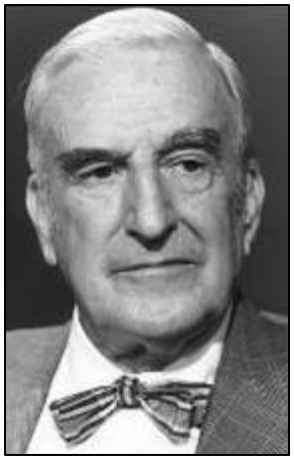
NCRP 1929 2009

Forty-Fifth
Annual Meeting Program



Thirty-Third Lauriston S. Taylor Lecture on
Radiation Protection and Measurements

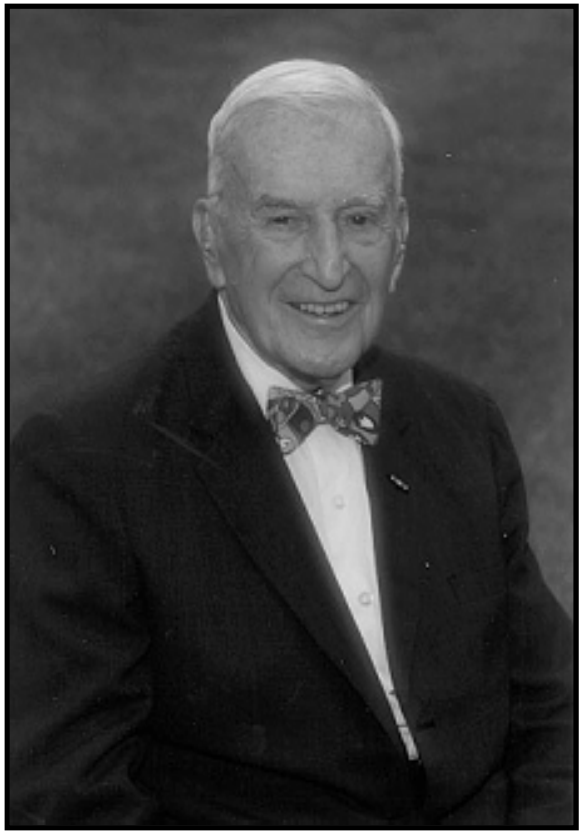
VANDERBILT UNIVERSITY

2 March 2009

John D. Boice, Jr.

Radiation Epidemiology: The Golden Age and Future Challenge

Laurie Taylor and First Taylor Lecture 1977



Lauriston S. Taylor Lecturers (1977-2008) Colleagues Over the Years

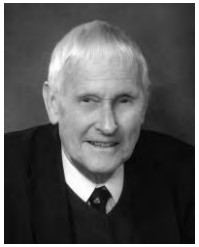
- Seymour Jablon (1987)
- Bo Lindell (1988)
- Arthur Upton (1989)
- Vic Bond (1991)
- Ted Webster (1992)
- Warren Sinclair (1993)
- Michael Fry (1994)
- Albrecht Kellerer (1995)
- Seymour Abrahamson (1996)
- Eric Hall (1998)
- Naomi Harley (1999)
- Jim Adelstein (2000)
- Julian Preston (2002)
- Charlie Meinhold (2003)
- Abel Gonzalez (2004)
- Jack Little (2005)
- Bob Brent (2006)
- Dade Moeller (2008)

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

- Studies of human populations exposed to ionizing radiation have been conducted for nearly 100 years (the GOLDEN AGE).

- Radiation epidemiology is now so sophisticated that human studies are the basis for radiation protection standards and for compensation schemes in response to claims of ill health from prior exposures.

NCRP 1929 2009



The Golden Age Epidemiologic Studies of Exposed Human Populations

√JAPANESE ATOMIC BOMB SURVIVORS

RADIOTHERAPY - CANCER
- √ Cervical
- √ Endometrial
- √ Childhood
- √ Breast
- √ Hodgkin Lymphoma

RADIOTHERAPY - NON-MALIGNANT DISEASE
- Spondylitis
- √ Thymus
- √ Tonsils
- √ Menstrual Disorders
- √ Scalp Ringworm
- √ Mastitis
- √ Infertility
- Otitis Media
- √ Ulcer
- Hemangioma

DIAGNOSTIC
- √ TB - Fluoroscopy
- √ Pelvimetry
- √ Scoliosis
- √ General

RADIONUCLIDES
- √ Thorotrast
- √ I-131
- √ Uranium
- P-32
- Ra-224
- Plutonium

OCCUPATION
- Ra Dial Painters
- √ Miners (Radon)
- √ Radiologists
- √ Technologists
- √ Nuclear Workers
- √ Atomic Veterans

ENVIRONMENT
- √ Chernobyl
- Weapons Fallout
- √ Natl Background
- Techa River

A Few Golden Studies

Medical

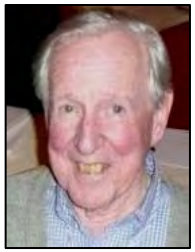
- Diagnostic fluoroscopic X-rays for tuberculosis
- Radiotherapy for cervical cancer
- Prenatal and preconception exposures

Environmental

- Radon
- Nuclear Facilities

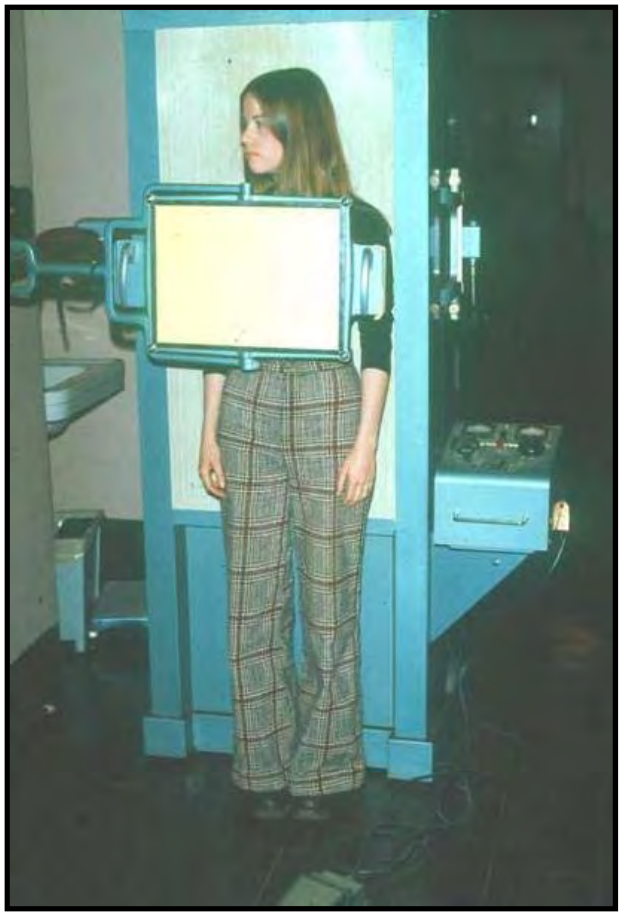
Occupational

- Rocketdyne – Atomics International



Studies of Low-Dose Exposures Accumulating to High Dose

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

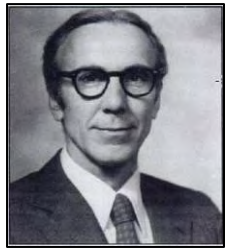


Breast Cancer
TB - Fluoroscopy, Massachusetts

	Exposed	Nonexposed
No. of women	2,573	2,367
No. chest fluoroscopies (ave)	**88**	--
Dose (ave)	79 cGy	--
Breast cancers		
Observed (O)	147	87
Expected (E)	113.6	100.9
O/E	**1.29**	0.86

29% Excess

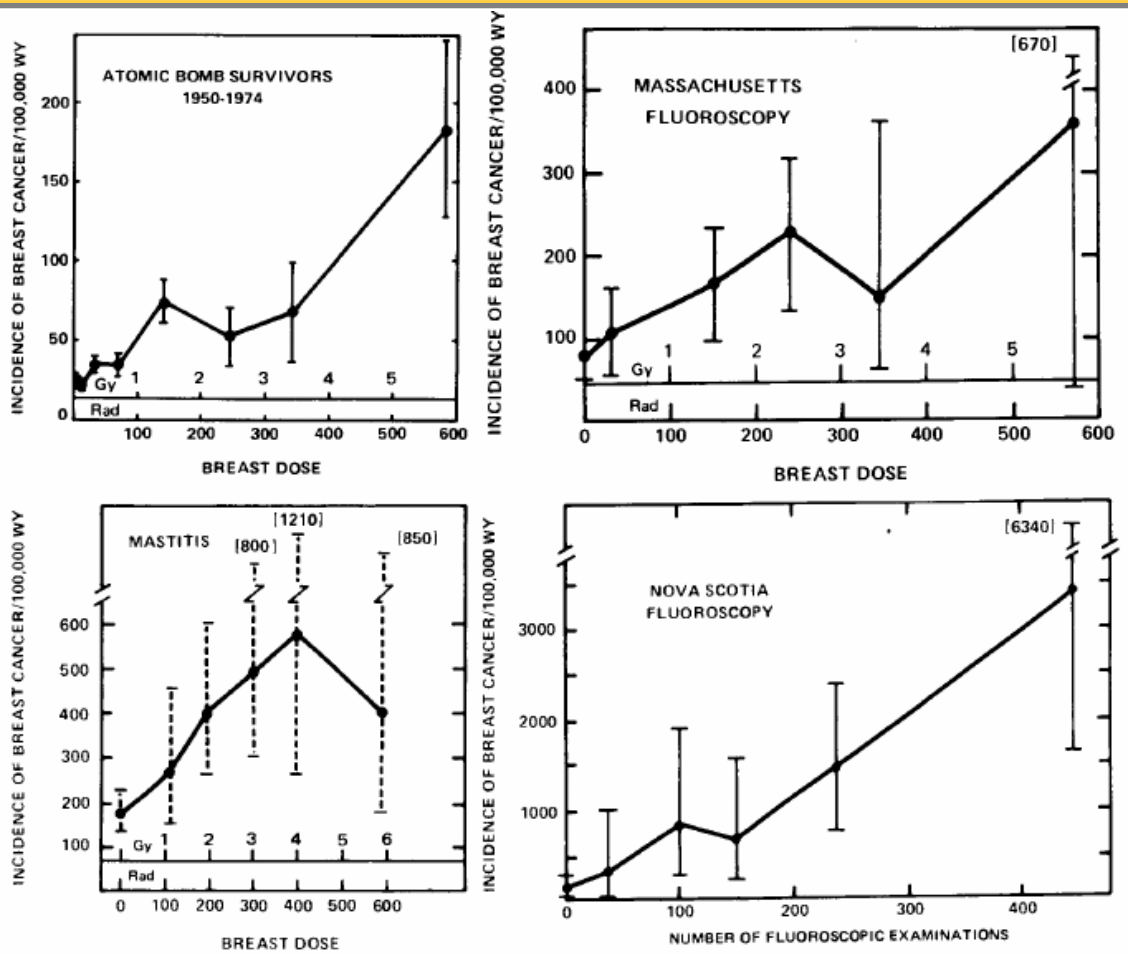
Boice et al, *Radiat Res* 126:214, 1991
Boice & Monson, *J Natl Cancer Inst* 59:823 1977



Dose Response – Pooled Analysis of Breast Cancer Studies

Breast Cancer

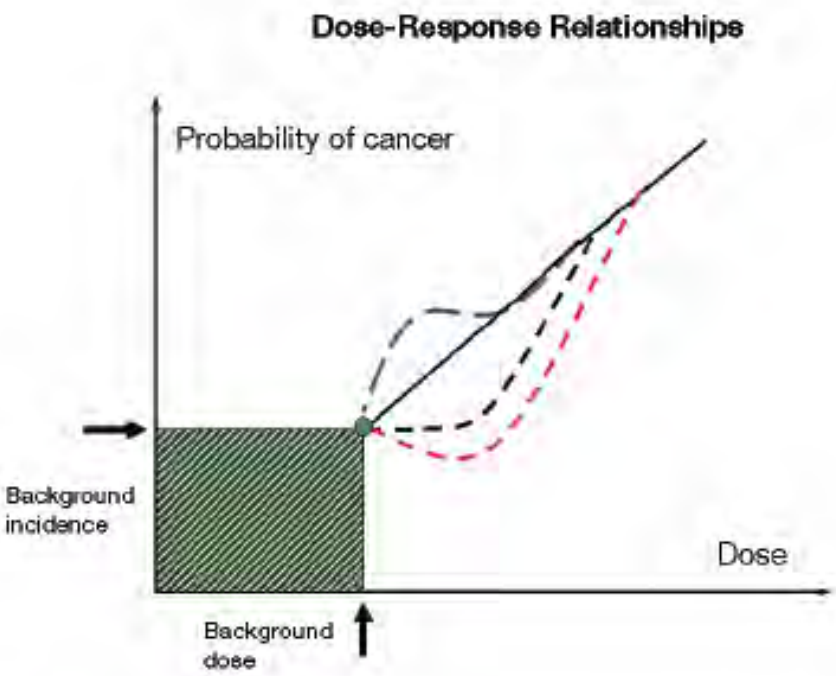
Consistent with linearity



Boice, *Radiology* 131:589, 1979

LNT – Plausible and Practical Although Risk Below 100 mSv Uncertain

(67) … the adoption of the LNT model combined with a judged value of a dose and dose rate effectiveness factor (DDREF) provides a prudent basis for the practical purposes of radiological protection, i.e., the management of risks from low-dose radiation exposure. (ICRP Publ 103, 2007)



Low Dose and
Low Dose-Rate Radiation
Effects and Models

Lung and Leukemia
TB - Fluoroscopy, Massachusetts

	Lung	Leukemia
No. exposed	6,285	
No. unexposed	7,100	
No. chest fluoroscopies (ave)	77	
Dose to lung or marrow	84 cGy	9 cGy
Observed (O)	69	17
Expected (E)	86	19
RR (95% CI)	**0.8** (0.6-1.0)	**0.9** (0.5-1.8)

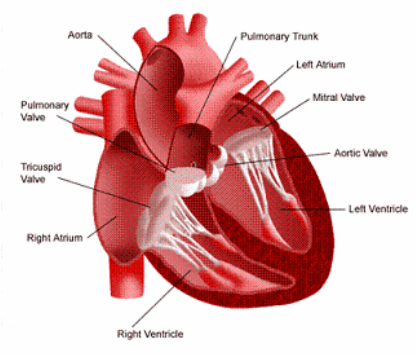
Davis et al, *Cancer Res* 49:6130, 1989

No excess lung or leukemia

Not all tissues respond similarly to fractionation.

Heart Disease
TB – Fluoroscopy, Massachusetts

Number exposed	6,285
Number unexposed	7,100
Heart dose	~90 cGy
Observed heart disease (O)	826
Expected (E)	908
RR (95% CI)	**0.9** (0.8-1.0)



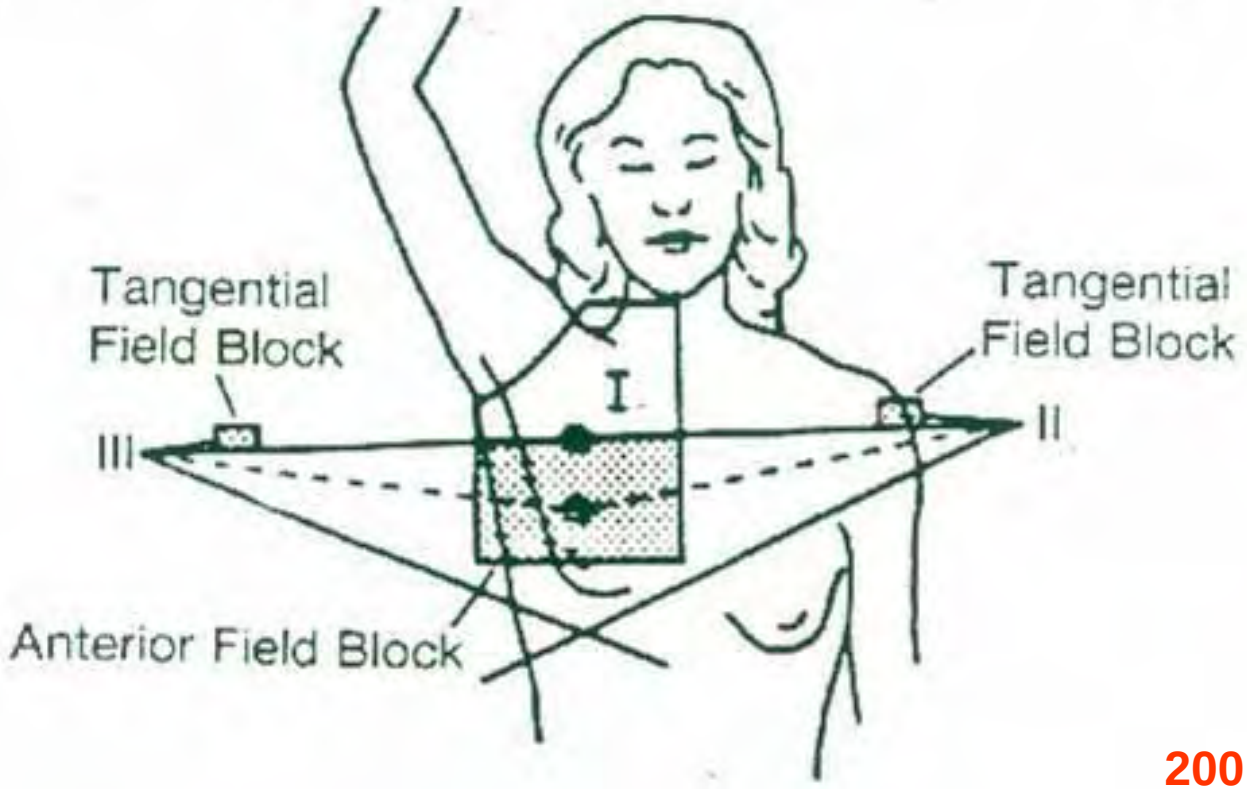
Davis et al, *Cancer Res* 49:6130, 1989

No excess heart

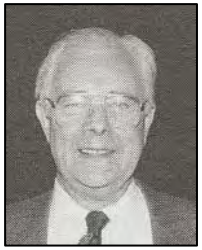
A Few Golden Nuggets
TB Fluoroscopy

- Low-dose fractions increase breast cancer
- Linearity fits the breast data
- Low-dose fractions NOT found to increase
  - Lung cancer
  - Leukemia
  - Heart disease
- Be cautious when generalizing

Treating Breast Cancer
Radiotherapy Dose to Contralateral Breast



200 cGy (ave)



Radiotherapy for Breast Cancer All Breast Cancers in Connecticut (1935-82) – Second Breast Cancer

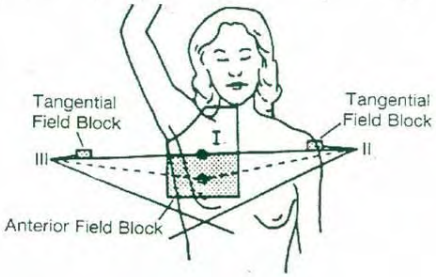
	RR	95% CI
All Subjects*	**1.19**	0.9-1.5
Time After Exposure (Yr)		
5-9	0.99	0.7-1.4
≥10	**1.33**	1.0-1.8
Age at Exposure (Yr)		
<35	**2.26**	0.9-5.7
35 -	1.46	0.9-2.3
≥45	1.01	0.8-1.4

*655 Cases, 1,189 Controls

Boice et al, *NEJM* 326:781, 1992

Risk after 10 years among young.
Example of age modification.

Unanswered Question
Genetic Susceptibility?
Second Breast Cancer



WECARE, 2nd breast (n=800) to study

Interaction Between Radiation and Genes*

Exposure	RR	95% CI
BRCA1 mutation	4.5	2.8-7.1
BRCA2 mutation	3.4	2.0-5.8
1 Gy (<40 y)	**1.6**	1.1-2.5
1 Gy (≥45 y)	1.0	0.9-1.3

Stovall, *IJROBP*, 2008
Bernstein, *Breast Ca Res*, 2004

**BRCAs*, *ATM*, *CHEK2*1100delC*

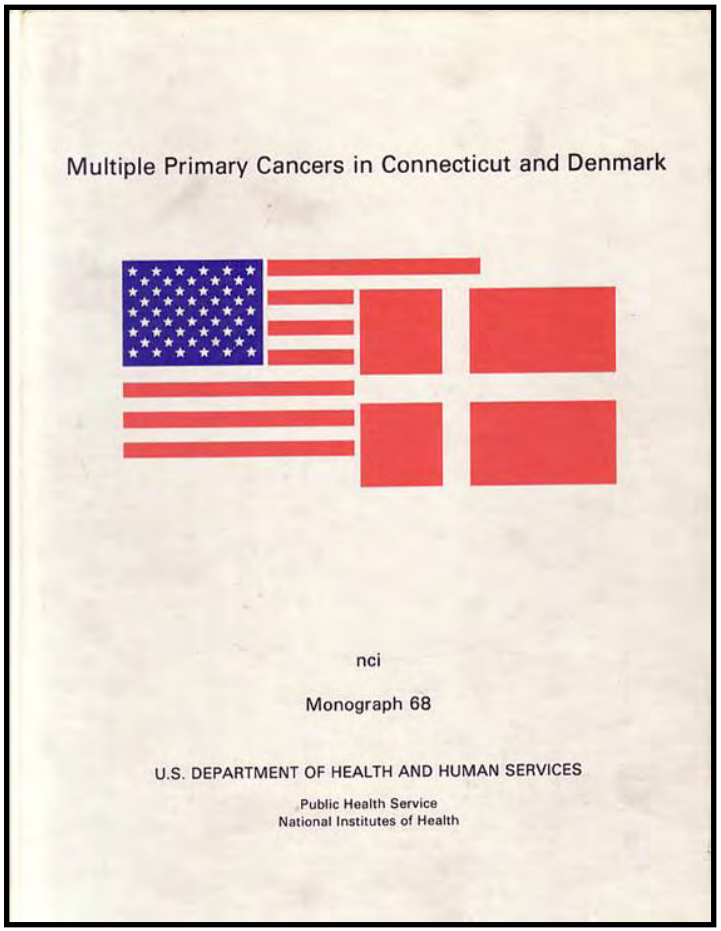
A Few Golden Nuggets
Breast Cancer Treatment

- Long latency (time) for second cancers to occur
- Age at exposure can have a profound effect – little risk for exposures over 45 y
- Genetic susceptibility at low doses is uncertain

Radiation Treatments
Multiple Primary Cancers

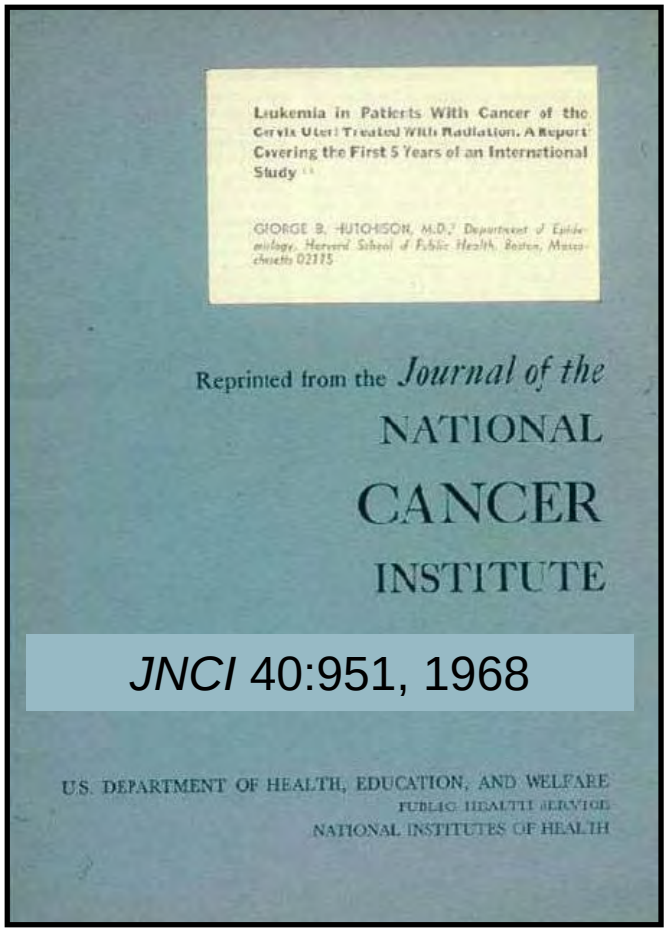
Warren and Gates, 1932, Definitions

Risk Quantification



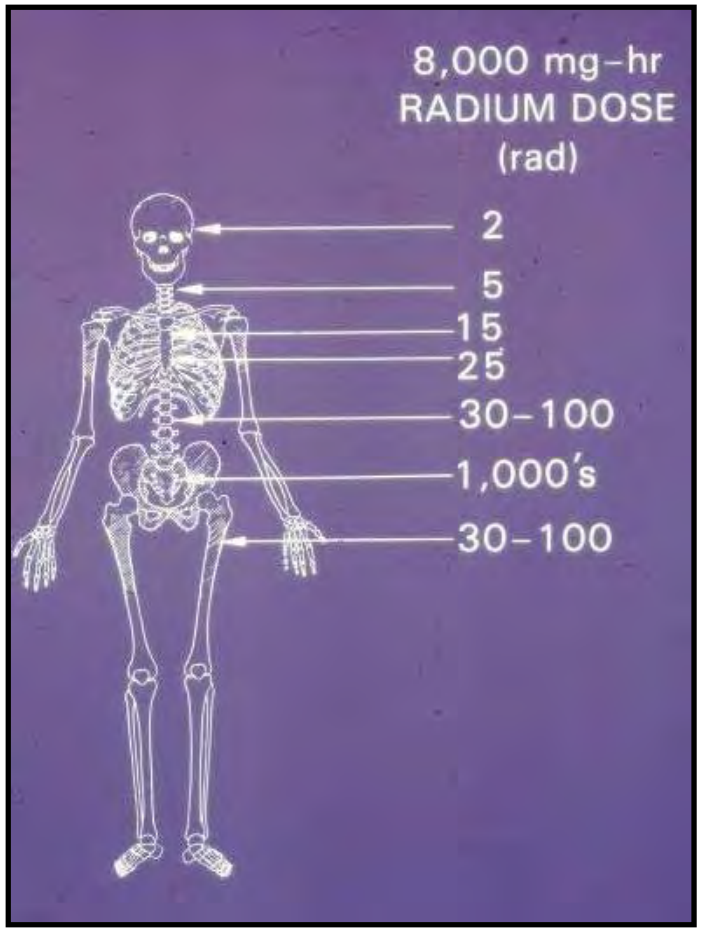
Study of Leukemia
Radiotherapy for Cervical Cancer

Third study in 1960s designed to quantify risk of leukemia



JNCI 40:951, 1968

Cervical Cancer and Leukemia
Large Doses, No Chemotherapy, Good Survival



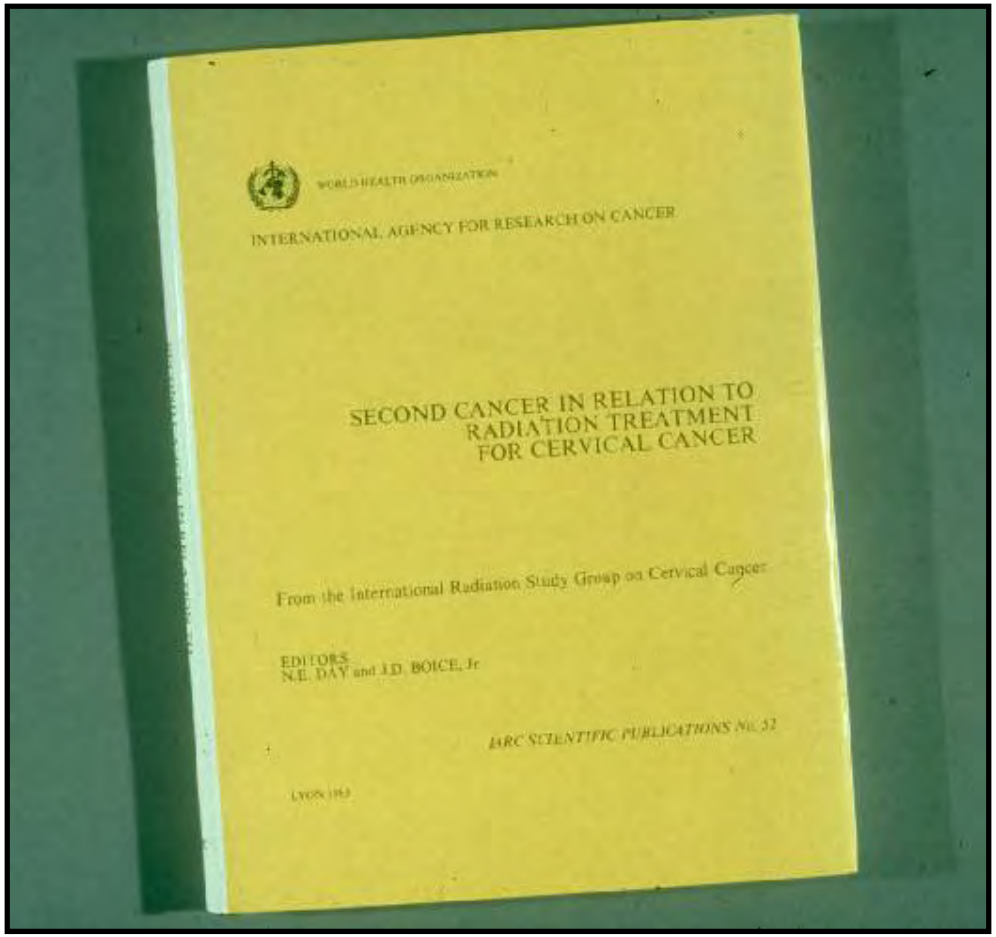
Cervical Cancer and Leukemia Blood Studies and Clinical Follow-up 30 Radiotherapy Centers in 9 Countries

Number	30,000 women
Dose	5-15 Gy (marrow)
Leukemia	
Observed	13
Expected	15.5
Risk	**No excess**

Boice & Hutchison, *JNCI* 65:115, 1980

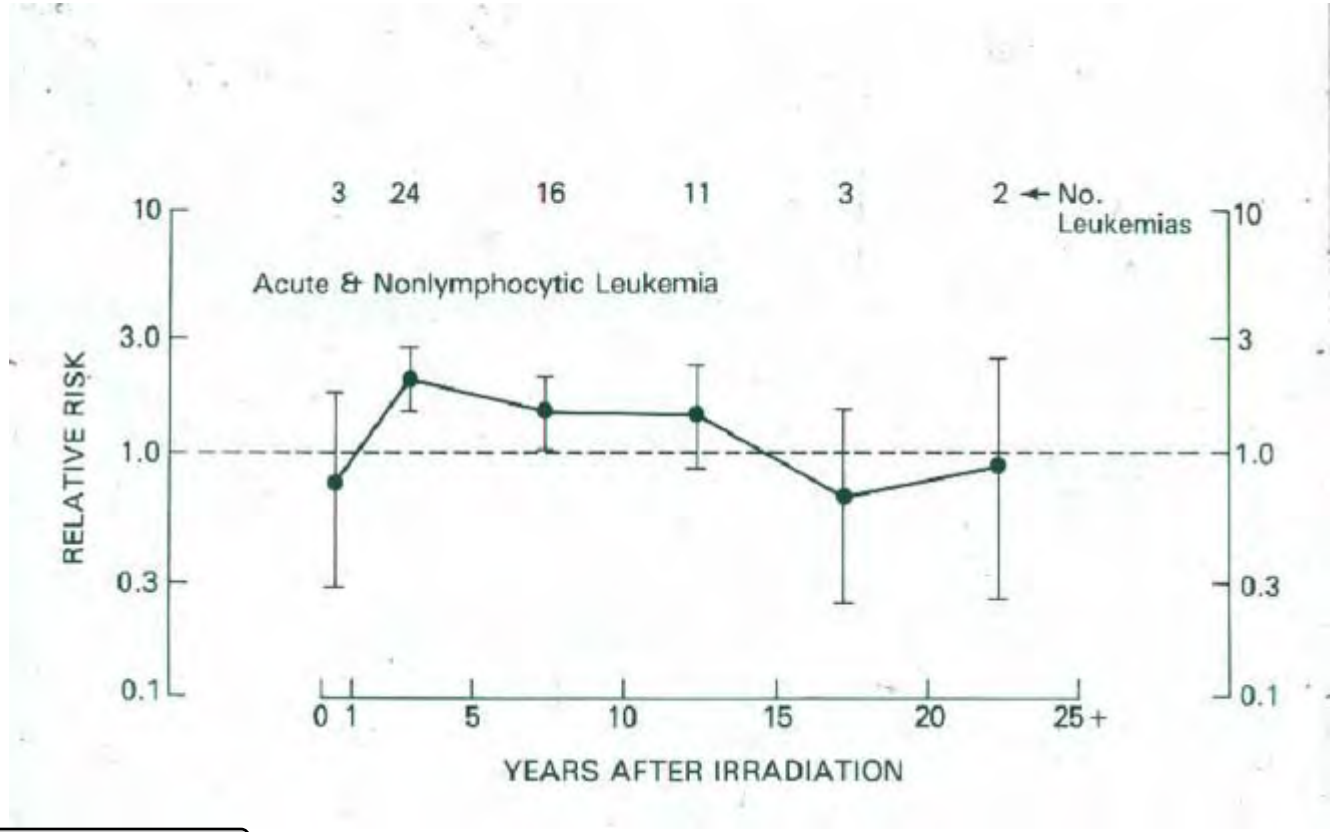
Huge dose but no risk

International Cervical Cancer Study Expansion – 16 Radiotherapy Centers and 17 Cancer Registries in 14 Countries



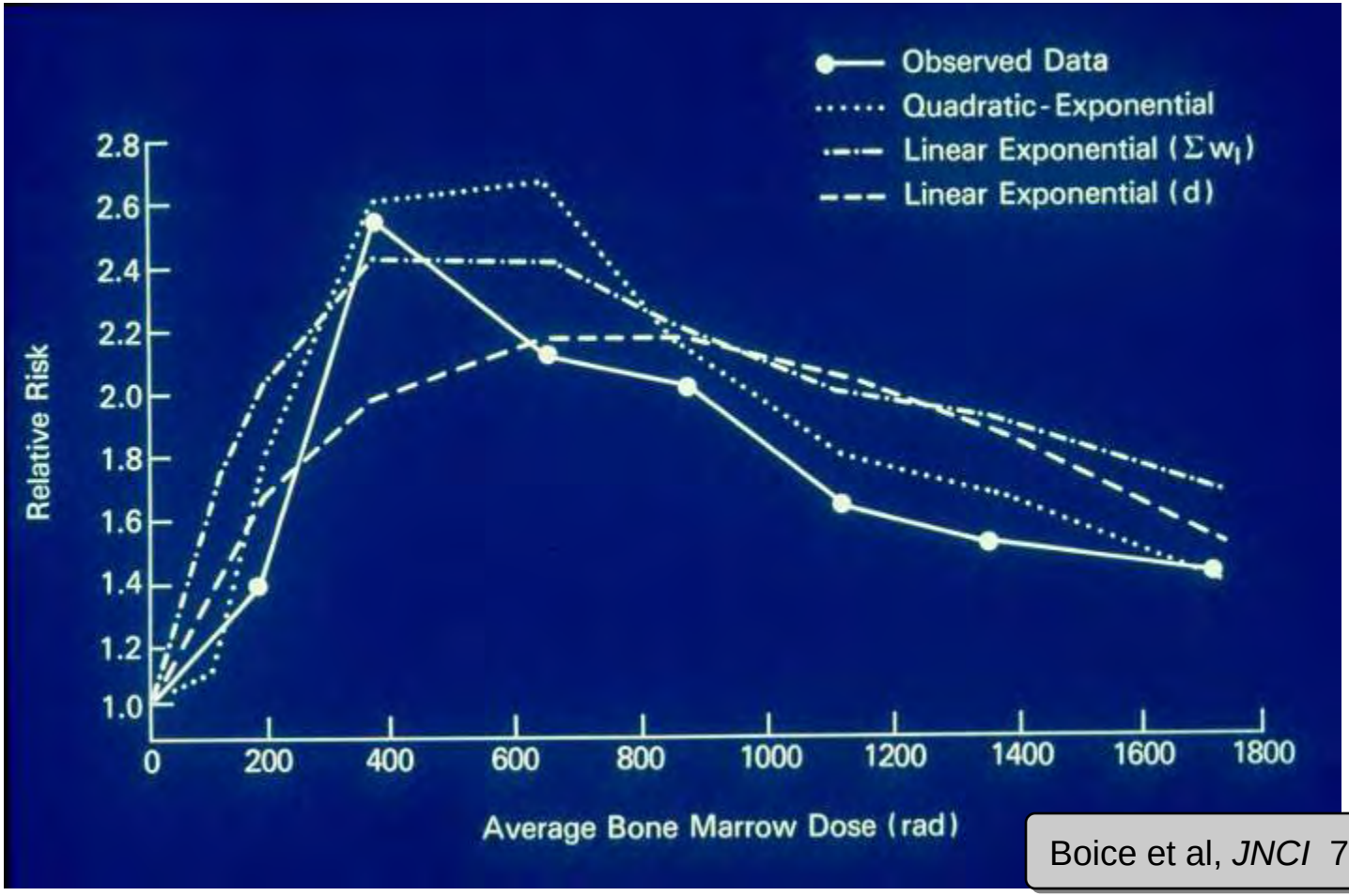
200,000 women

Characteristic Wave-like Pattern for Radiation-Induced Leukemia



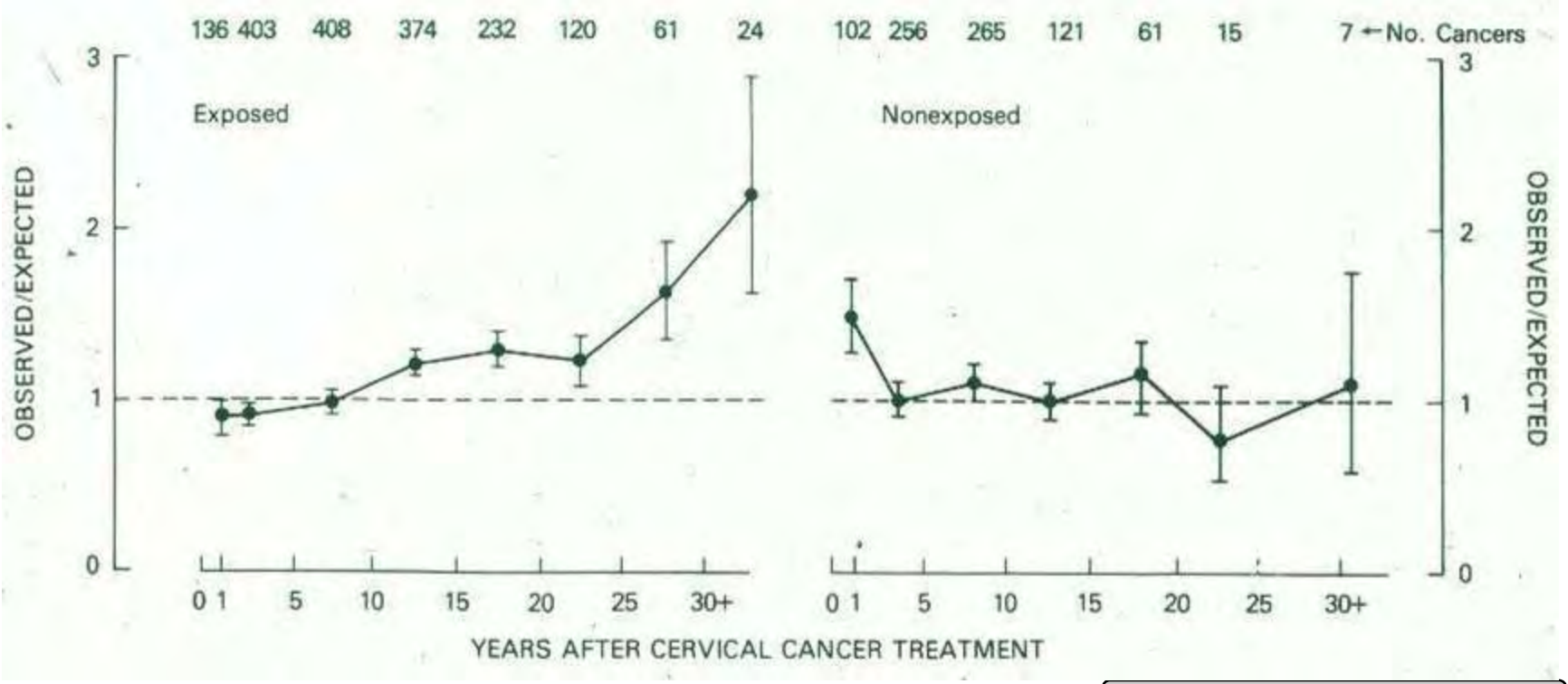
Boice, *JNCI*, 74:955, 1985

Bone Marrow Dosimetry Downturn at High Doses



Boice et al, *JNCI* 79, 1987

Solid Cancers After Radiotherapy
Long Minimum Latency



Boice, *JNCI* 74:955, 1985

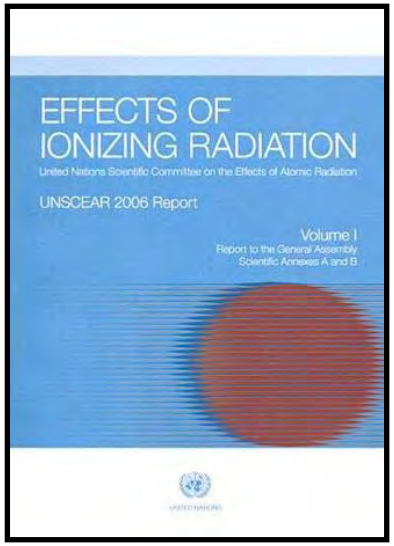
Not all cancers have been convincingly increased following radiation in human studies (UNSCEAR 2008)

There is **little evidence** for an association with radiation for:

- chronic lymphocytic leukaemia
- pancreatic cancer
- prostate cancer
- cervical cancer
- testicular cancer
- uterine cancer
- non-Hodgkin's lymphoma
- Hodgkin's disease
- multiple myeloma

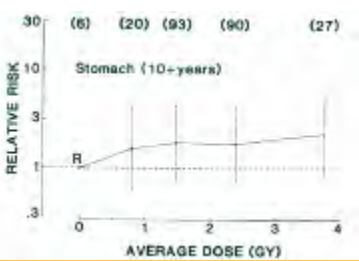
And other associations have only been seen following **very high doses** (radiotherapeutic):

- small intestine
- rectum
- uterus
- kidney



Opportunities for Low-Dose Studies
Cervical Cancer - Lightly Irradiated Sites

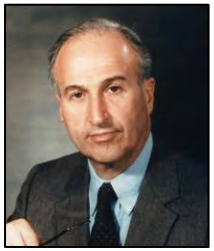
Second Cancer	Number Cases	Organ Dose (ave. GY)	RR at 1 Gy (90% CI)
Stomach	338	2.0	1.69 (1.0 - 3.3)
Pancreas	211	1.9	1.00 (0.7 - 1.6)
Kidney	134	2.0	1.71 (1.0 - 3.2)
Thyroid	43	0.1	2.35 (0.6 – 8.7)
Breast	838	0.3	1.03 (0.1 - 2.3)



Boice, *Radiat Res* 116:3,1988
Chaturvedi, *JNCI* 99:1634, 2007

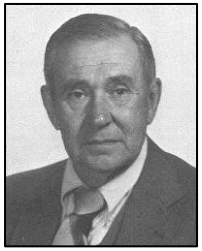
Golden Nuggets
Cancer Treatments

- High dose to small volumes may kill rather than transform most cells
- Long latency for solid cancers to develop
- Short latency for leukemia to develop
- Opportunity for low-dose studies - scatter
- Caution – new technologies (IMRT, Intensity-Modulated Radiation Therapy) result in increased dose to all normal tissue



Pregnancy and Medical Radiation

Is the low-dose association causal?



Oxford Prenatal X-ray Survey

Childhood cancer	Cases	% X-ray	RR
Leukemia			
Lymphatic	2,007	14	1.5
Myeloid	866	14	1.5
Lymphoma	719	13	1.4
All leukemia/lymphoma	4,771	14	1.47
Wilms	590	15	1.6
CNS	1,332	13	1.4
Neuroblastoma	720	14	1.5
Bone	244	11	1.1
Other solid	856	15	1.6
All solid	3,742	14	1.47

Bithell, Stewart, *Br J Cancer* 31:271, 1975

Biologically plausible to have same RR?

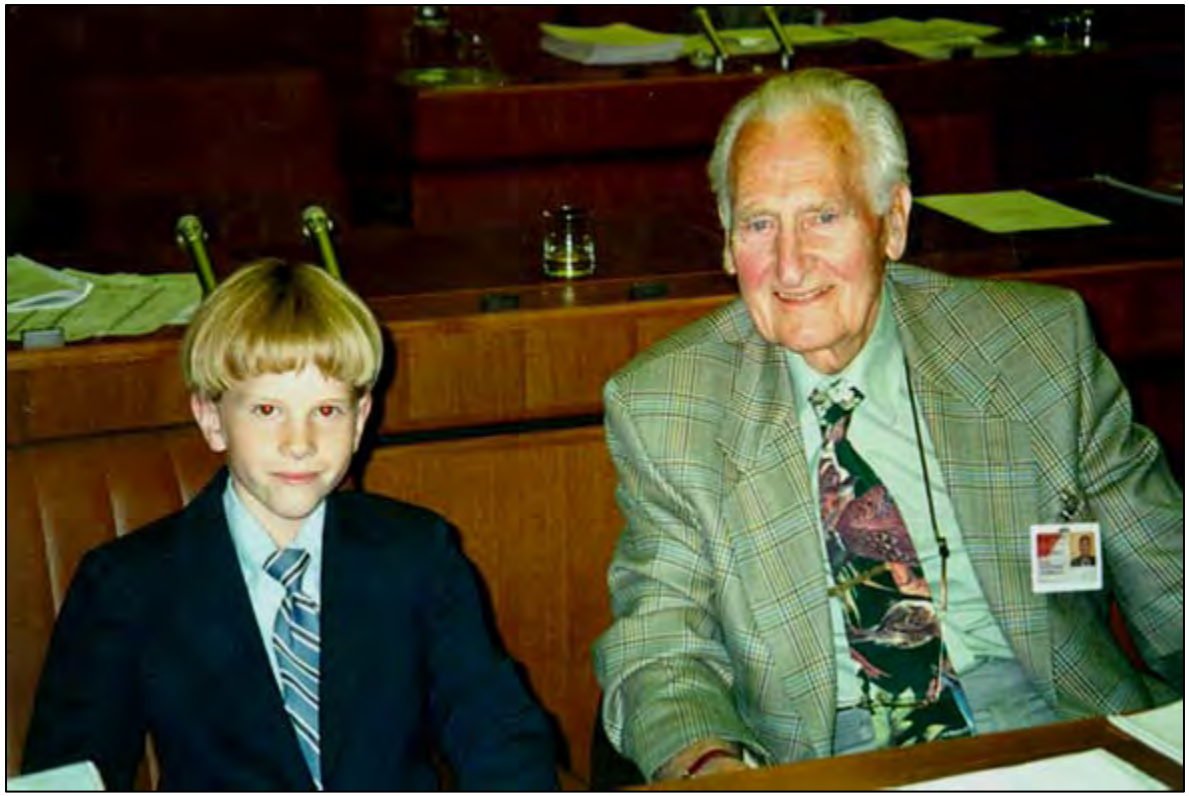
Biological Plausibility Questioned

"… the equality of relative risks associated with obstetric x-rays for leukemia and solid tumors is perplexing given the variability in tissue radiosensitivity, dissimilar origins, and different incidence patterns."

Association does not mean causation.

Miller, *NCRP Proc 6* (Apr), 1984
Boice and Miller, *Teratology* 59:227, 1999

Sir Richard Doll – Causal Interpretation



UNSCEAR, Vienna, 1996

Prenatal X-ray – Leukemia Sweden, 1973-87, Medical Records

	Leukemia cases (578)	Controls (578)	RR	95% CI
All exposed	121	113	**1.11**	0.8-1.5
No. x-rays				
0	503	511	**1.00**	
1	113	101	**1.16**	0.9-1.6
2	8	12	**0.72**	0.3-1.8
Type x-ray				
Abdominal	68	61	1.14	0.8-1.7
Other	34	32	1.04	0.6-1.7

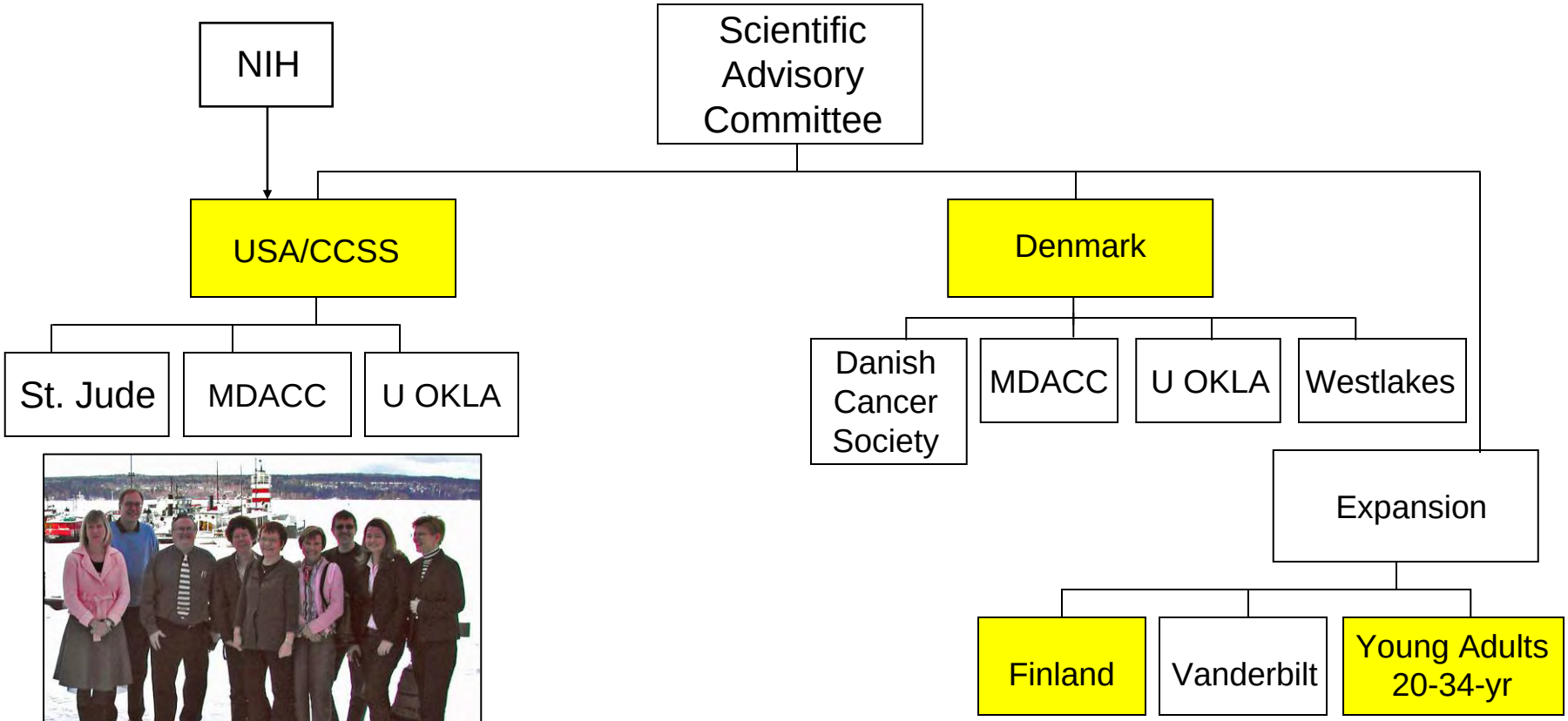
Naumberg et al, *Radiat Res* 156:718, 2001

Golden Nuggets
Prenatal X-ray and Cancer

- Many associations – but all in case-control studies (possible biases in selection and recall)
- No cohort studies positive, including atomic bomb survivors
- Biological plausibility questioned
- Causal nature of low-dose association questioned, particularly for solid cancers

Preconception Studies
Children of Cancer Survivors

Children of Cancer Survivors
Genetic Consequences of Cancer Treatment



Boice et al, *Health Phys* 85:65, 2003

Preliminary Results (CCSS)

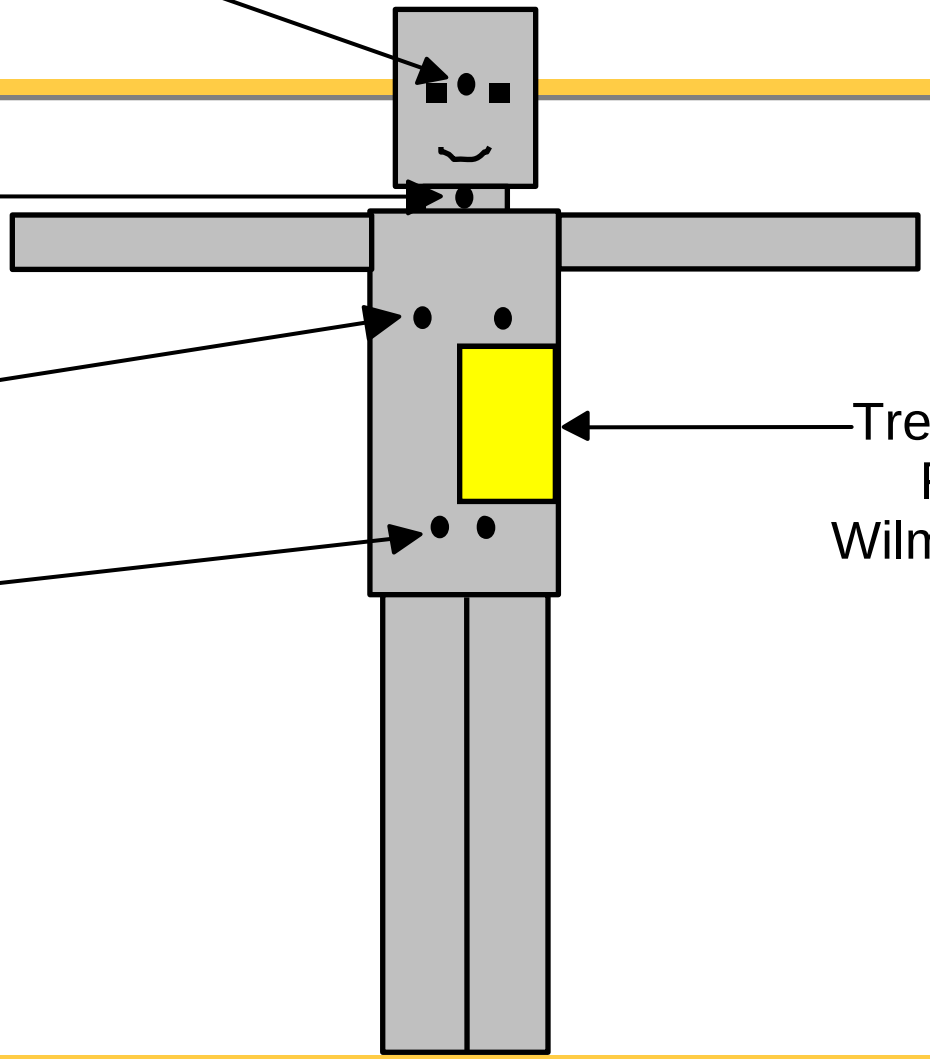
Genetic Disease in Children of Survivors and Sibling Controls

Type of genetic disease	Survivors (n=4,214)	Controls (n=2,339)	RR
Cancer	10 (0.2%)	4 (0.2%)	1.4
Cytogenetic Abnormality	5 (0.1%)	3 (0.1%)	0.9
Single Gene Disorder	25 (0.6%)	10 (0.4%)	1.4
Simple Malformation	117 (2.8%)	78 (3.3%)	0.8
Total	157 (3.7%)	95 (4.1%)	**0.9**

Mulvihill et al, *Am J Hum Genet* 69:A391, 2001

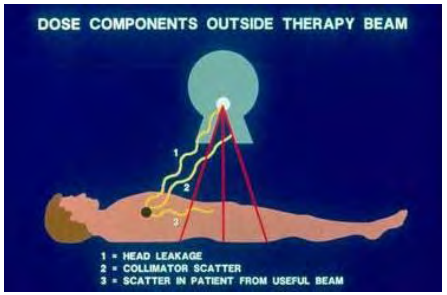
No increase in birth defects

Dosimetry Models

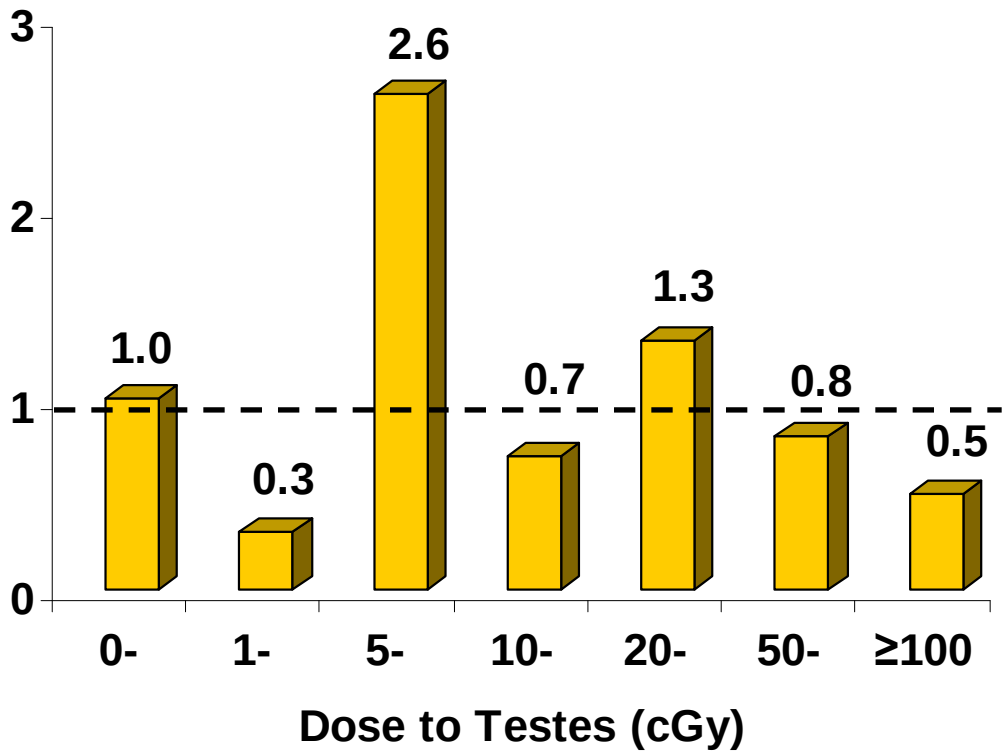


Stovall et al, *IJROBP* 60, 2004

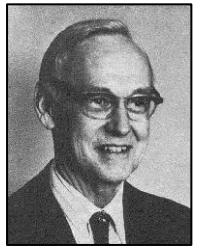
Stillbirths and Neonatal Deaths
Children of Male Cancer Survivors



Relative Risk
of Stillbirth and
Neonatal Death

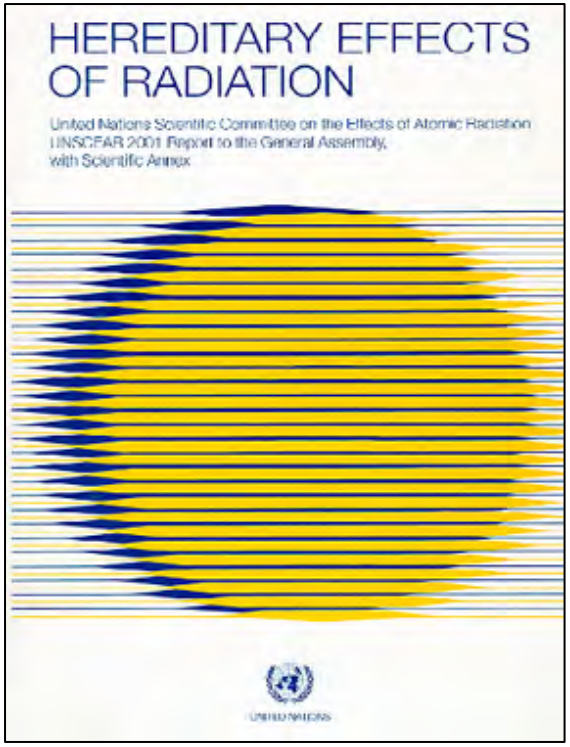


Trend p_1 = 0.32 (-), Pilot

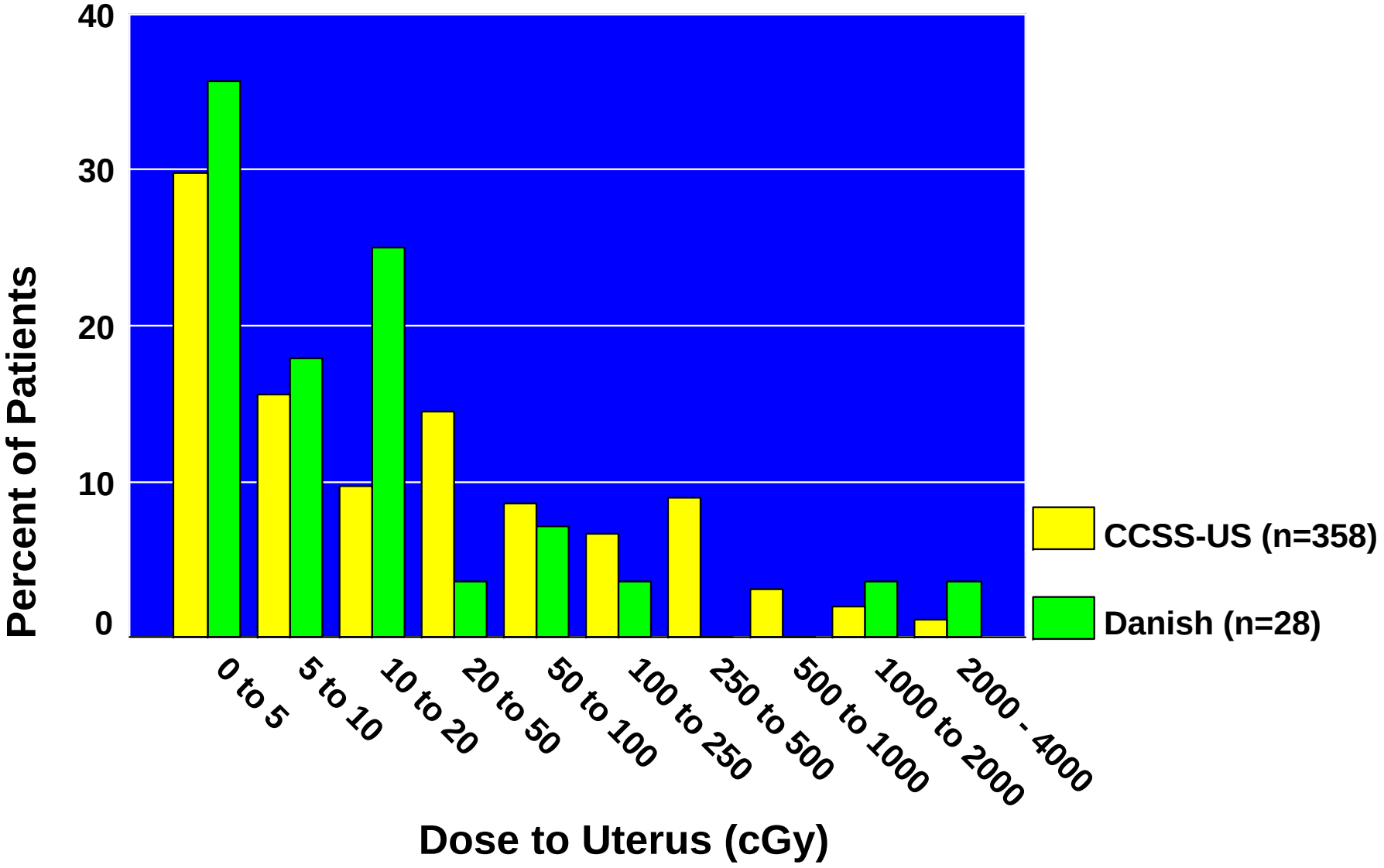


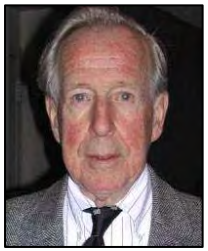
Epidemiology has not Revealed Heritable Effects in Humans

No radiation-induced genetic diseases have so far been demonstrated in humans... estimates of risk have to be based on mouse experiments. UNSCEAR 2001

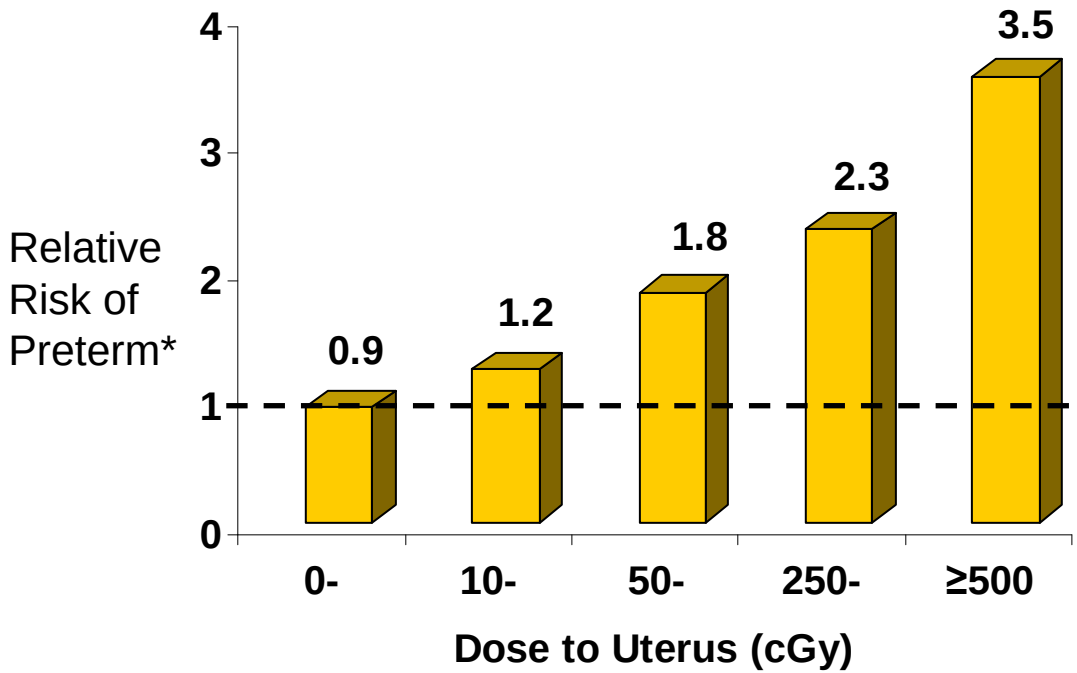


Girls Treated with Radiation
High Dose to Uterus (n=386)





Risk of Preterm Birth Increases with Uterine Dose



	Preterm	Fullterm	RR
*Referent: Children not treated with radiation	121	496	1.0

Signorello et al. *JNCI*, 2006

Similar association with low birth weight and small for gestational age

Golden Nuggets
Preconception Radiation

- No genetic effects detected
- Radiotherapy to uterus can result in low birth weight and preterm babies

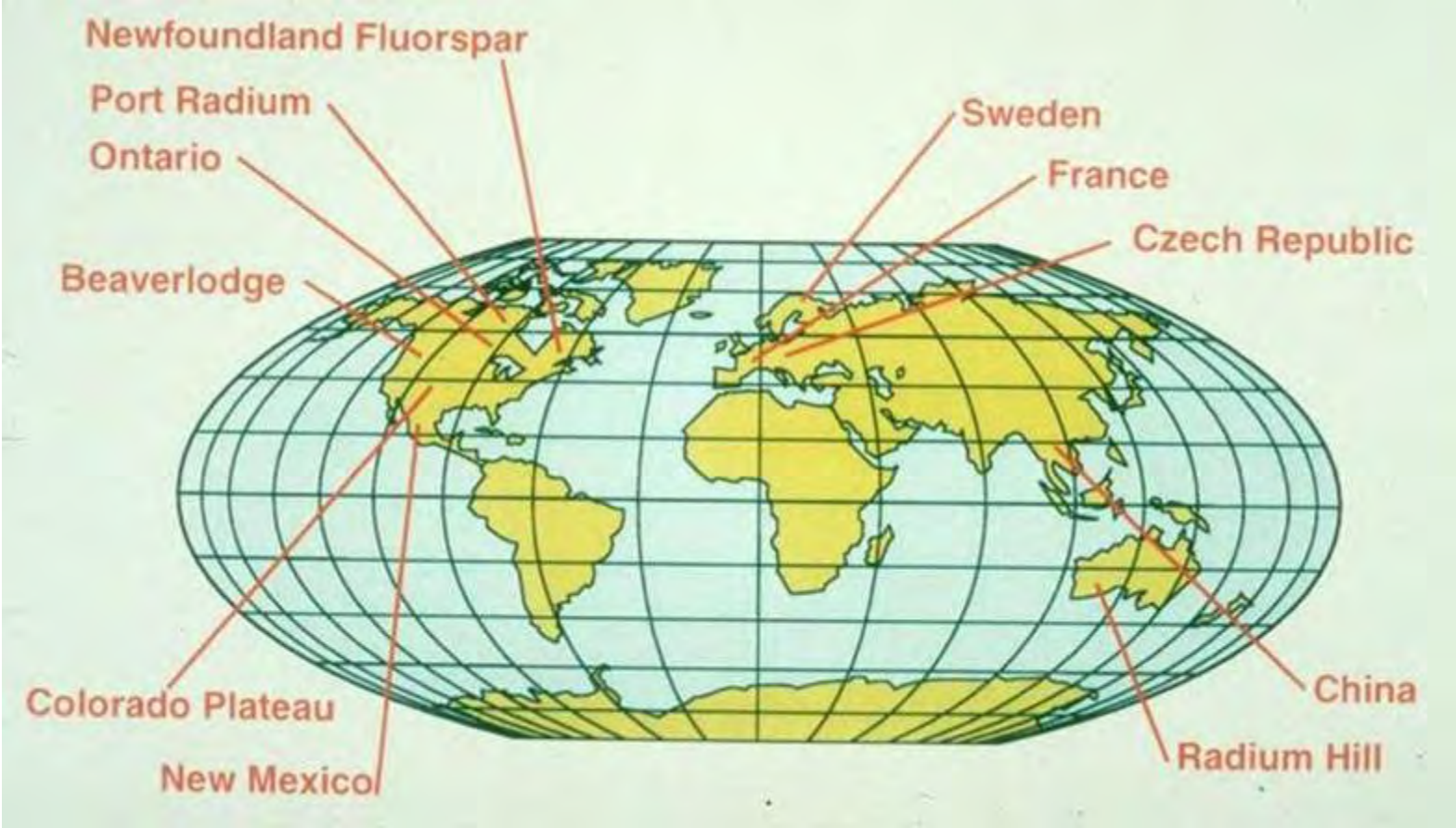
RADON AND LUNG CANCER RISK

RADON AND LUNG CANCER RISK:

A JOINT ANALYSIS OF 11 UNDERGROUND MINERS STUDIES

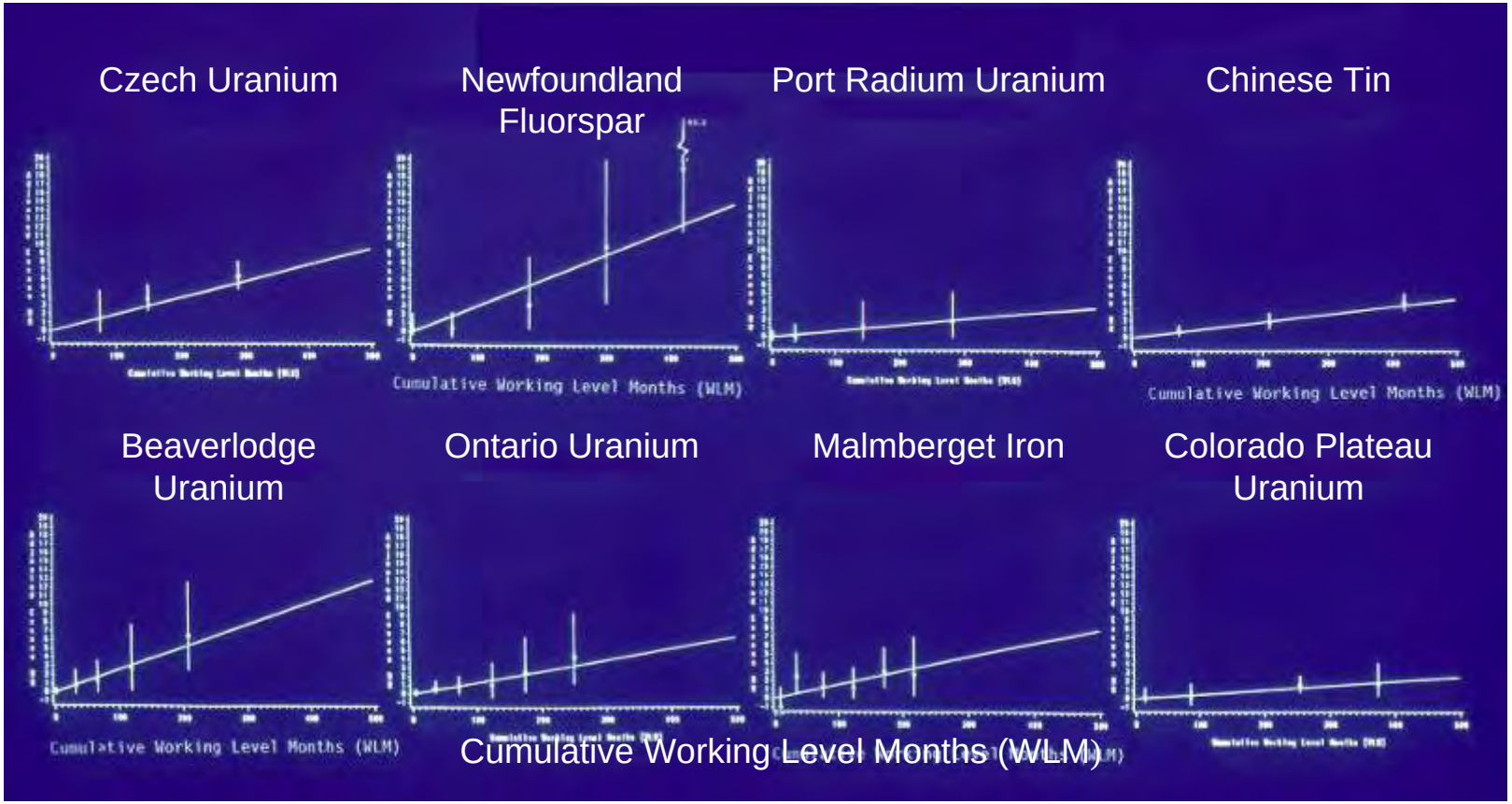
NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Pooled Analysis of Underground Miner Studies

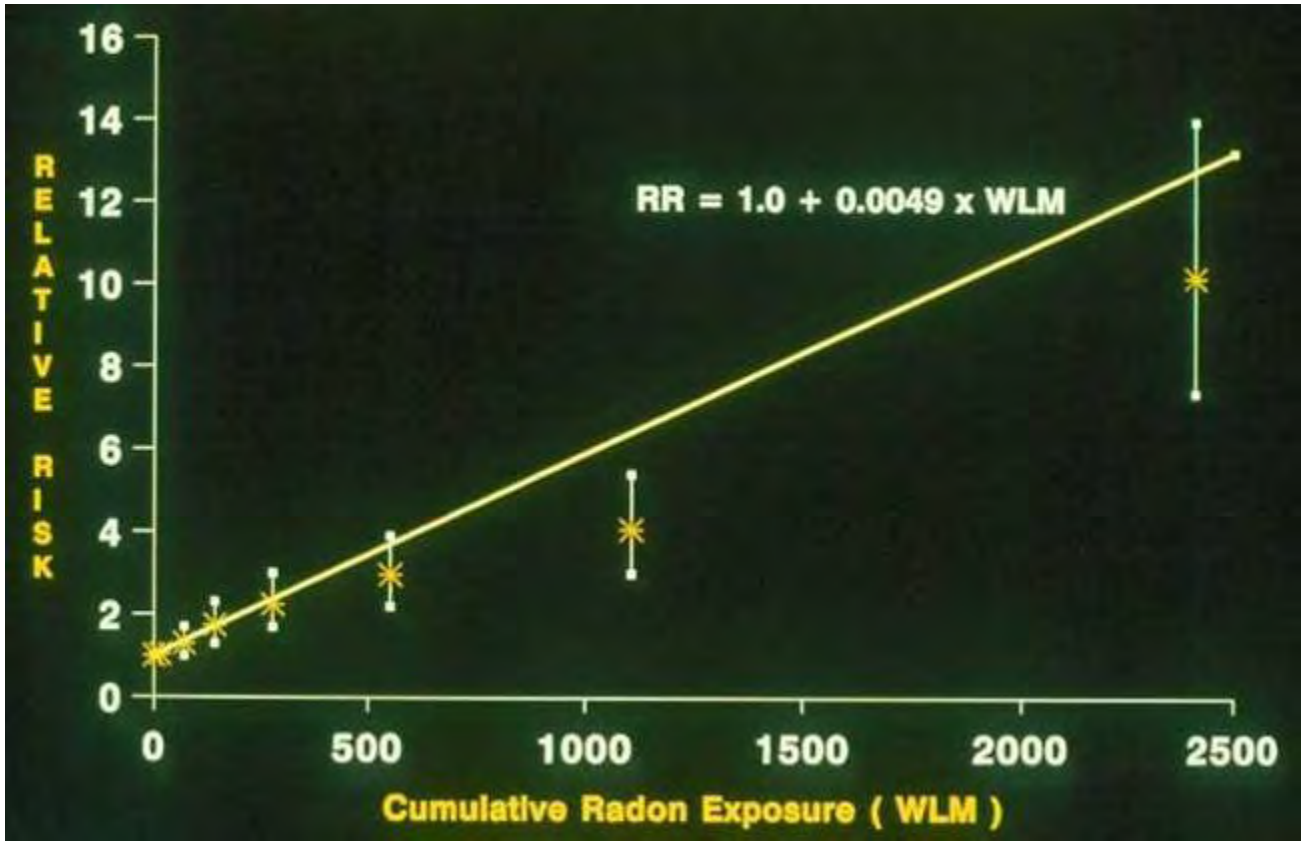


The Study Team - 1992

Lung Cancer Dose Responses in Miners Consistency in the Epidemiology



11 Underground Miner Studies
68,000 Miners – 2,700 Lung Cancers



Lubin et al, 1993

1 pCi/l ~ 0.2 WLM / yr.

Washington Post, February 6, 1986

New Meaning to “The Nuclear Family”

Radon Studies in Homes (Case-Control)

United States
- √ New Jersey
- √ Missouri
- Iowa
- Connecticut
- Utah/Idaho

Canada
- Winnipeg

Europe
- Southwest England
- Western Germany
- Czech (cohort)

Nordic Countries
- √ Sweden
- Finland

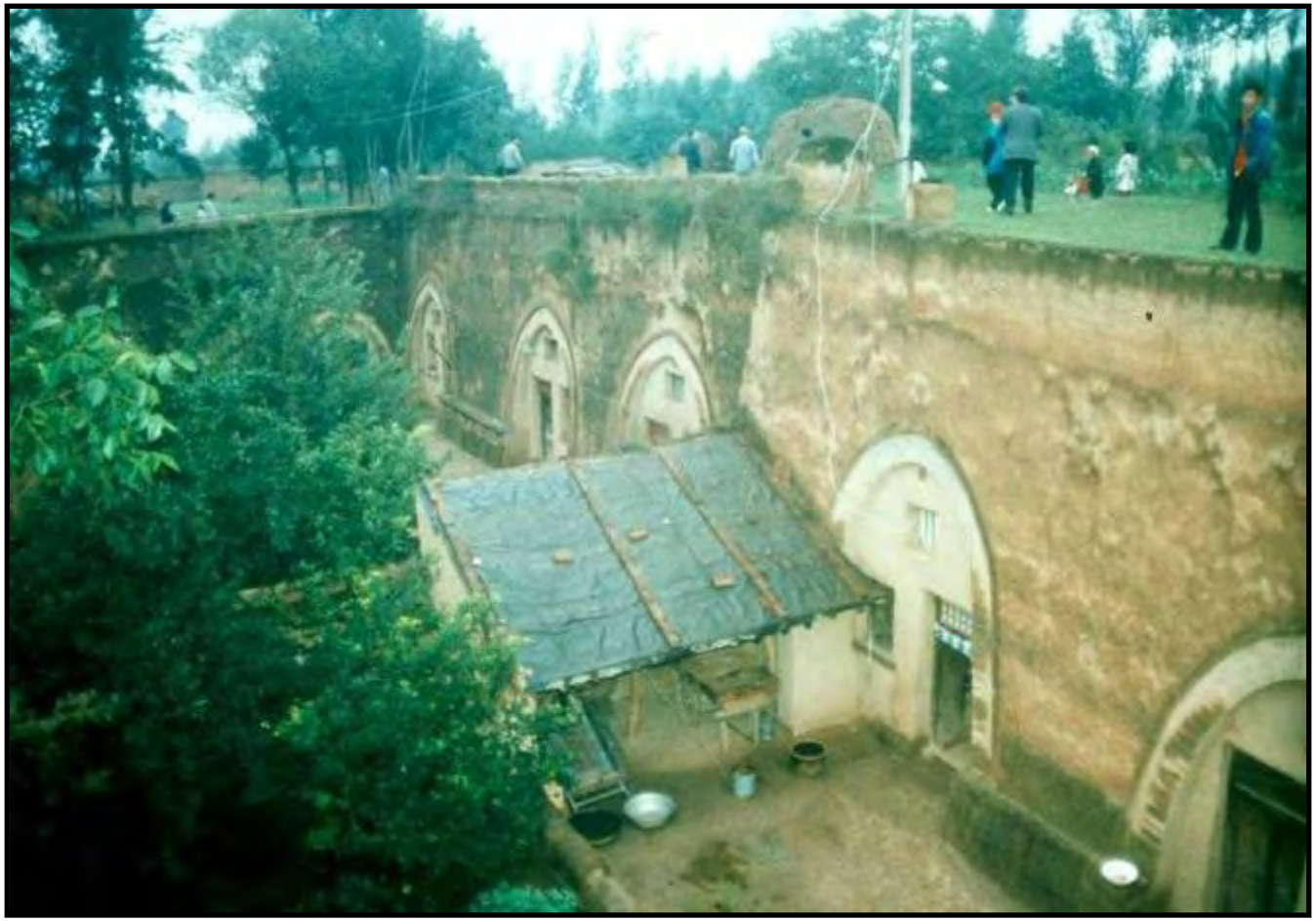
China
- √ Shenyang
- √ Gansu

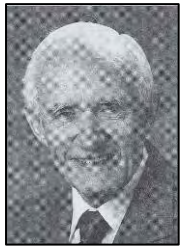
Pooled
- √ Lubin (1997, 1999)
- North America (Krewski, 2005)
- Europe (Darby, 2005)
- √ China (Lubin, 2004)
- World (Darby, in progress)

BEIR VI, 1999; Field, *Rev Envir Health* 16, 2001

People's Republic of China
Gansu Province

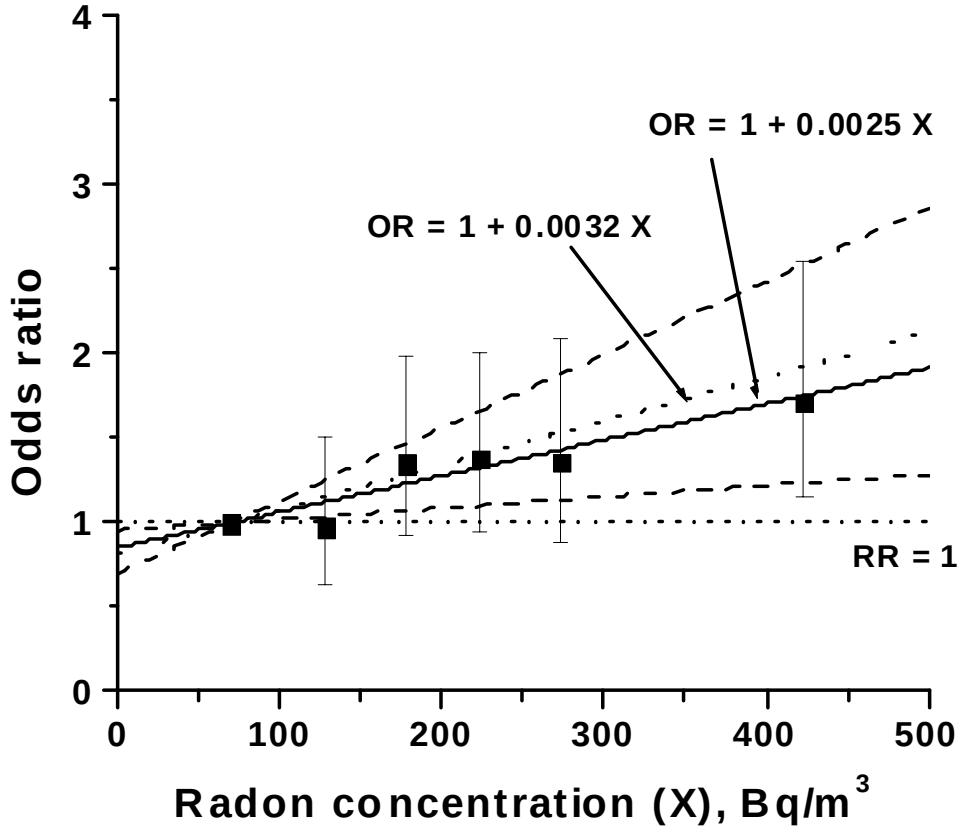
Gansu Province
Underground Dwellings





Gansu Province Underground Dwelling

Gansu China - Radon Study



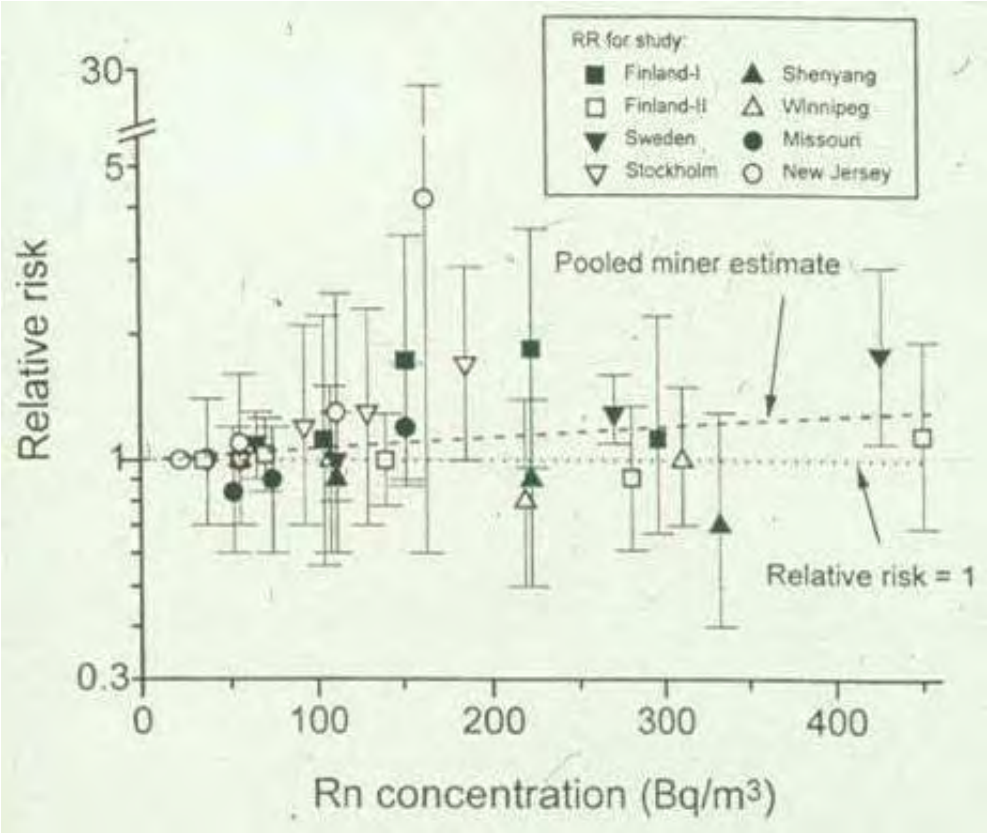
Consistent with linearity

4 pCi/l = 150 Bq/m^3

Wang et al. *Am J Epidemiol* 155:554 2002

Lubin et al. *Int J Cancer* 109:132, 2004

Indoor Radon Meta-Analysis
Lung Cancer



Difficult to detect low-dose risks, yet significant trend when studies combined

Lubin & Boice, *JNCI*, 89:49, 1997

4 pCi/l = 150 Bq/m^3

Radon Interacts with Smoking to Enhance Risk

A nearly multiplicative interaction

NRC, BEIR, 1999

Smoking
Compared with Radiation/Radon

RR	Cigarettes Per Day	A-Bomb Dose, Sv	Miners WLM	Radon Indoor Bq/m^3
1.0	0	0	0	< 40
4.6	**1-9**	**3.4**	735	**4,500***

*140 pCi/L

Boice, *Radiat Res*, 146:356, 1996

Smoking <10 cig/day equivalent to being high dose A-bomb survivor

Golden Nuggets
Radon

- The epidemiology is consistent
- Linearity fits all the data
- Indoor risk low and hard to detect but case-control studies consistent with the miner study predictions
- Interaction with smoking is nearly multiplicative
- Best way to lower radon risk is to stop smoking

Descriptive Studies
Nuclear Facilities (Sellafield, U.K.)

Cancer in Populations Living Near Nuclear Facilities

JAMA 256: 1991

Overall Relative Risk
US Nuclear Facilities Study

Disease	Before Startup	After Startup
Leukemia		
Childhood	1.08	1.03
All Ages	1.02	0.98

Time Pattern

Risk higher before than after facilities began operating

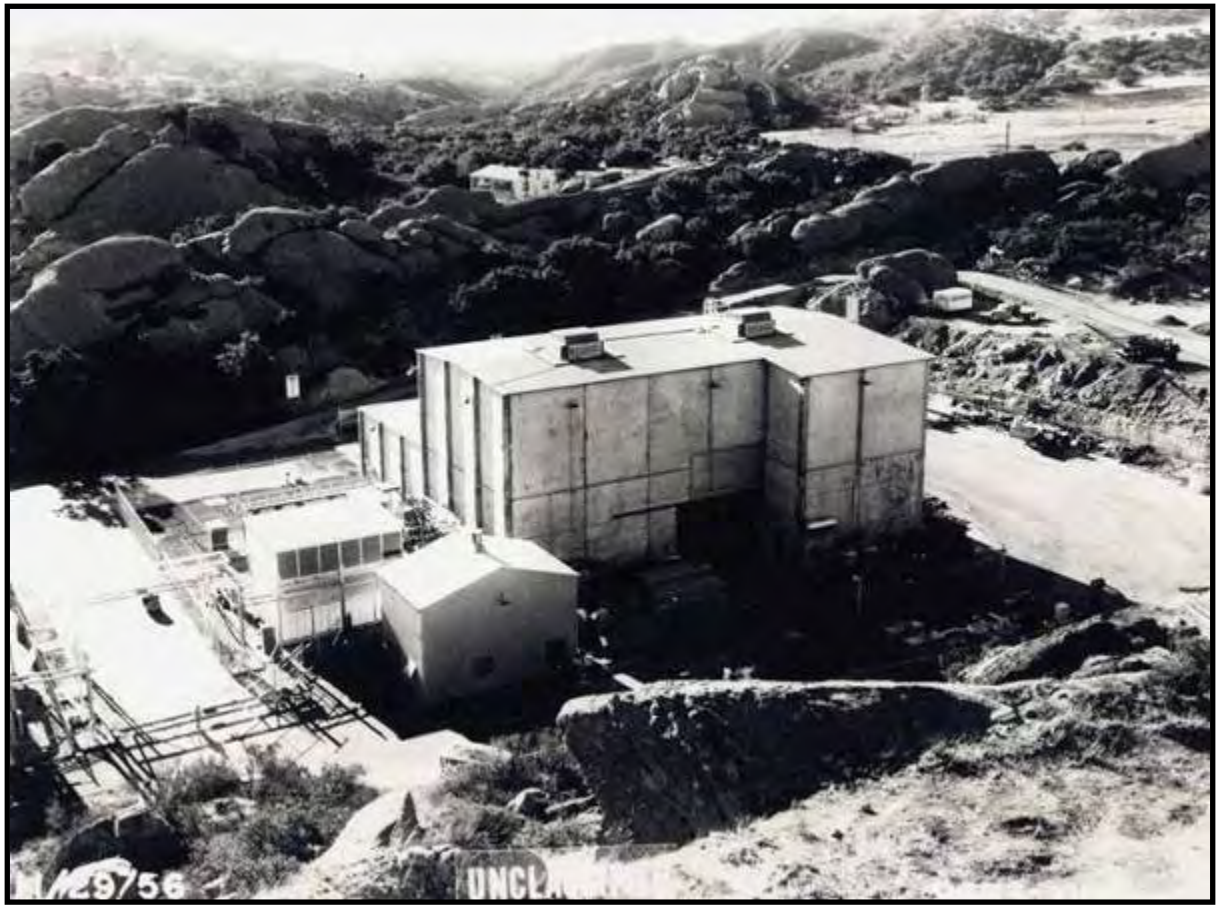
Jablon et al, *JAMA* 265:1403-1408, 1991

Golden Nuggets
Descriptive Studies

- Doses to individuals not known
- Can’t adequately control for confounding
- But large numbers and
- Great societal interest
- Be cautious, e.g., low statistical power (dose is very low) and bias can lead to spurious results
- Generate hypotheses not to test them

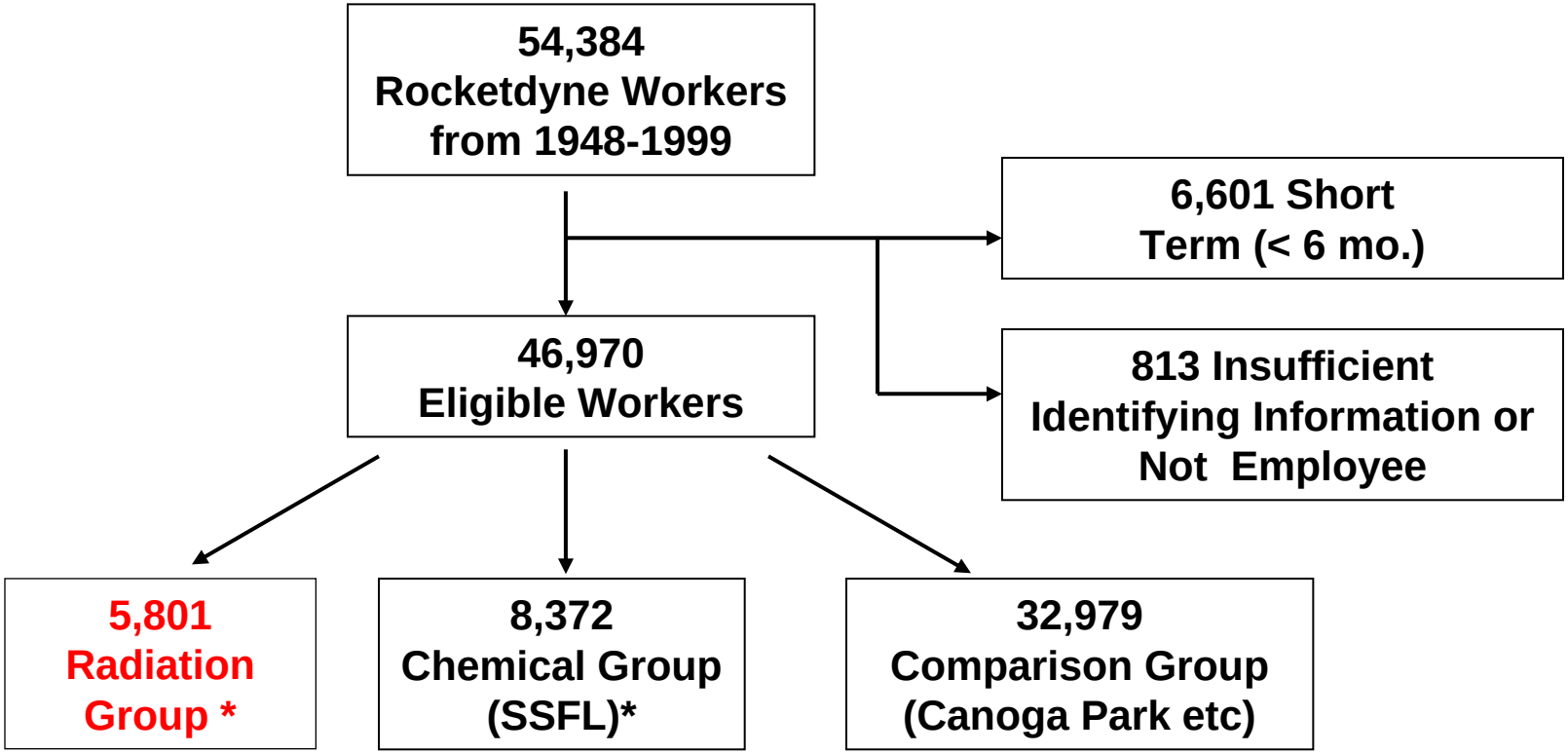
Radiation Worker Studies
Rocketdyne – Atomics International
Santa Susana Field Laboratory

Sodium Reactor Experiment - 1956



First commercial power reactor – provided electricity for Moonpark.

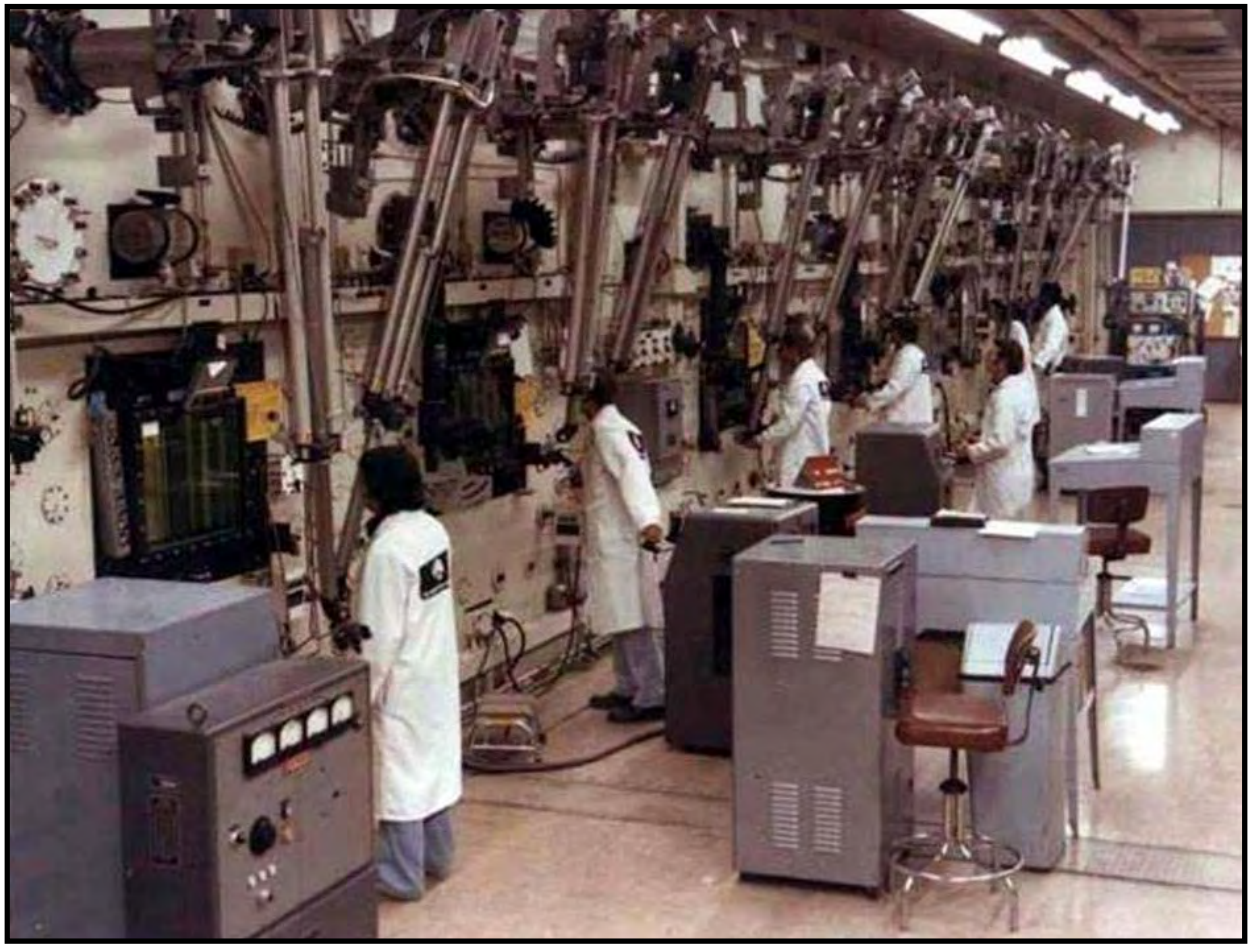
Rocketdyne Worker Population



***182 workers included in both groups**

99.2% of eligible workers as of 12/31/99 were traced.

Hot Laboratory (1978)



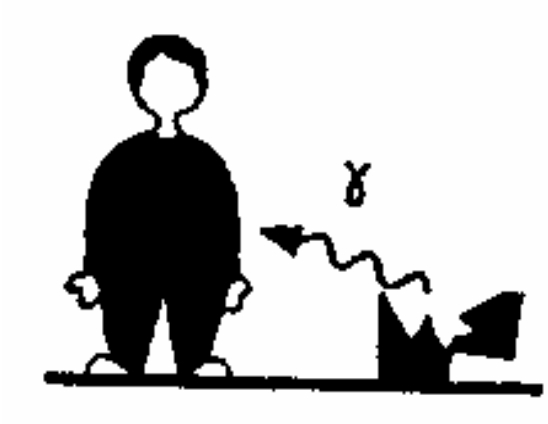
Largest at the time

Types of Exposure

- Gamma
- X-ray (radiographers)
- Neutrons

- Uranium, Plutonium
- Americium, Polonium
- Thorium, Strontium
- Cesium, Tritium

External

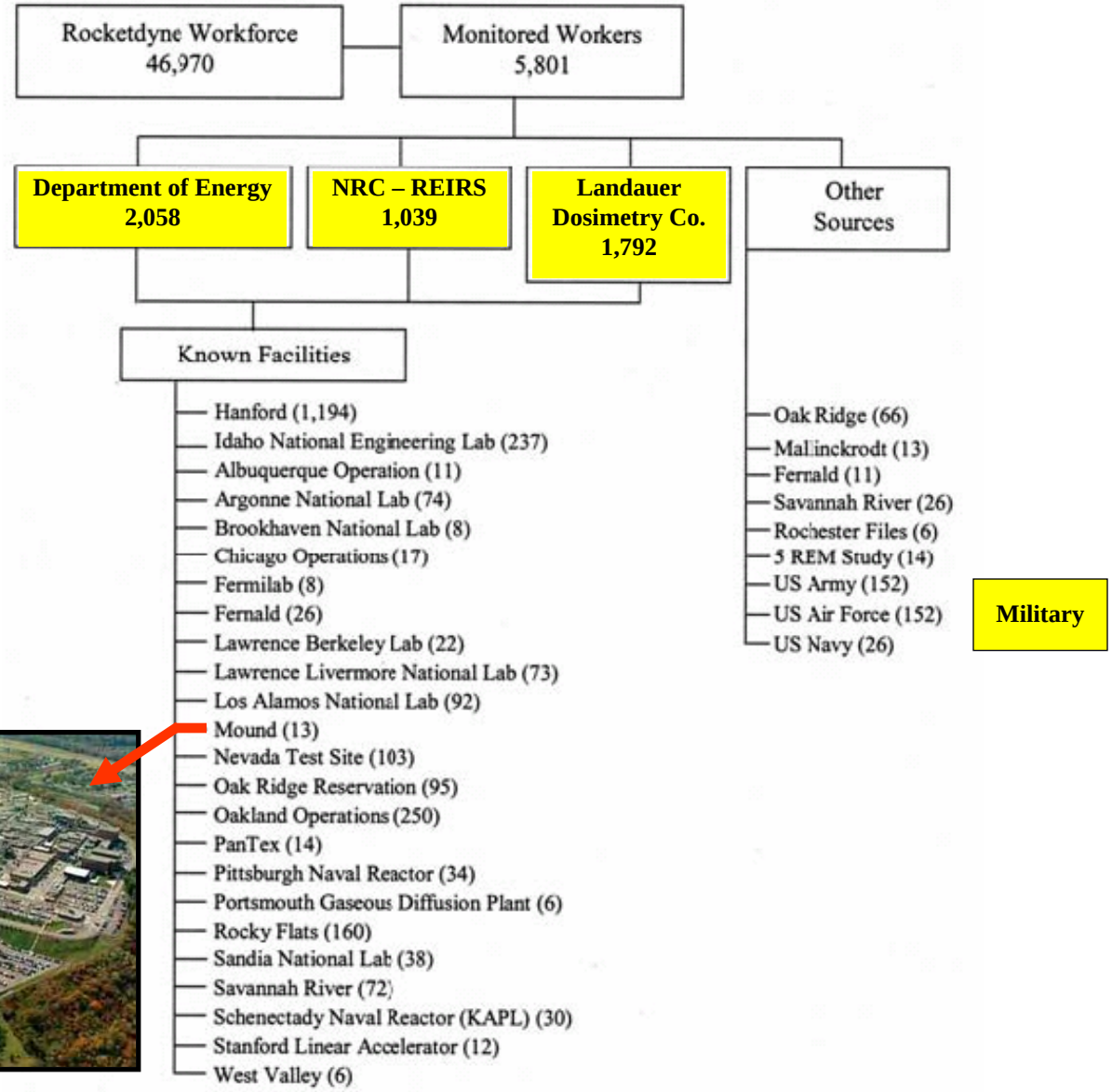


Uniform dose
Delivered during exposure
Film (TLD) badge reading

Internal

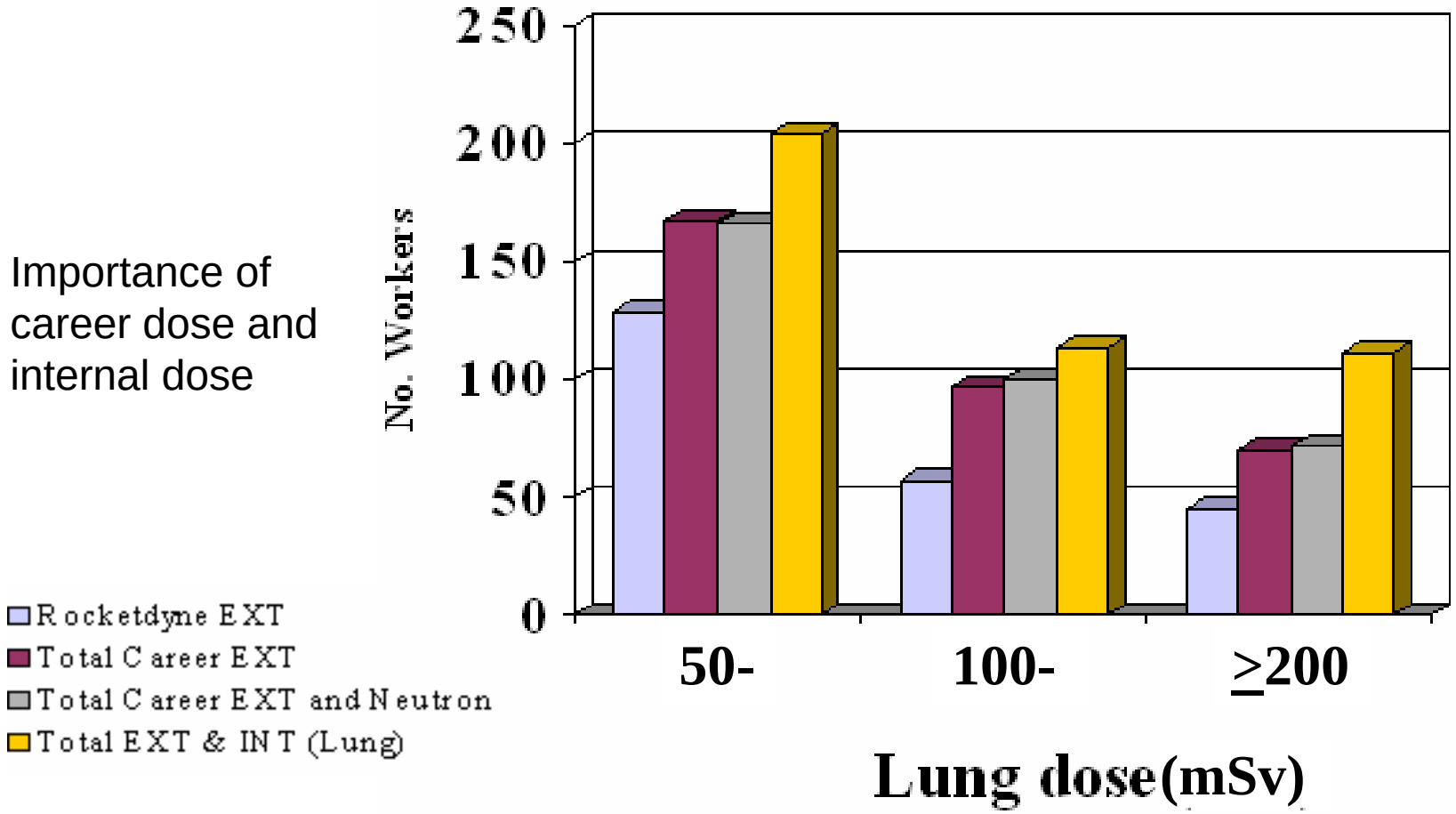
Non uniform dose
Protracted in time
Bioassay measurements

Sources of Radiation Exposure Histories

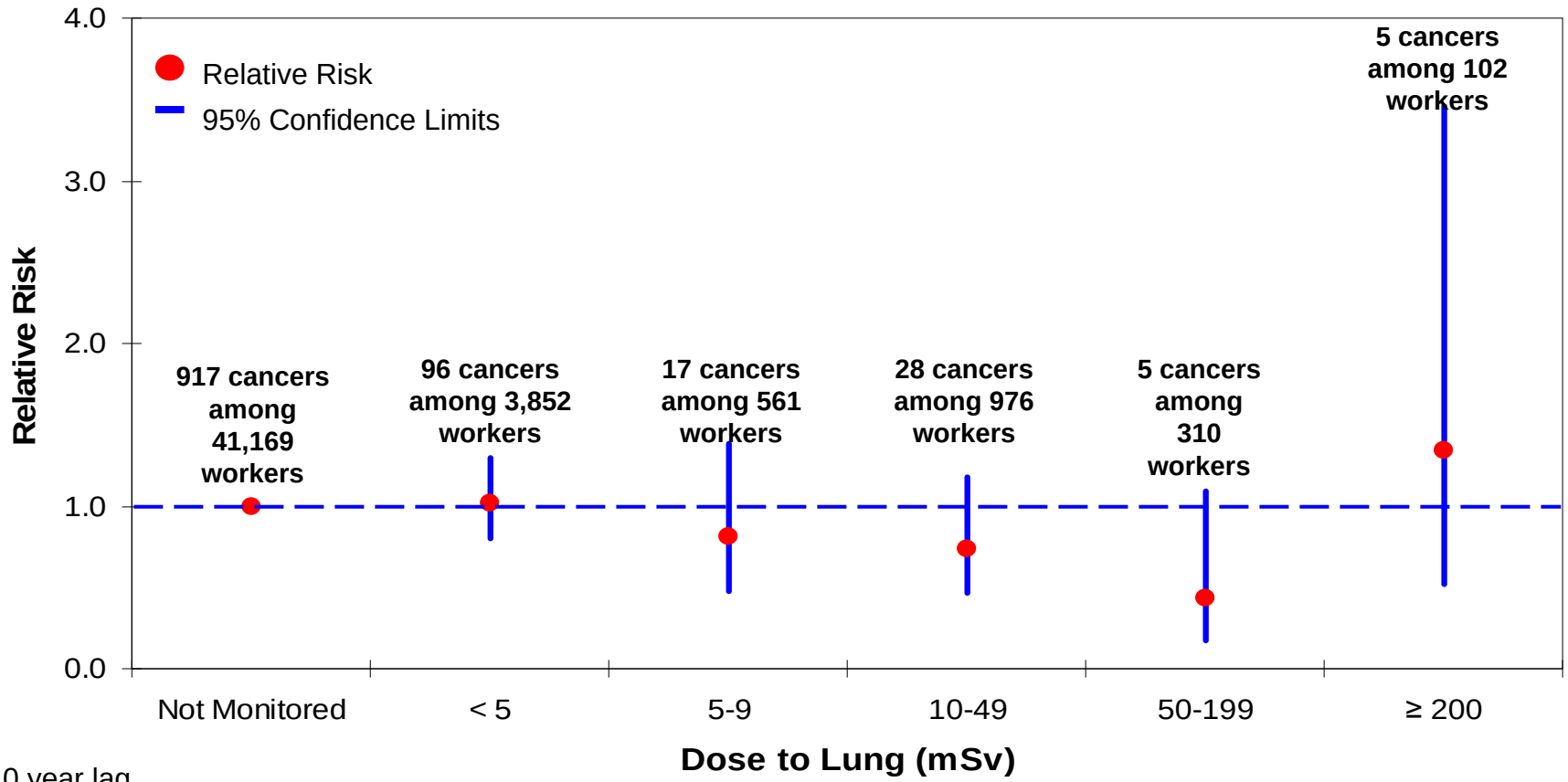


Lung Dose by Dose Categories

Importance of career dose and internal dose



Little evidence that radiation increased the risk of dying from lung cancer but small numbers



10 year lag
1 mSv = 100 mrem

Summary
Worker Study - Rocketdyne

- Importance of career dose (1 in 4 worked elsewhere)
- Importance of internal dose (41% of lung dose)
- Single study has low statistical power to reveal effects
- More (and combined) U.S. worker studies are needed

What More Could be Done
Is There More Gold to Mine?

- Occupational Studies
- Nuclear Weapons Test Participants
- Cancer Survivors – Low Dose Scatter
- Prenatal Studies – Cancer Patients Who Are Pregnant
- High Background Radiation – e.g., Tibet

Department of Energy Cohorts Could Be Extended

- **Oak Ridge Group** (N=147,134)
  - Fernald
  - K-25 (Oak Ridge Gaseous Diffusion Plant)
  - Linde Ceramics Plant
  - Mallinckrodt Chemical Works
  - Savannah River Site
  - Y-12, Tennessee Eastman (pre 1947)
  - Y-12 post 1947
  - Oak Ridge National Laboratory (X-10)
  - Other ?
- **Los Alamos Group** (N=30,035)
  - Los Alamos
  - Mound
  - Rocky Flats
  - Pantex
  - Other?
- **Hanford** (N=32,643)

"… **the US multi-site cohort studies seem to have petered out.** This is very disappointing because if an effect of occupational exposure among nuclear industry workforces in the West is to be found then one would expect the combined workforce of the US Department of Energy nuclear sites to be the prime candidate for its manifestation. **One can only hope that the results of NRRW-3 will be the spur for an increased effort from the USA.**"

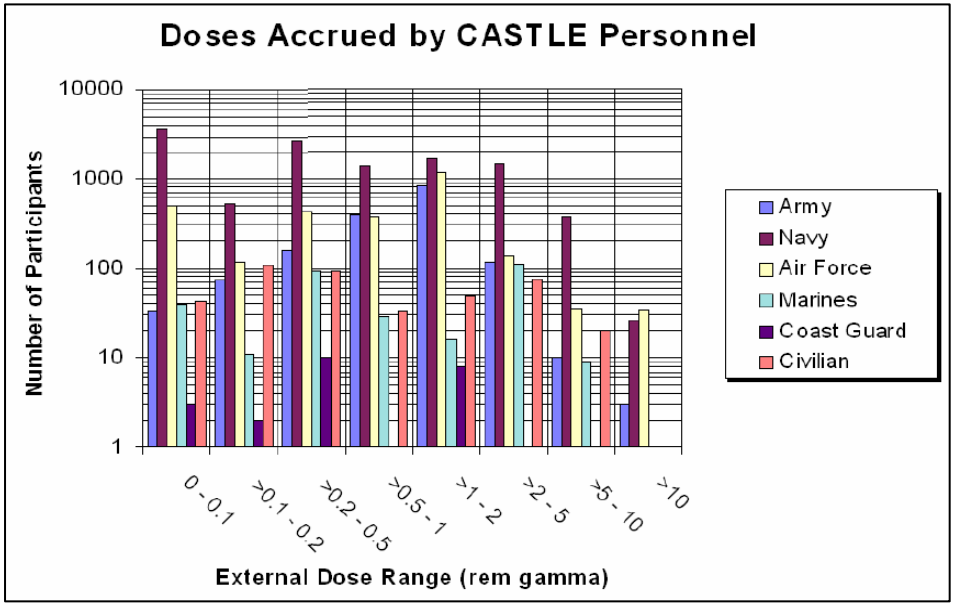
Wakeford, *JRP*, 2009

USA Occupational Studies
Early Utility Workers

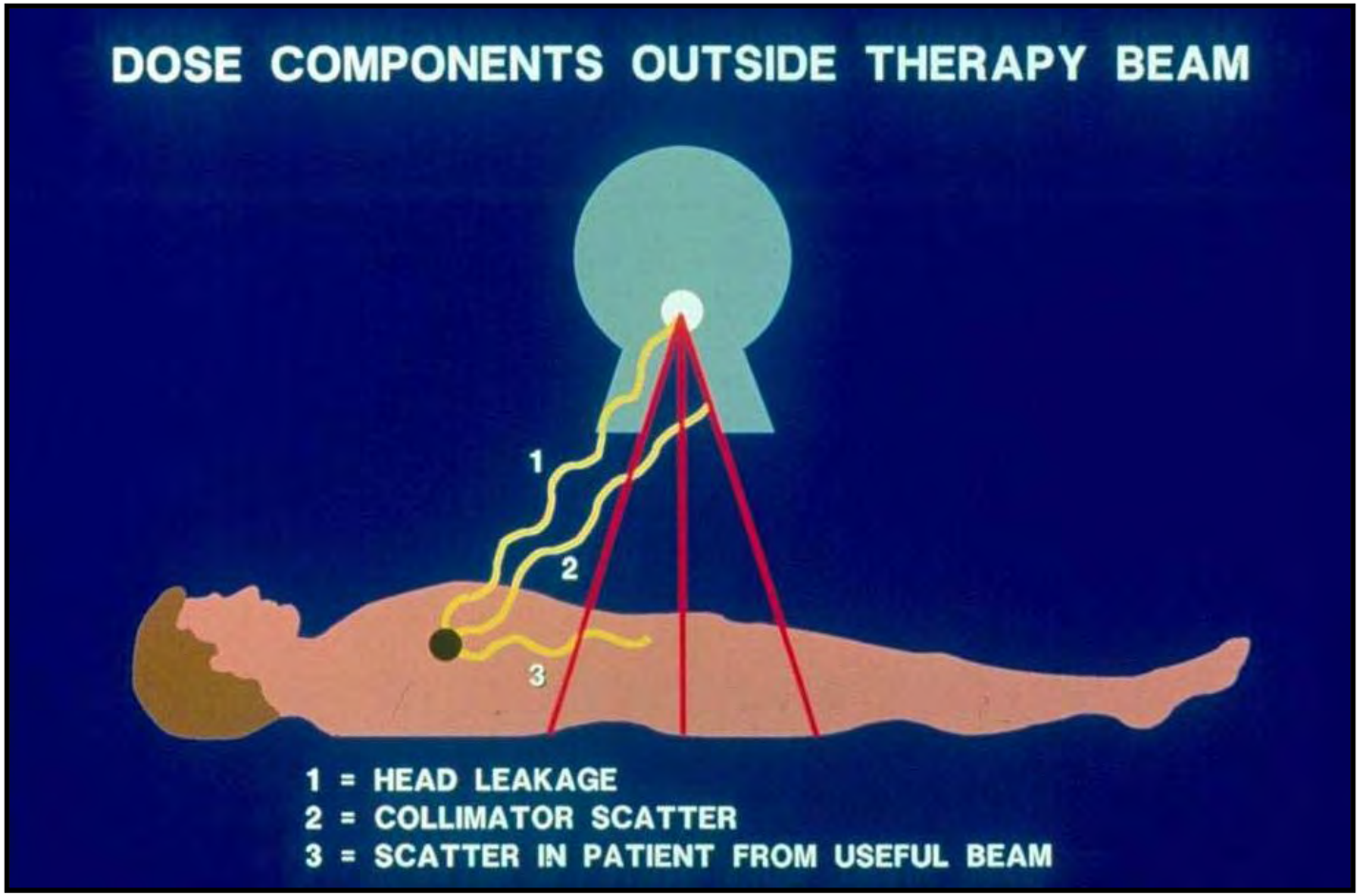
- U.S. Early Utility Workers
  - large numbers, good dosimetry, range of doses
  - 600,000 workers, all years
  - **early workers** received the highest doses
  - **5 (N-18 years)** rem "rule" allowed 3 rem per quarter (30 mSv) and up to 12 rem per year (120 mSv)
  - cumulative doses over 100 rem were possible (1000 mSv)
- Navy Shipyard Workers
- Nuclear Navy
- DOE Cohorts

Nuclear Weapons Test Participant Studies

- Large numbers (125K), complex dosimetry, DoD $300M, 60 y follow-up, radionuclides
- 451 leukemias at last follow-up

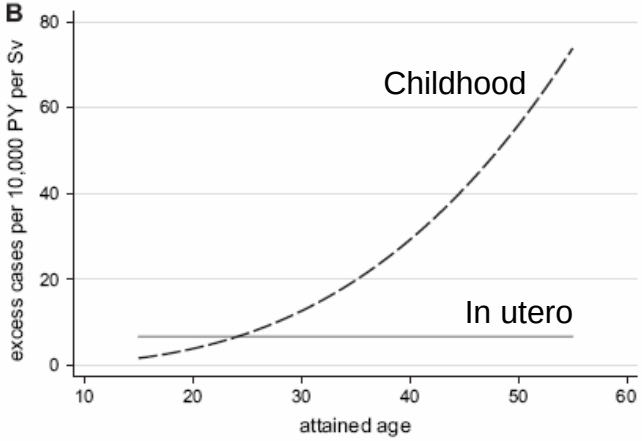


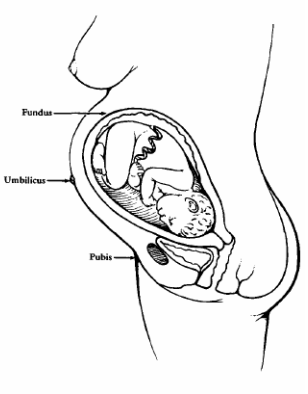
Cancer Survivor Studies
Opportunity for Low Dose Studies
Dose Outside the Treatment Field

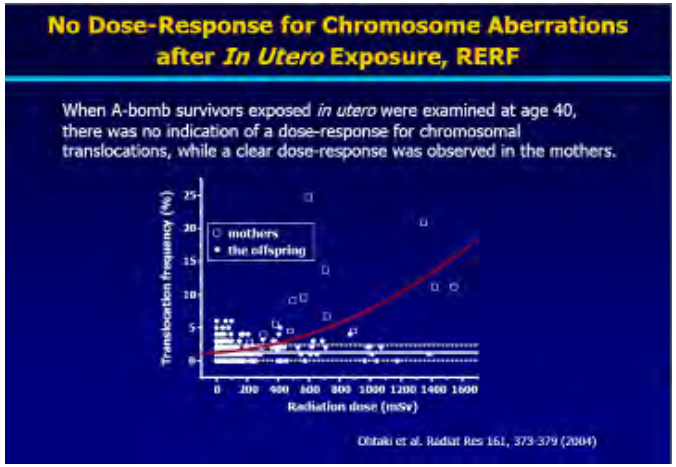


Prenatal – Sensitive Subgroup

- Cancer patients who are pregnant at time of radiotherapy
- Fetal dose: 1-150 cGy







High Background Radiation Example - Cosmic Rays

- Defined and stable population
- Tibet (4,230 m)
- Precise dosimetry
- 1.8 vs. 0.5 mSv/y
- 110 vs. 30 mSv/60y
- Exam thyroid
- Cataracts (NASA?)

Golden Nuggets
What Epidemiology Tells Us

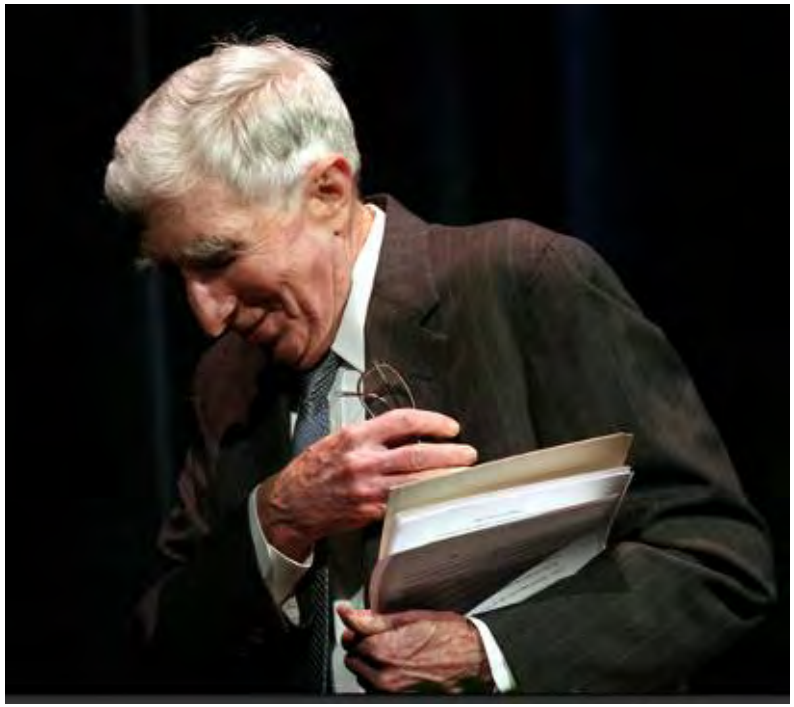
- a single exposure can increase your cancer risk for life
- many small exposures can increase your cancer risk
- the young are more susceptible than the old
- the fetus, however, is not more susceptible than the child
- no genetic (heritable) effects have been found
- females are more susceptible than males
- risks differ by organ or tissue
- some cancers not convincingly increased after exposure
- high doses kill cells and result in lower risks
- there's more to be learned

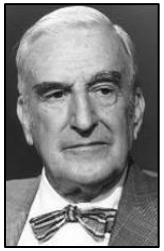
Conclusion
Rephrasing John Updike (Dec 2008)

An **aging epidemiologist** has the not insignificant satisfaction of a **shelf of publications** behind him that, as they wait for their ideal readers to discover them, will outlast him for a while.

The pleasures, for him, of research — the first flush of inspiration, the patient years of study conduct, the final analyzes and final draft manuscript, the merry-go-round of conference presentations, the back-and-forthing with reviewers and journal publishers, the page proofs, and at last the glossy prints (now electronic pdf's) — remain, and retain creation's giddy bliss.

Among those diminishing neurons there lurks the irrational hope that the last study might be his best.





Family – Jennifer and 4 Sons 2009

Justin, Jack, Shannon, John, Jennifer, Jason, Brittin