Received Gradually Over Time

Needed to **manage occupational exposures**

Medicine

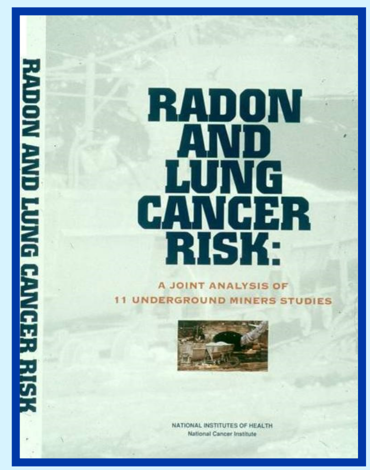
Industrial Radiography

4- Why is Radiation Epidemiology Needed ?

Much is Known about Radiation Health Effects When Exposure is Received All at Once (Briefly)

The Major Gap is Understanding the Health Effects from Exposures Received Gradually Over Time

Needed to **manage or address environmental exposures**

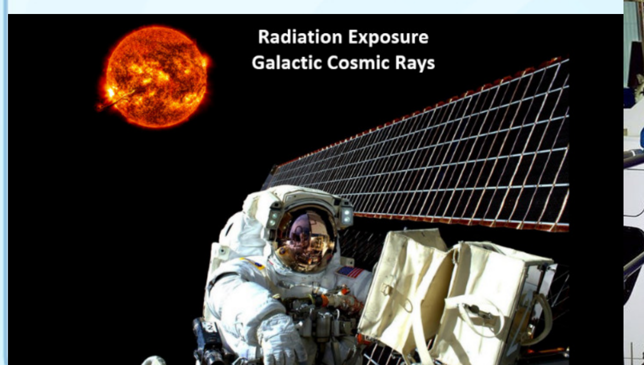


5- Why is Radiation Epidemiology Needed ?

Much is Known about Radiation Health Effects When Exposure is Received All at Once (Briefly)

The Major Gap is Understanding the Health Effects from Exposures Received Gradually Over Time

Needed for **guidance for space & high altitude travel**



6- Why is Radiation Epidemiology Needed ?

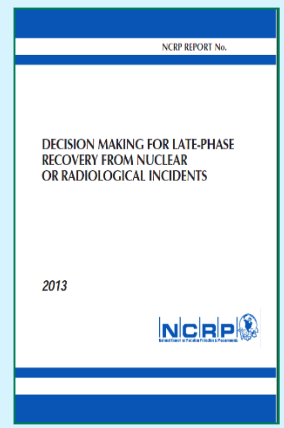
Much is Known about Radiation Health Effects When Exposure is Received All at Once (Briefly)

The Major Gap is Understanding the Health Effects from Exposures Received Gradually Over Time

Needed for **public policy & decision making**

- GAO Report on Low Dose Radiation Needs, 2017
- Low-Dose Radiation Research Act of 2017 – HR 4675 (Passed the House of Representatives – Senate next)

- Setting Standards for Occupational and Environmental Exposures
- Compensation Schemes for Prior Radiation Exposures



Radiation Epidemiology

- What is Radiation Epidemiology?
- What Makes a Study Good (Reliable)?
- What Makes a Study Bad (Unreliable)?
- What Makes a Study Ugly (Flawed)?
- Summary and Recommendations

Types of Epidemiologic Studies

TYPE	Intrinsic Quality	Susceptibility to Bias (Errors)
Experimental (rare)	Highest	Least
Cohort (Follow-up)		
Case-Control (Start with Disease then Exposure)		
Ecologic (Geographic or Correlation)	Lowest	Most

No Study is Perfect

- Most radiation epidemiologic studies are observational.
- There are known and unknown biases and confounding influences that can distort study findings.
- There are intrinsic limitations to study design.
- Meta-analyses are becoming more common but concerns relate to the selection of studies to include, and the influence of poor but large studies.

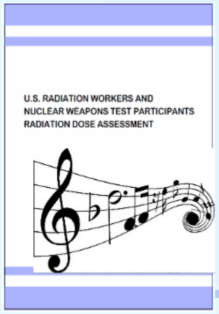
Epidemiologic Concerns that Could Produce Spurious Results

- Chance (random variation)
- Bias (systematic error)
- Confounding (e.g., differences in smoking histories)

- A study can be good (reliable), bad (unreliable), or ugly (flawed and provides either wrong information on radiation risk or no information)

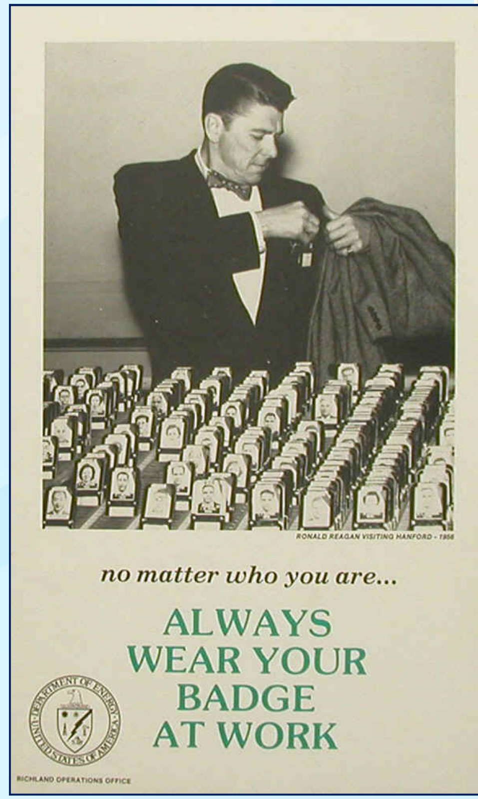
What Makes a Radiation Epidemiology Study Good?

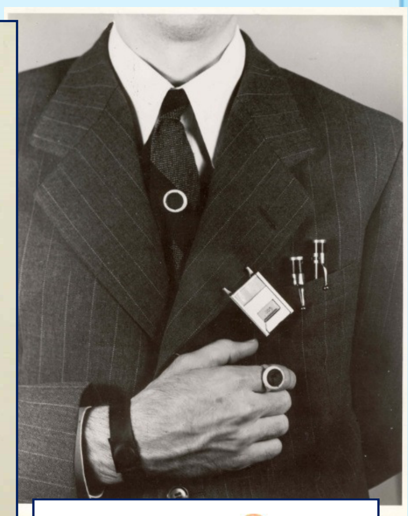
- Dosimetry (exposure assessment) is very good
- Information bias is minimized (i.e. information on health outcomes is comparable for exposed and non-exposed)
- Selection bias is minimized (i.e. no selective inclusion or exclusion of subjects in relation to exposure or outcome)
- Confounding influences can be controlled (i.e. the determinants of disease risk other than radiation)
- Sample size large enough to have the statistical ability to detect effects and to minimize the role of chance
- These issues are of great concern when exposures are low and the exposure rate is low



Dosimetry is Key to Good Epidemiology

- Key concern is limitations in exposure assessment
- Goal – accurate and precise estimates of organ-specific absorbed doses
- Need estimates for individuals & address uncertainties
- Measurement errors, challenges with intakes of radioactive substances



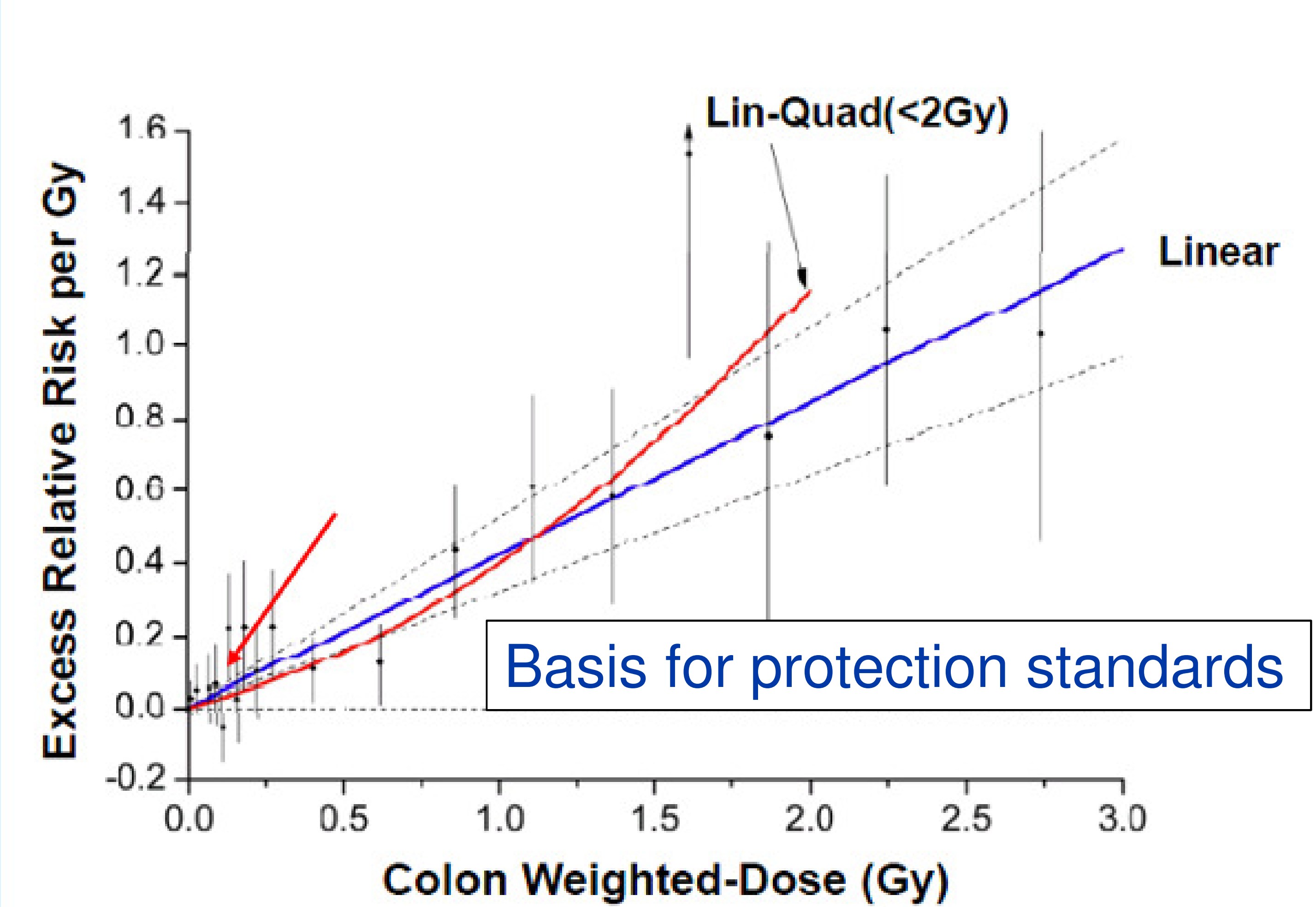


Till et al, *Dosimetry used in Epidemiologic Studies. IJRB* 2017
Bouville et al, Dosimetry for the MPS. *Health Phy* 2015.

Two Examples of Good Radiation Epidemiology Studies

- Japanese Atomic Bomb Survivor Study (The Life Span Study, LSS)
- TB-fluoroscopy studies

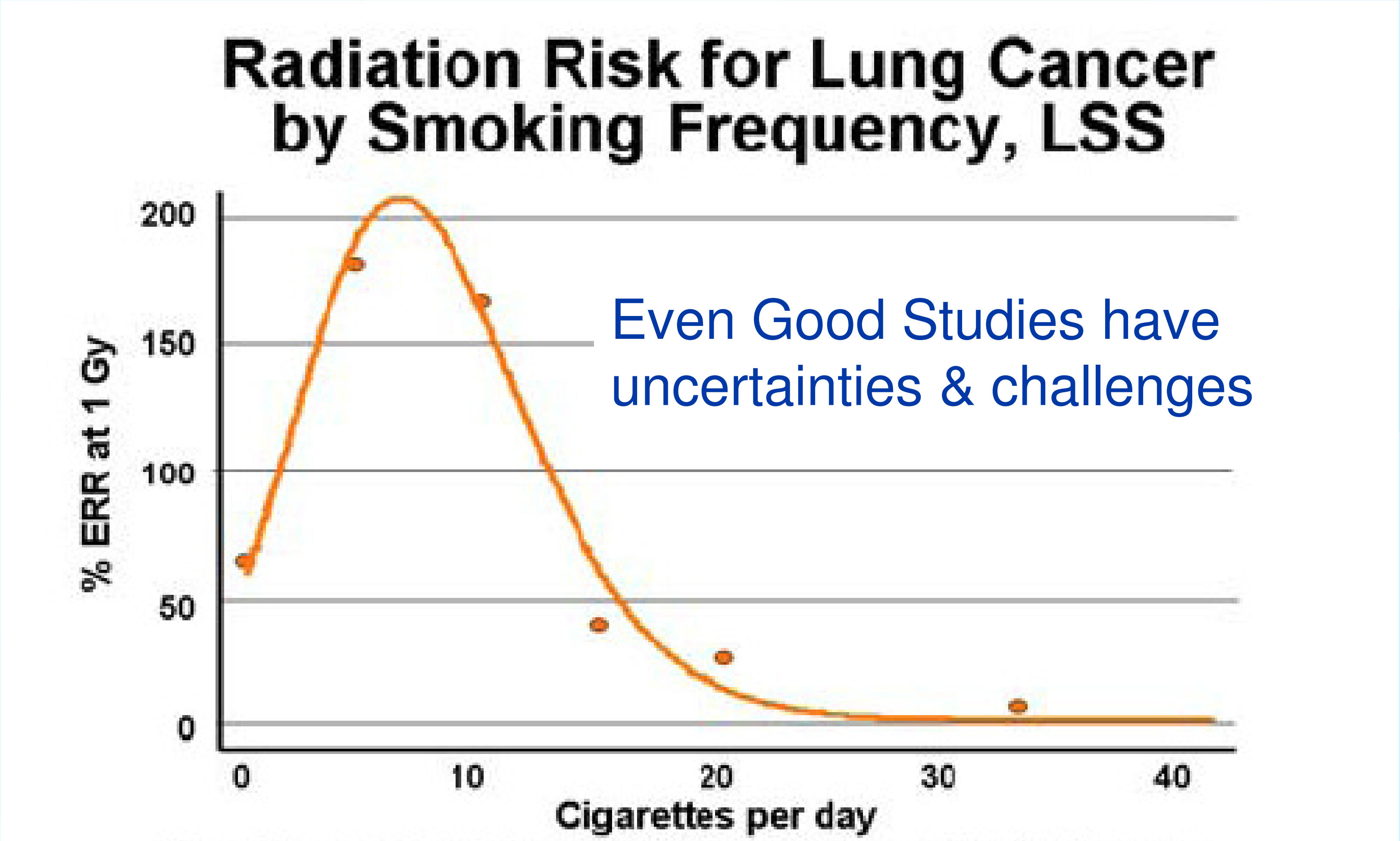
Dose Response for Solid Cancer Deaths Among Japanese Atomic Bomb Survivors, 1950-2003



Ozasa et al, *Rad Res* 177; 2012

Atomic Bomb Survivor Study – Why a Good Study?

- Well-defined population – census 1950
- Dose estimates – refined over 70 years
- Follow-up – near perfect for mortality
- Ascertainment of deaths (outcome) – near perfect
- Analysis – state of the art statistical methods used by most radiation epidemiologists throughout the world
- Interpretation – balanced, and data are available to the world
- Not without limitations
  - An acute exposure of a 1945 population
  - How representative of populations today exposed gradually over years?
  - Study size of 86,000 is somewhat small compared with recent worker studies
  - Challenging to adjust for confounders



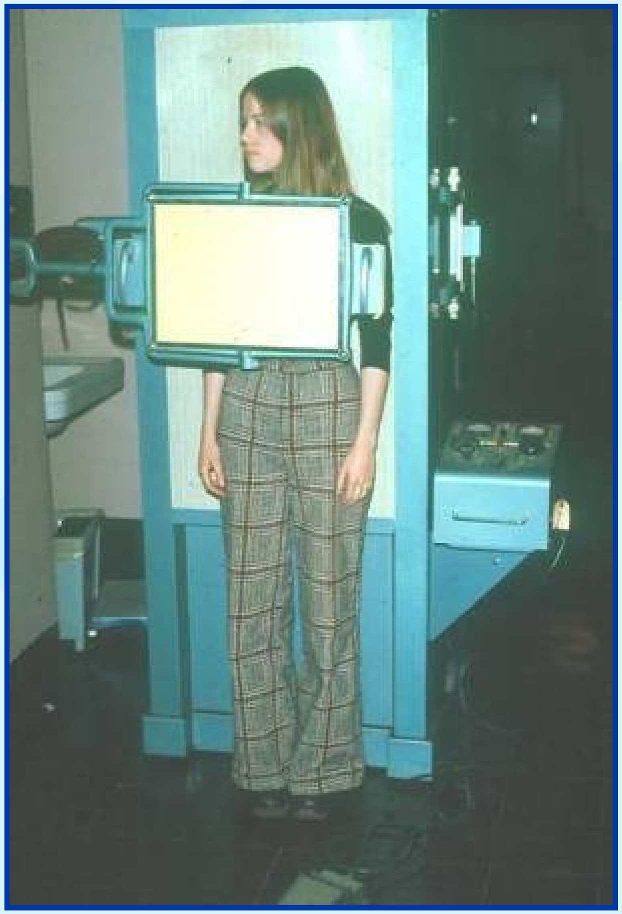
*Gender-averaged excess risk relative to unexposed person with same smoking history

(Adapted from: Furukawa et al, Radiat Res, 174:72-82, 2010)

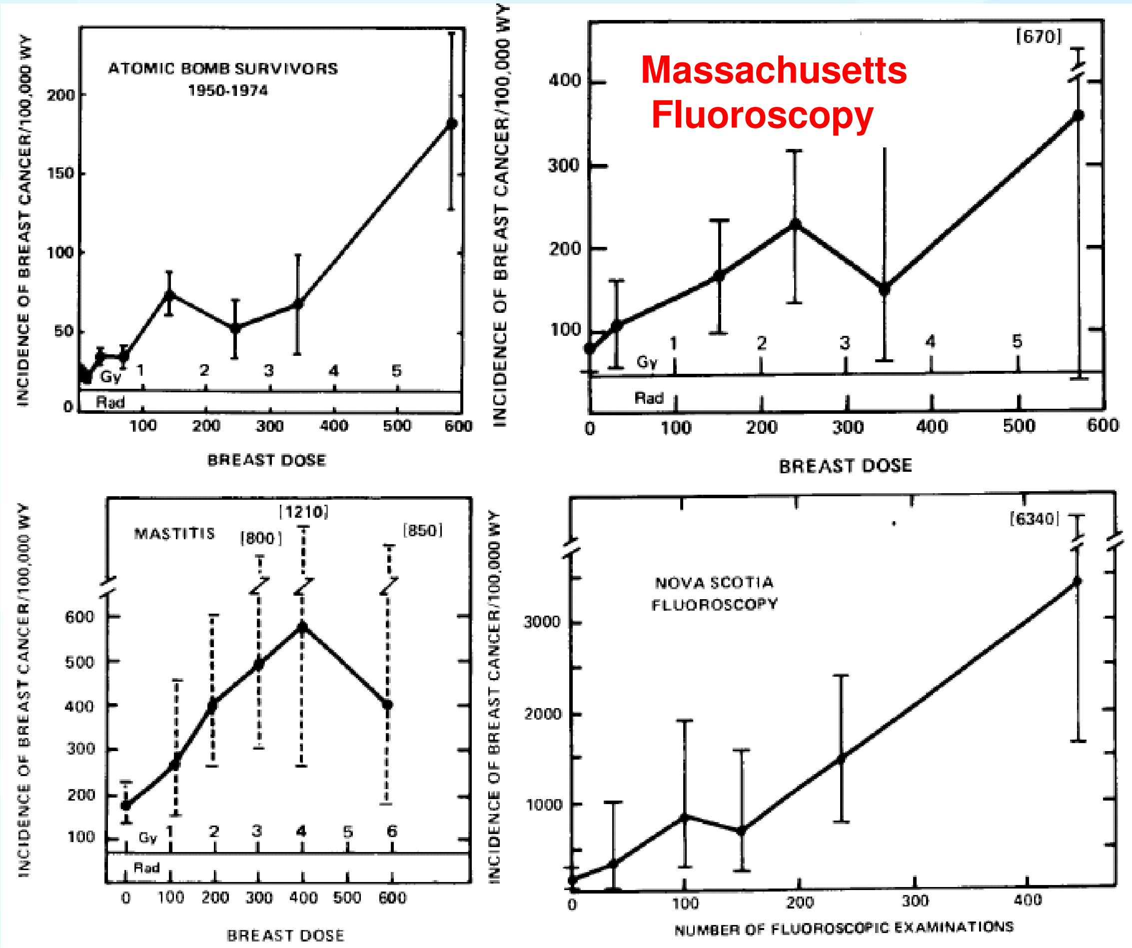
Courtesy of K Kodama, RERF 2011

Studies of Low-Dose Exposures Accumulating to High Dose

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



Dose Response – Consistent with Other Breast Cancer Studies



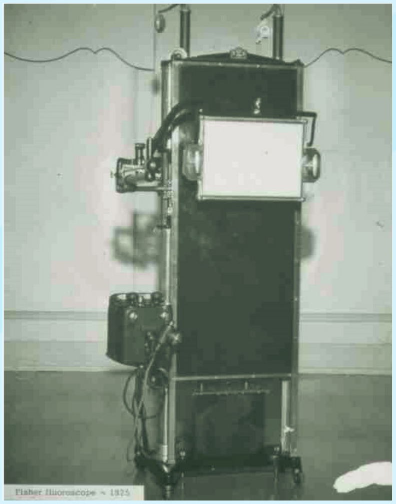
Boice, *Radiology* 131:589, 1979

Consistent with a straight line fit

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

No Dose Response for Lung
TB - Fluoroscopy, Massachusetts

	Lung
# exposed	6,285
# unexposed	7,100
# chest fluoroscopies (avg.)	77
Dose to lung or marrow	840 mGy
Observed (O)	69
Expected (E)	86
RR (95% CI)	**0.8** (0.6-1.0)



No excess lung cancer

Not all tissues respond similarly to fractionation

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

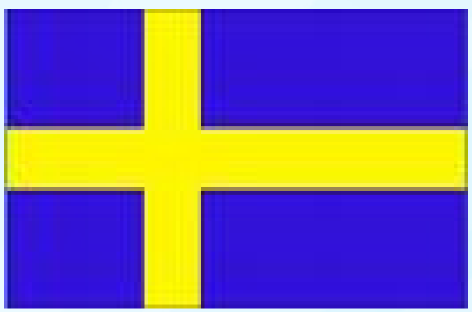
Be cautious when generalizing

TB-Fluoroscopy – Why a Good Study?

- Complete patient identification from medical records in TB sanatoriums.
- Good dosimetry: Numbers of fluoroscopies known, patients & physicians interviewed, original fluoroscopes available, top medical physicists involved
- Follow-up near perfect because of special Massachusetts town books (comparable by dose)
- Outcome complete (deaths) and comparable by dose
- Analyses are robust – in collaboration with the atomic bomb study statisticians.
- Consistent with the other *good* studies.

Example of Reverse Causation In a Good Study

- Thyroid cancer following I-131 scans for evaluation of thyroid conditions in Sweden among 35,000 adults (thyroid dose 0.94 Gy, avg.)



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

Dickman et al. *Int J Cancer* 106(4):580–587; 2003.

Risk Among All Subjects

Reason for I-131 Scan (No. Cancers)	RR of Thyroid Cancer
All Reasons (105)	**1.8***

- Significant thyroid cancer risk overall (RR 1.8*) among the 35,000 scanned

Note that the adult thyroid gland is not considered radiosensitive.

Risk by Reason for the I-131 Exam

Reason for I-131 Scan (No. Cancers)	RR of Thyroid Cancer
All Reasons (105)	1.8*
Suspicion of Tumor (69)	**3.5***
Other Reasons (36)	0.9*

- **I-131 did not cause thyroid cancer, but suspicion of thyroid tumor caused the I-131 examinations.**

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

Reverse Causation and Confounding by Indication Occur in Epidemiologic Studies

- Confounding by indication - when the medical condition or suspicion of an underlying disorder was the cause of the radiation examinations.
- Imaging for thyroid conditions with I-131
- Imaging for brain conditions with Thorotrast (Thorium Dioxide)
- CT imaging – the reasons for the exams were unknown

Boice. Radiation epidemiology and CT studies. *Annals ICRP* 2015

Radiation Epidemiology

- What is Radiation Epidemiology?
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What Makes a Radiation Epidemiology Study Bad?

- Selection bias (subjects included or excluded based on exposure or outcome)
- Information bias (information on health outcomes is not comparable for exposed and non-exposed subjects)
- Plausible confounding
- No dosimetry or poor quality
- The participation, follow-up and outcome ascertainment were severely incomplete and different by exposure status
- Inconsistent with “good” studies
- Focus on subgroup analyses that were not *a priori*

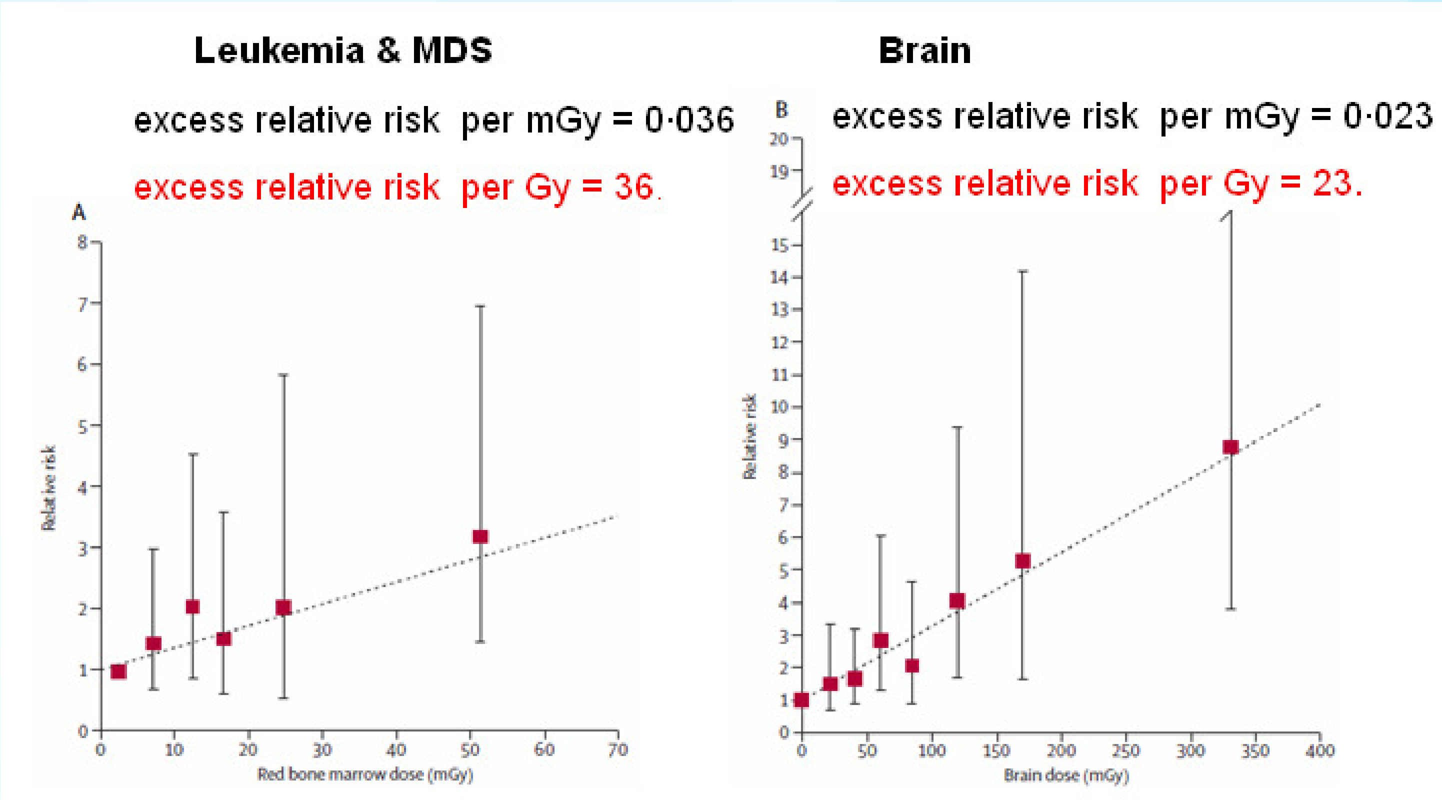
Examples of Bad (Unreliable) Studies

- UK CT examinations & childhood cancer
- Australian CT examinations & childhood cancer

Charles Schultz, Peanuts

United Kingdom CT Study

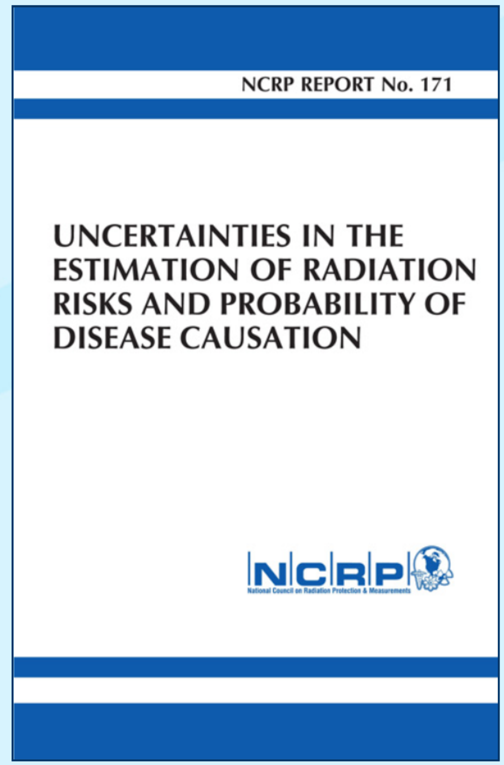
- Record linkage study of leukemia and brain cancer following CT scans to 178,000 persons at ages 0–21
- Significant findings at very low doses – but no dosimetry
- Not leukemia but leukemia plus MDS



Pearce et al., *Lancet* 2012

Major Epidemiologic Limitation
No Information on Why Scans Performed

“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* – X-rays aren’t ‘causing’ cancers, the underlying medical conditions are ‘causing’ X-rays.



Australian CT Study

- Data linkage study of 680,000 children (0-19 y) who received CT scans - no dosimetry

- 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
  - Leukemia (myeloid)
  - Hodgkin lymphoma

But not for these radiosensitive cancers :

- Breast Cancer
- Lymphoid Leukemia

Brain cancer was increased whether or not the brain was exposed.

Mathews et al., *BMJ* 2013

United Nations 2013

- Lack of information about indications for the CT scans indicates the 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)

- No individual dosimetry

- Inconsistencies with epidemiologic studies on age at exposure, latency, radiation risk estimates.

UNSCEAR

Studies Addressing Reverse Causation

- **Germany**: A considerable proportion of cancer patients (especially those with lymphomas and solid tumors) had medical conditions indicating an increased cancer risk and signs possibly suggestive of cancer at time of first CT.

  (Krille et al. *Rad Env Bio* 2015)

- **France**: Adjustment for cancer-predisposing factors (PF) reduced the excess risk estimates related to cumulative doses from CT scans. No significant excess risk was observed in relation to CT exposures. (Journy et al. *Br J Cancer* 2015)

- **USA**: CT exams for shunt treatments for hydrocephalus, no risk found but small numbers. (White et al. *J Neurosurg Ped* 2014)

Radiation Epidemiology

- What is Radiation Epidemiology?
- What Makes a Study Good (Reliable)?
- What Makes a Study Bad (Unreliable)?
- What Makes a Study Ugly (Flawed)?
- Summary and Recommendations

What Makes a Radiation Epidemiology Study Ugly?

- Similar (but more severe) problems as in Bad studies: selection and information bias, confounding present
- NO dosimetry
- Population ill-defined and participation and follow-up severely incomplete
- But also, the study design may be inadequate and not up to the task at hand, e.g. correlation (ecologic) studies can be well-design and conducted, yet they can provide no information on estimating radiation risks

Examples of Ugly (Flawed) Radiation Epidemiologic Studies

- Fukushima thyroid screening
- Cancer around nuclear facilities in the U.S.

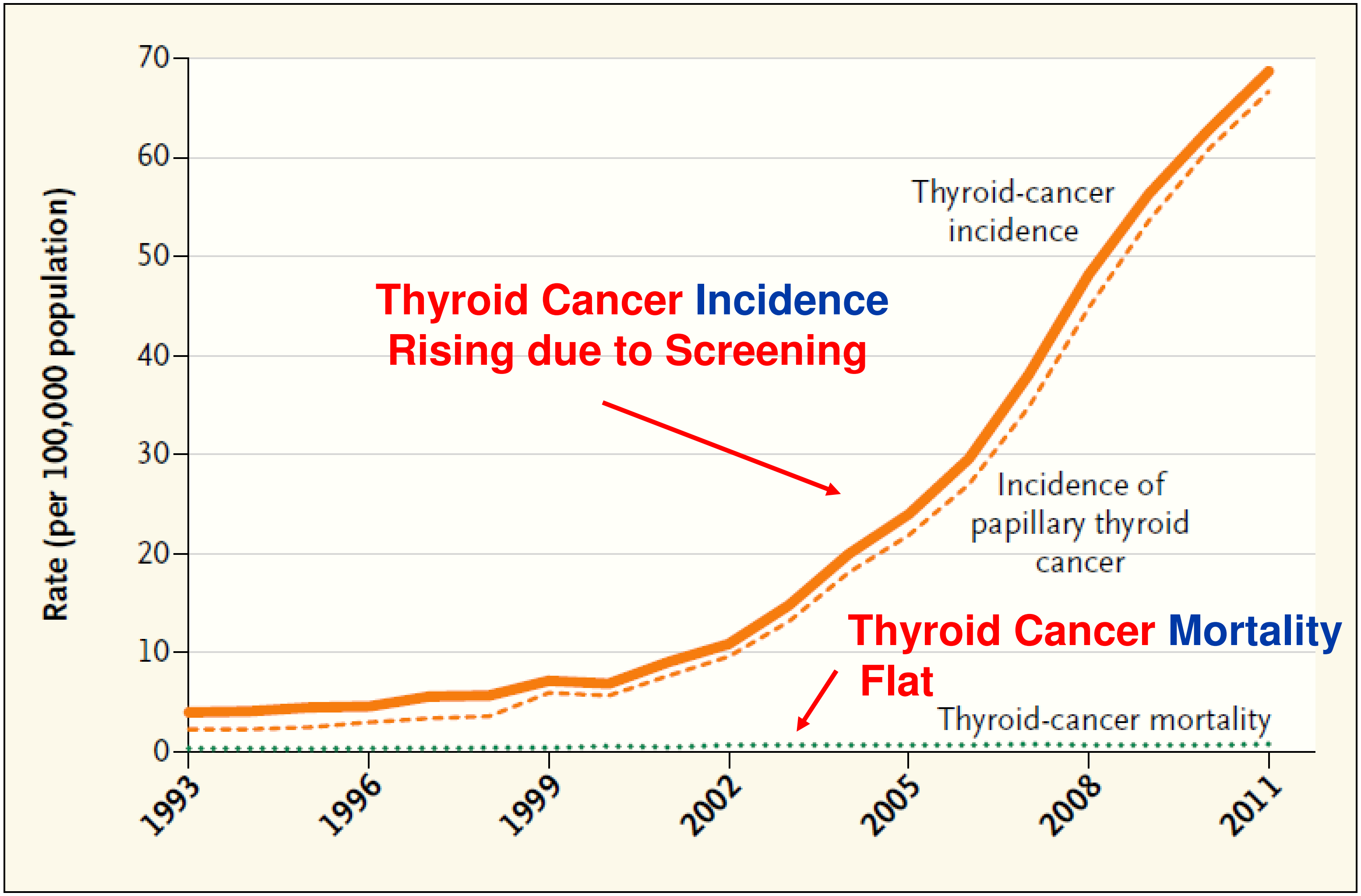
A New Study: Excess of thyroid cancer detected in Fukushima is because of radiation, not "screening effect."

(*Epidemiology* May 2016)

- Tokyo (AP): A new study says children living near the Fukushima nuclear melt downs have been diagnosed with thyroid cancer at a rate **20-50x** that of children elsewhere, a difference the authors contends **undermines the government's position** that more cases have been discovered in the area only because of stringent monitoring.
- A bit overstated and conclusions a bit inflammatory?
- Screening by ultrasound is known to increase the rates of thyroid tumors, i.e., by detecting indolent tumors that might never become symptomatic.

*Tsuda et al. *Epidemiology*, May 2016.

Korea's Thyroid-Cancer "Epidemic" -- Due to Screening and Overdiagnosis



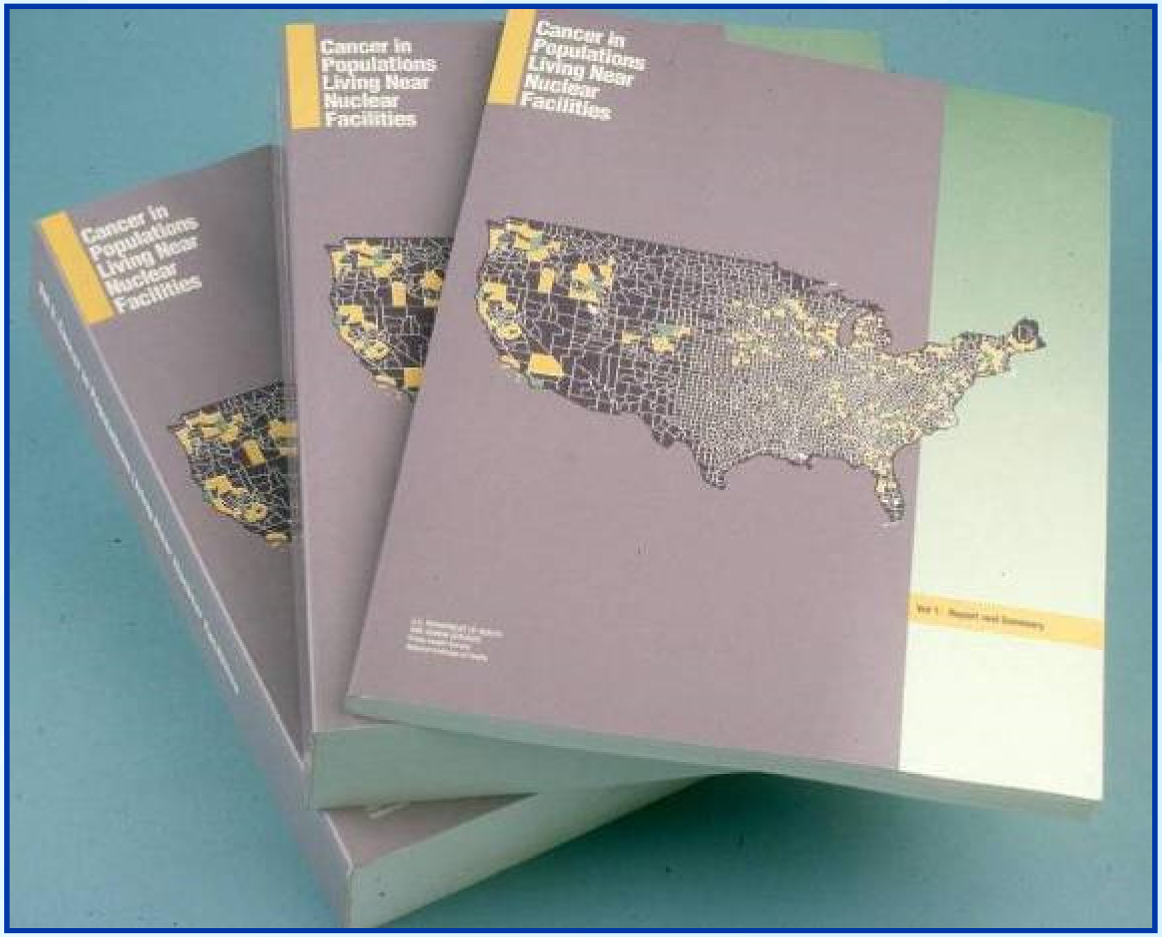
Thyroid-Cancer Incidence and Related Mortality in South Korea, 1993–2011.

Ahn HS et al. *NEJM* 2014

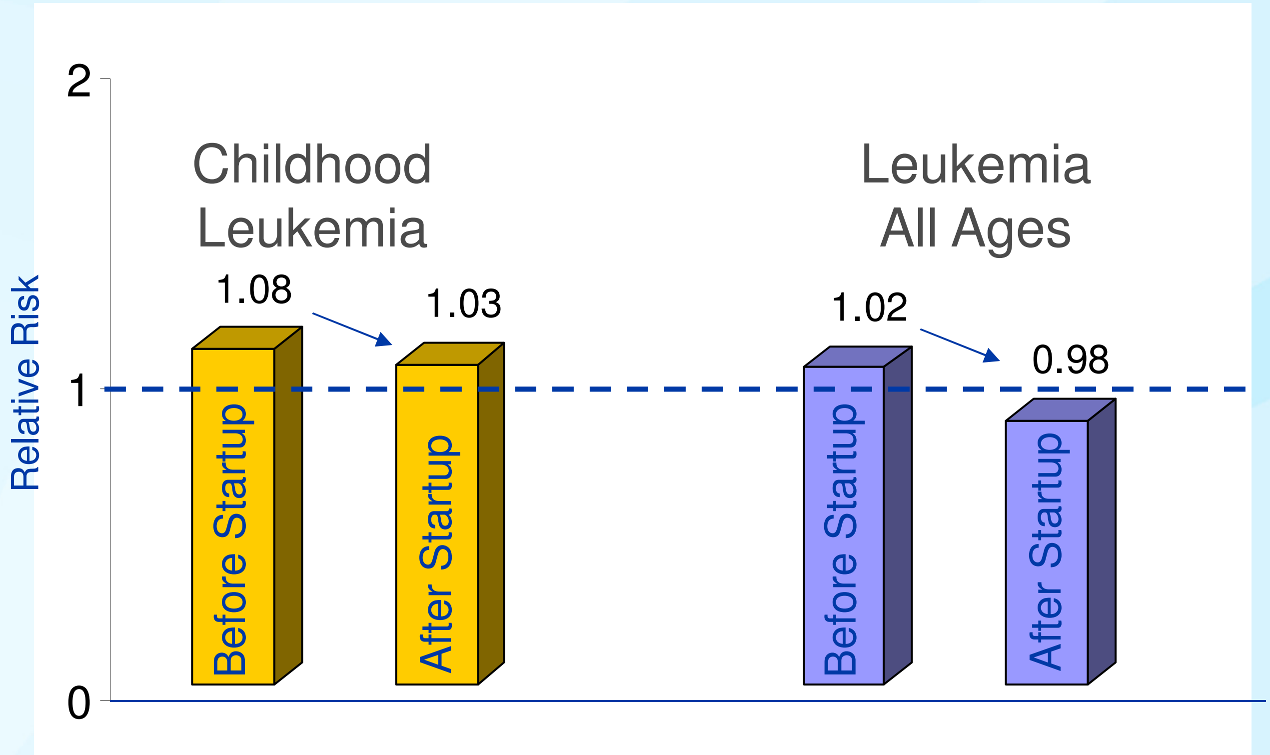
Why the Screening Study is Ugly (Terminally Flawed)

- The risk was enormous: 20-50 time population rates (this would be the highest radiation risk of all time)
- Latency (< 4y) too short and not consistent with the world's literature
- Age at exposure association (teenagers & not children had the highest rates) not consistent with the world's literature
- No dosimetry and no geographical variation by dose (regions)
- Similar screening results found in areas not affected by Fukushima
- And doses much too low to have any effect
- The screenings were designed to be surveys to show compassion, provide assurance, and reduce anxiety – they did the opposite

Cancer in Populations Living Near Nuclear Facilities *JAMA* 256: 1991



Overall Relative Risk of Leukemia Before and After Nuclear Facility Startup



Jablon et al, *JAMA* 265:1403-1408, 1991

Risk higher before than after facilities began operating

Why the Nuclear Facility Study is Ugly

- Despite large numbers, sound investigators (NCI) and published in JAMA…
  - A correlation (ecologic) study does not have information on individuals but groups – no individual dosimetry and no individual data on potential confounding factors
  - Individuals may not have lived in the area long before dying there
  - Correlation is not causation (cigarette sales correlated with refrigerators)
  - Correlation studies are good for generating hypotheses, not for testing them.

Take Home Message

- What is Radiation Epidemiology?
- What Makes a Study Good (Reliable)?
- What Makes a Study Bad (Unreliable)?
- What Makes a Study Ugly (Flawed)?

Summary and Recommendations

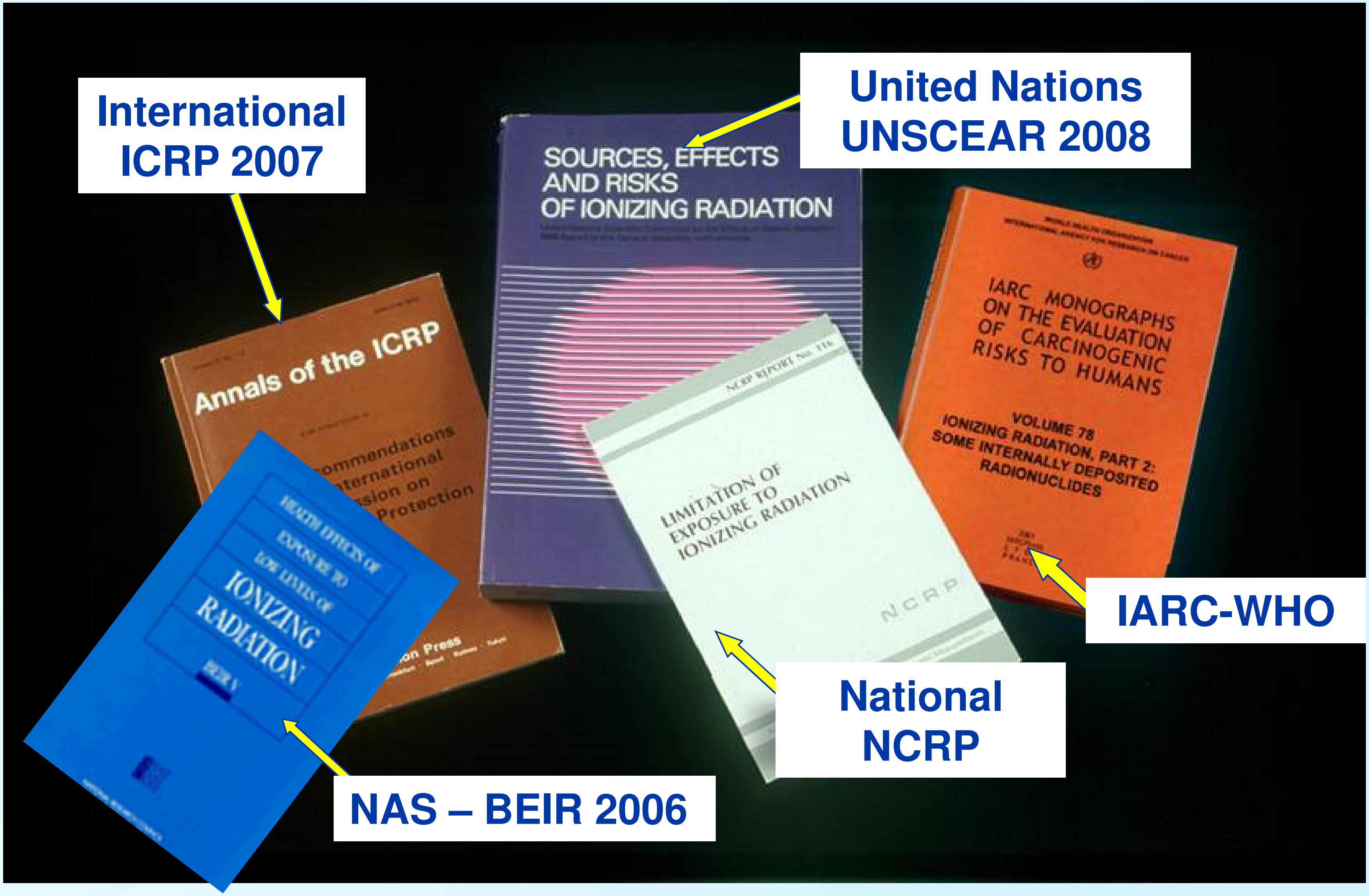
Take Homes - 1

- We live in a world of ever increasing radiation exposures
- Radiation epidemiology is needed
- There are not enough radiation professionals
- ALL studies have limitations, some are useful, some are not
- How can you separate the wheat from the chaff?

Take Homes - 2

- How can you separate the Good from the Bad and Ugly?
  - Sound methodology (population well-defined, follow-up and outcome ascertainment complete, adequate study size)
  - Minimal bias and adequate control of confounding
  - HIGH QUALITY DOSIMETRY
  - Comprehensive statistical analysis
  - Consistent with other Good studies and biologically plausible
- Don’t believe everything you read, even if the impact factor is 50!
- Be skeptical, there is a lot of Bad and Ugly out there!

Radiation Reports and Committees



If you benefited please tell the CDC that "it was so typically brilliant of them to have invited a radiation epidemiologist."

The New Yorker, Nov 26, 2001, Wm Hamilton

But please don't bother if not so brilliant!

Thanks Steve Simon

Thank you