RADIATION EXPOSURE EFFECTS IN HUMANS: A Guide for IRB Risk Evaluations

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The National Academies

DIVISION ON EARTH & LIFE STUDIES

Nuclear and Radiation Studies Board

HUMAN SUBJECTS WORKING GROUP

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KEY QUESTIONS

- What do we know about bio effects of exposure to ionizing radiation?
- What evidence is there for certain health effects in humans?
- What is the estimate of risk for adverse health effects in humans?
- What levels of radiation exposure are humans exposed to in medical procedures?
- What is the relevance of the potential health risks to the human subject and the IRB?

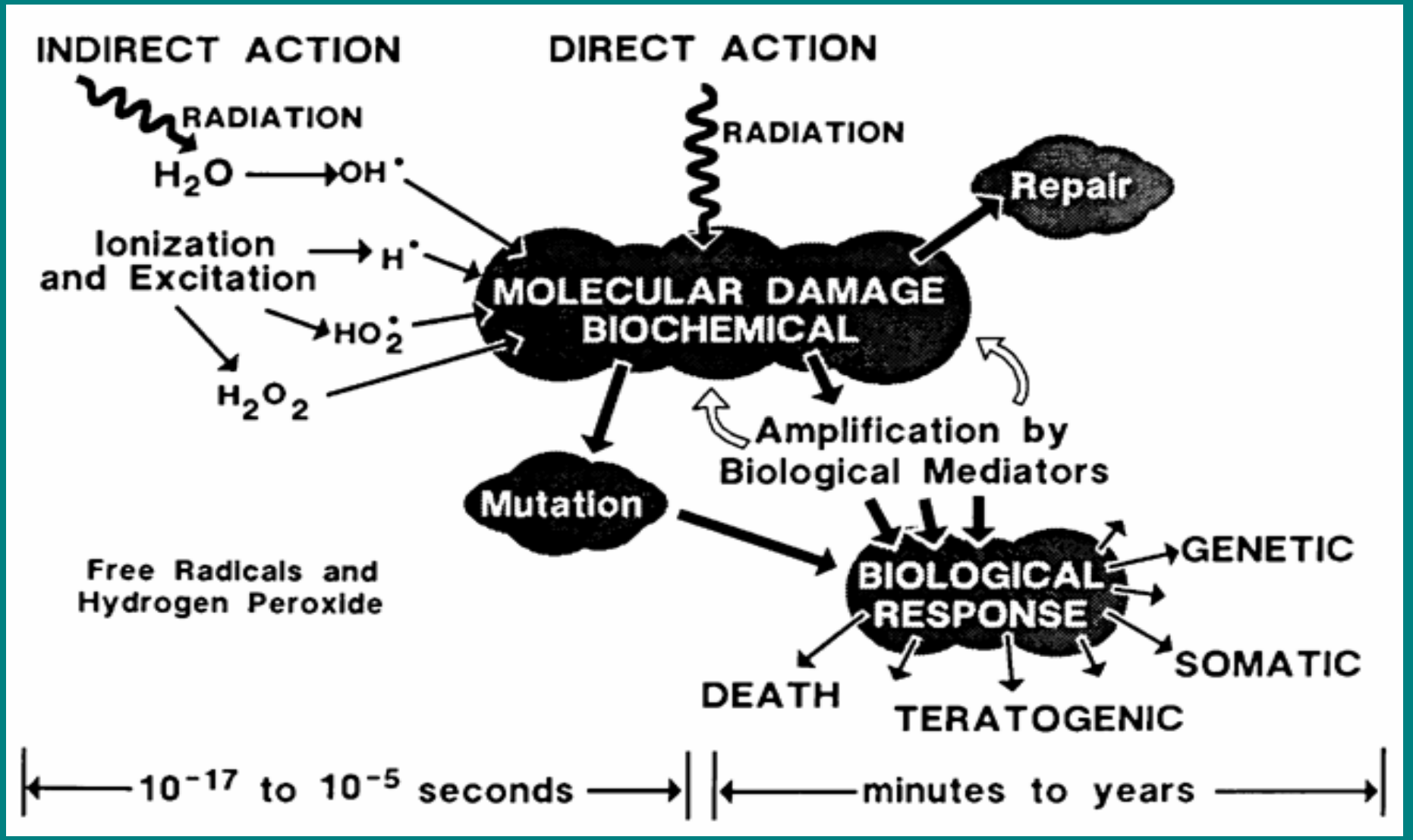
OUTLINE

- Review of Radiobiological Mechanisms
  - Indirect action
  - Direct Action
- Deterministic Effects
  - Cutaneous
  - Ocular (cataracts)
  - Gonadal (sterility)
  - Chronic radiation disease
  - Consequences of In Utero Exposures
- Stochastic Effects
  - Genetic effects (mutations)
  - Cancer
- Analyses of Effects in Human Populations
  - Radiation Effects Research Foundation (RERF)
  - BEIR VII
  - Quantifying Radiation Risk
- Doses from Diagnostic Medical Exposures
- Summary (What does this mean to the patient and IRB?)

STATE OF KNOWLEDGE

- Effects of ionizing radiation are well-known (especially compared to most toxic agents)
- Mechanisms are proposd or identified, albiet with some missing gaps
- A dose-effect response curve is known with measured and reasonable certainty at moderate doses and high doses, but must be modeled at low doses
- Data exists in humans for most effects

RADIOBIOLOGICAL MECHANISMS



Textbook of Military Medicine, Part 1 Volume 2, 1989

MECHANISMS

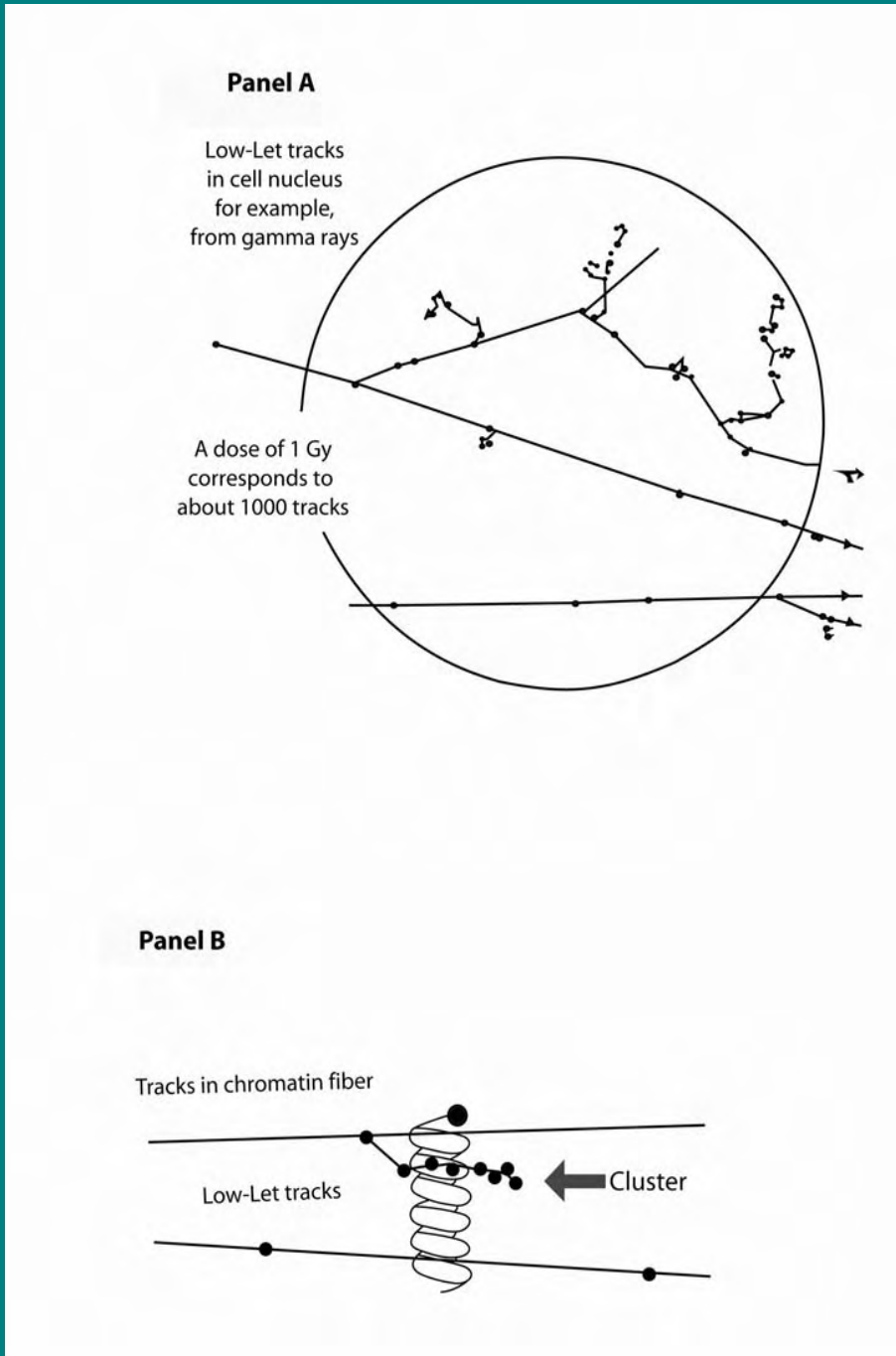
- Radiolytic chemistry

  (e^-, H_2O^+, e^-_{aq},H*, OH* free radicals)

  vs endogenous oxidative products
- DNA damage

  (SSB, DSB, LMDS, damaged bases)
- Deletions and chromosome aberrations
- Mutations ⇒ transformation/cancer
- Mitotic inhibition/cell death or apoptosis

BEIR VII FIG 1-8: Illustration of primary and secondary electron tracks producing clusters (see arrow) of ionization events. Panel A: the calculated number of tracks is based on a nucleus with a diameter of 8 mm. The track size is enlarged relative to the nucleus to illustrate the theoretical track structure. Panel B: the arrow identifies an ionization cluster near a DNA molecule to represent the possibility of locally multiply damaged sites. Only a segment of an electron track is illustrated in Panel B.

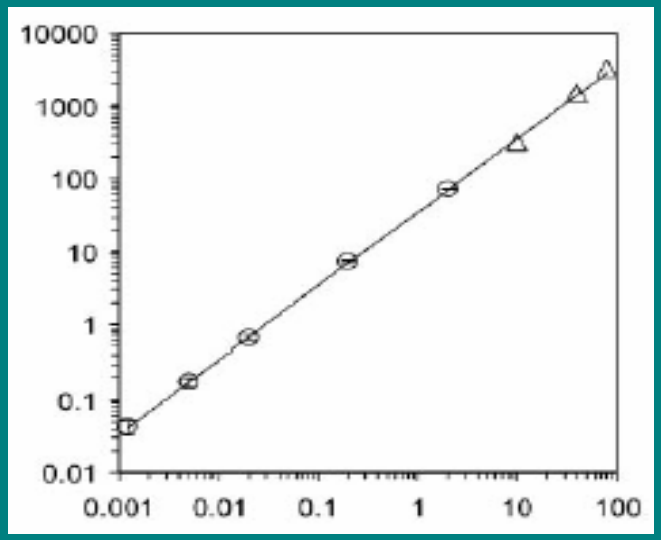


BIOMARKERS OF LOW DOSE DNA DAMAGE & REPAIR

γH2AX: a minor histone (1-2% total H2A)

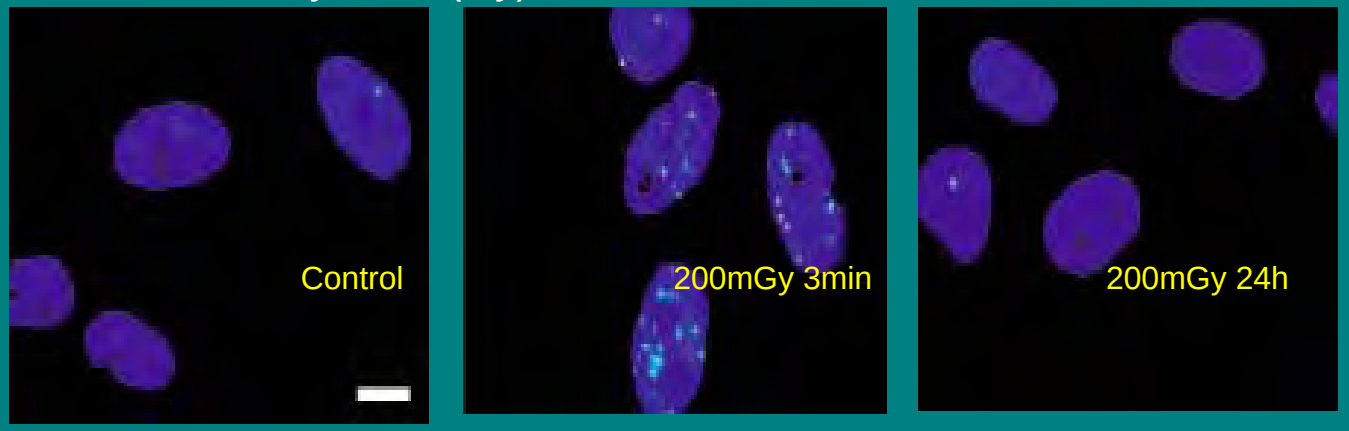
- **Phosphorylated on serine-139 under "stress"**
- **A marker of changes in chromatin conformation from DNA double strand breakage, excision repair and DNA replication**
- **$H2AX^{-/-}$ mice are genomically unstable & cancer prone**

Formation and repair of γH2AX foci in normal human cells at very low doses of ionizing radiation



Formation of foci (double strand breaks) is a linear function of dose down to background levels

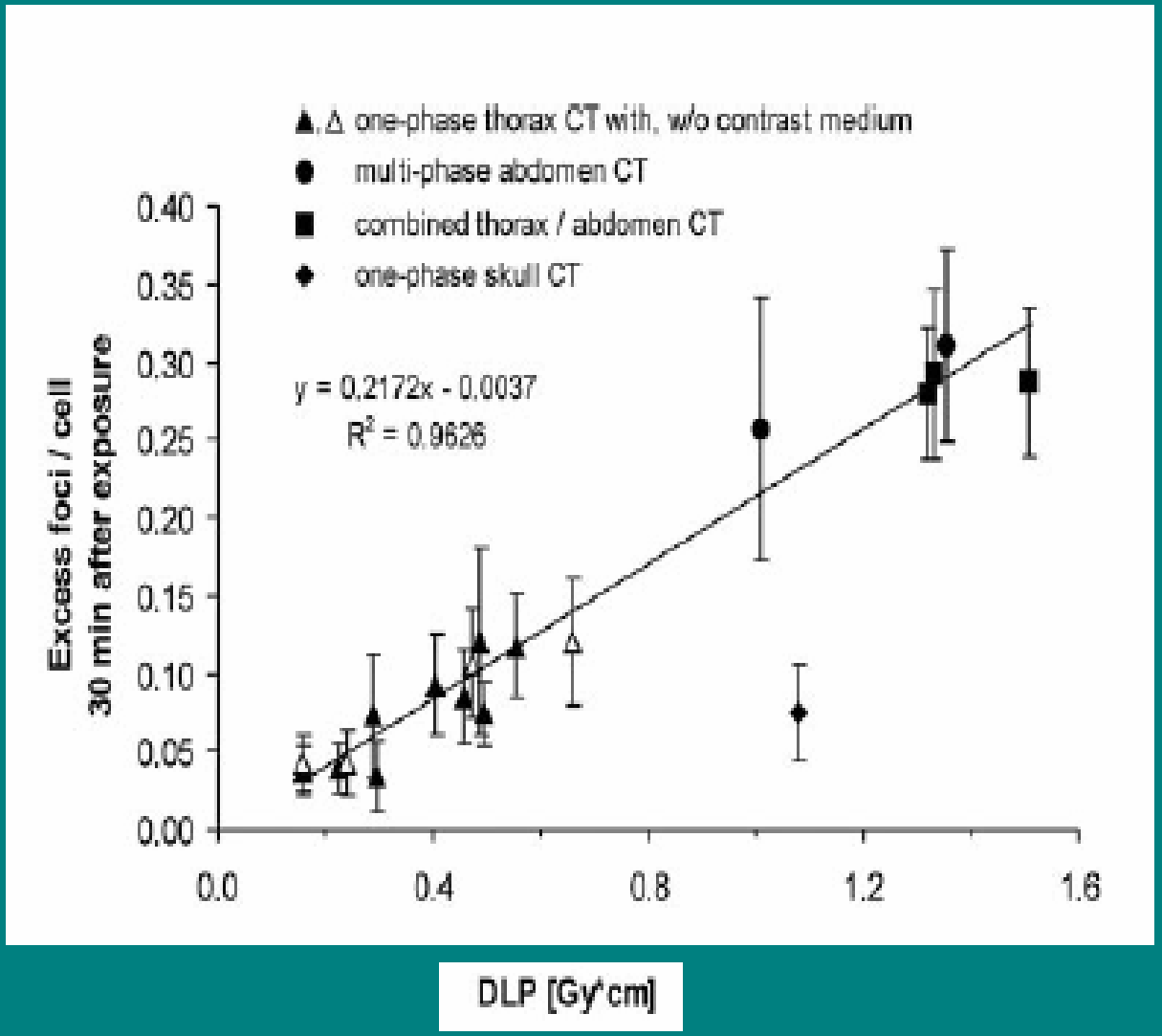
35 DSBs per cell per Gy,
- below 0.03Gy into stochastic region



Repair is almost complete over 24h

Rothkamm & Lobrich. PNAS 100:5057-502 (2003)

CT SCANS CAUSE RADIATION DAMAGE



- CT scans gave doses of 4.8-17.4 mGy to unit volumes.
- Calculated as Dose Length Products (DLP) for different body scans.
- Data points correspond to single CT examinations

Lobrich et al ”In vivo formation and repair of DNA double strand breaks after computed tomography examinations.” PNAS 102:8984, 2005

CHROMOSOME ABERRATIONS (DICENTRICS)

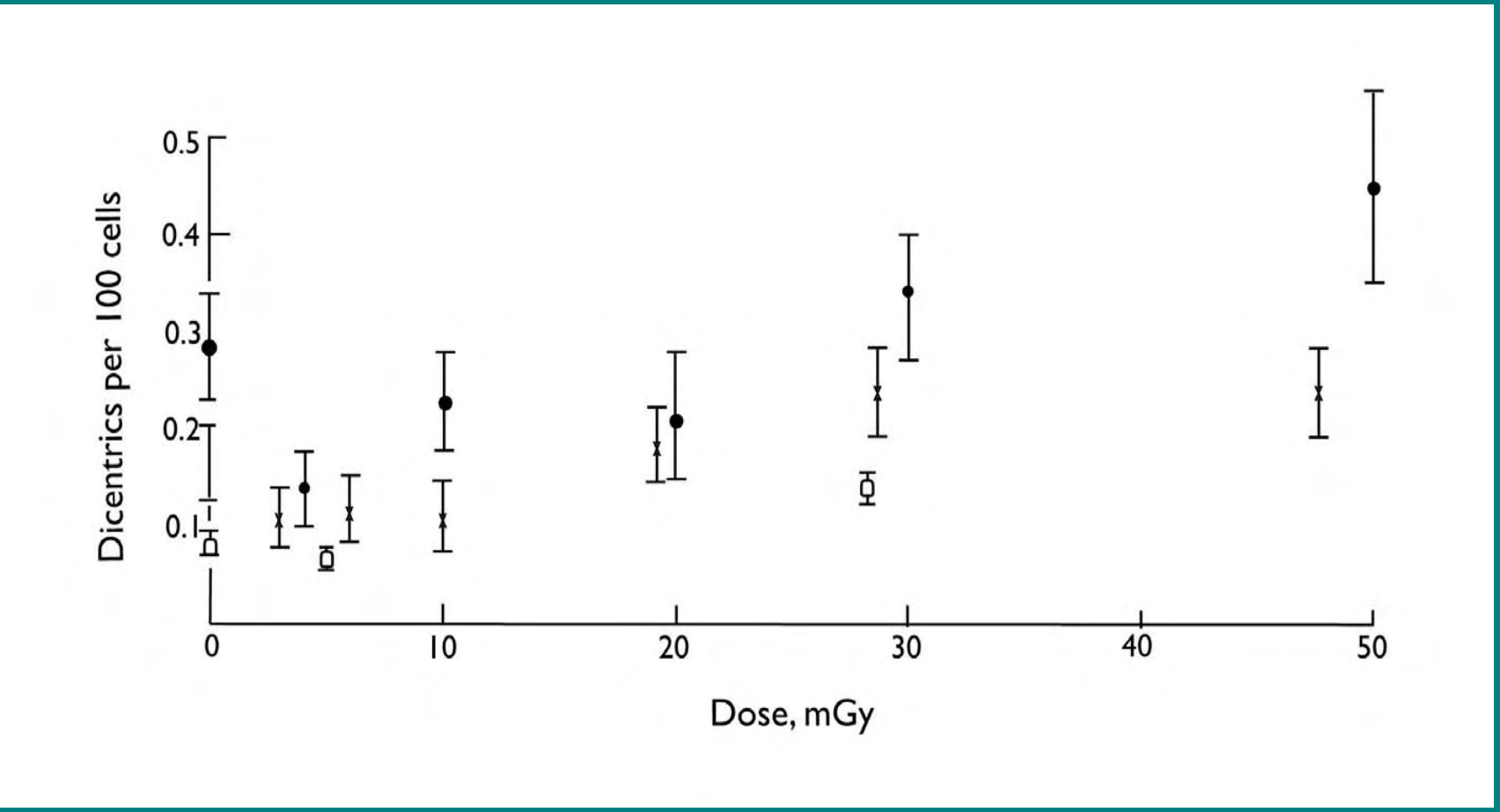


Figure 2-5 Dicentric yields as a function of dose.

•, Pohl-Ruling and others (1983); x, Lloyd and others (1992), experiment 1; ☐ experiment 2. From Lloyd and others (1992).

MUTATIONS

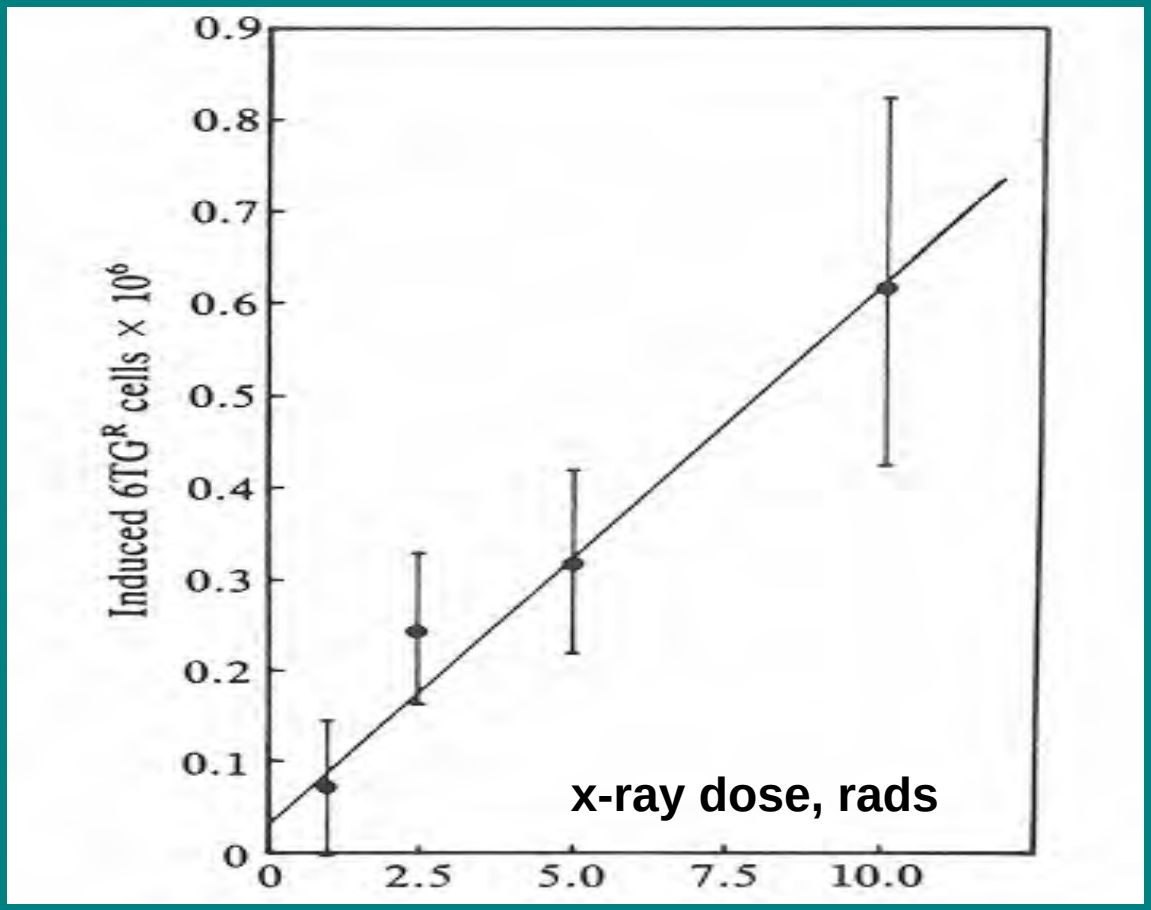
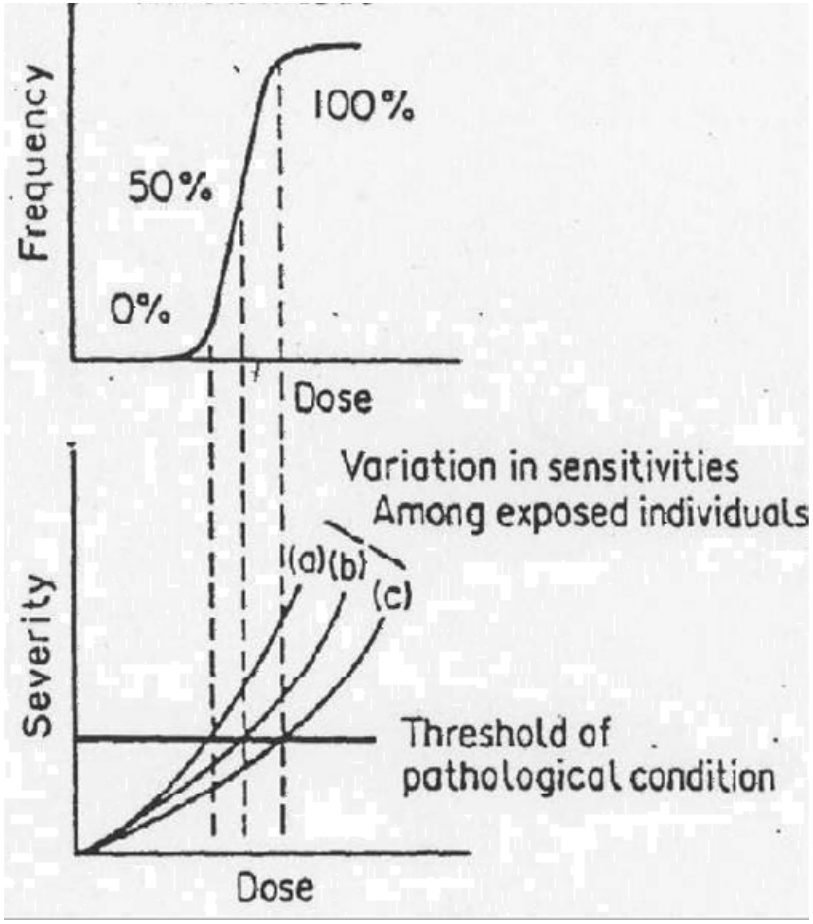


Figure 2-7 Frequency of 6TGR cells induced by 1–10 rads (0.01-0.1 Gy) of x-rays in TK6 human lymphoblastoid cells. Data points (with standard deviations) are from regression analyses of mutations induced per day at various dose rates (1–10 rads/day; 0-30 days) as described in Grosovsky and Little (1985).

Deterministic Effects of Ionizing Radiation



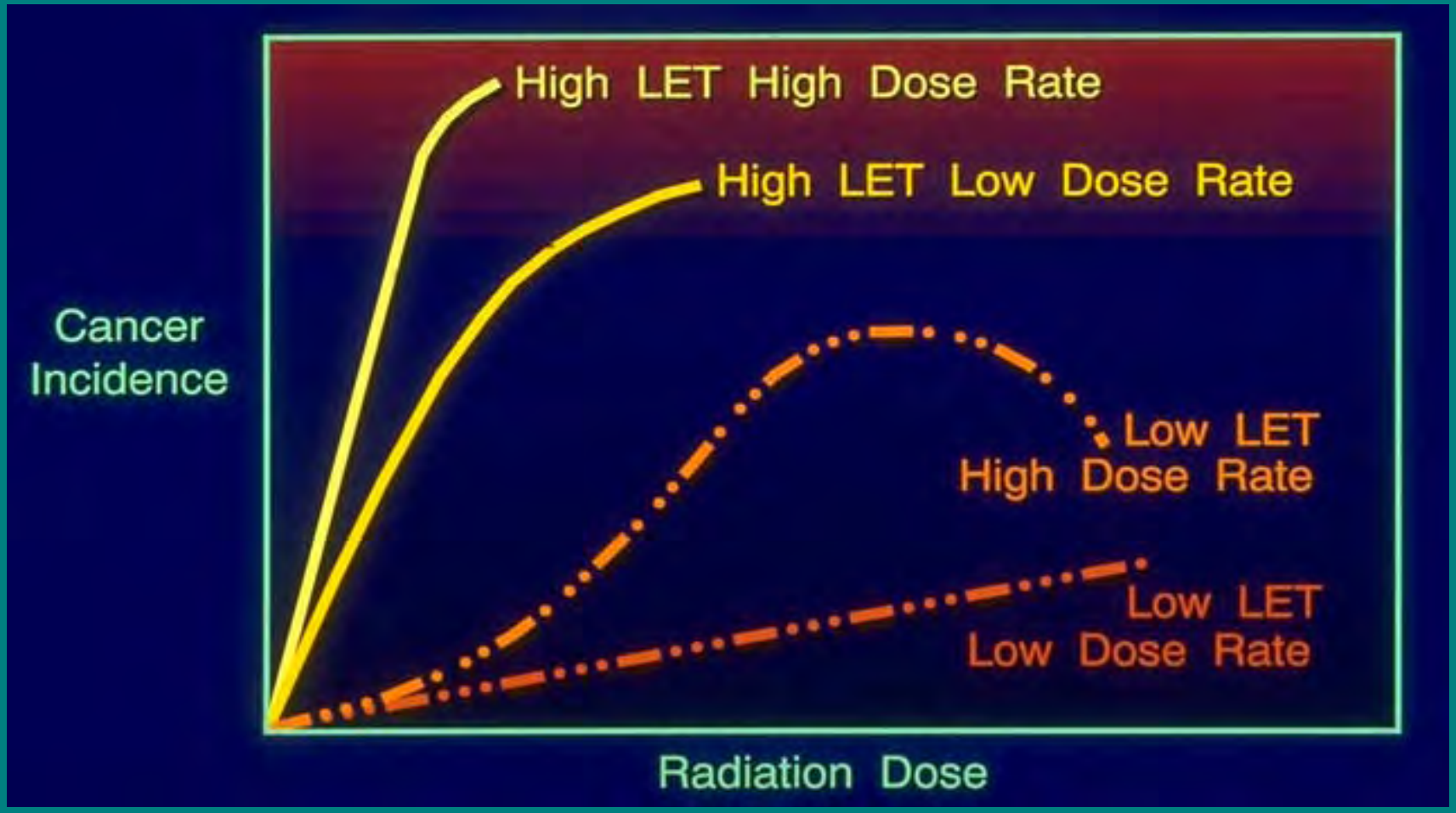
- Characteristics
  - Minimum dose required to produce effect - threshold
  - Magnitude of effect increases with dose
  - Clear, unambiguous causal relationship between exposure and effect
- Examples
  - Acute Radiation Syndrome
  - Cutaneous injury
  - Occular injury
  - Sterility
  - Chronic Radiation Disease

Annals of the ICRP 14(3), 1984

Factors Influencing Cancer Risk Estimates

- Epidemiological Factors
  - Statistical uncertainties
  - Dosimetric uncertainties
  - Generalizability of risk assessment
  - Evaluating increase against a significant background incidence
- Must be mathematically modeled
  - Extrapolation from high dose/dose rate to low dose/dose rate
  - Projection over a lifespan
  - Transfer of risk between populations

Effectiveness of Dose and Dose Rate



Stochastic Effects: Hereditary

- Three principal categories of genetic diseases
  - Mendelian
    - Autosomal dominant (Polydactyl, Huntington's chorea)
    - Autosomal recessive (Sickle-cell anemia, cystic fibrosis)
    - X-linked (Hemophelia, color-blindness)
  - Chromosomal aberrations (Down's syndrome, embryonic death)
  - Mutlifactorial diseases (neural tube defect, cleft palate, diabetes, hypertension)
- Radiation-induced genetic diseases are not unique
- Data on hereditary effects comes almost entirely from animal studies (i.e. Mega-mouse study)

What are the Risks to Future Children? Hereditary Effects

- Magnitude of hereditary risk per rem is 10% that of fatal cancer risk
- Risk to study participants who would likely receive low doses is very small; 5 rem increases the risk of severe hereditary effects by ~ 0.02%
- Risk of severe hereditary effects to an exposed population receiving high doses is estimated as ~ 0.4% per 100 rem

Estimating Hereditary Risks

- Doubling Dose Method
  - Dose required to double spontaneous mutations
  - Estimated to be 1 Gy for low dose rate exposure in humans (based on mice data)
- Direct Method (incidence of disorders observed in the first generation)
- No statistically significant indicators of hereditary effects have been observed in the progeny of atomic-bomb survivors

GENETIC EFFECTS

- Radiation-induced heritable diseases have not been demonstrated in humans.
- <0.2 Gy doses are unlikely to double the risk of untoward pregnancies (based on 70,000 children of atomic-bomb survivors).
- Studies of nuclear workers' children have not convincingly linked exposure to heritable diseases.
- Genetic risk ~0.2% per Gy or 1 case in 500 live births per Gy (ICRP 2004).
- Doubling dose ~1 Sv (UNSCEAR 2001).

Estimates of Genetic Effects From Parental Exposure of 10 mSv

Type of Disorder	Current Incidence*	Additional Cases*	
		First Generation	Equilibrium
Autosomal Dominant			
Clinically severe	2,500	~5-20	25
Clinically mild	7,500	~1-15	75
X-Linked	400	<1-8	40
Chromosomal			
Unbalanced translocations	600	~5-20	negligible
Trisomies	3,800	<1-9	negligible
Irregularly inherited	1,200,000	60	1,900
Congenital abnormalities	20-30,000	~10-30	~10-100
TOTAL	1,245,000	~85-160	~2,050-2,140

*** - per 1,000,000 live born**

(NCRP-126)

BEIR VII – GENETIC RISK

- A “doubling dose” = 1 Sv (1 Gy) was estimated using human data on spontaneous mutation rates of disease-causing genes and mouse data on induced mutation rates. Genetic changes must be compatible with embryonic development and viability.
- 3,000-4,700 cases per 10^6 F1 per Gy or 0.4% to 0.6% of the baseline of 738,000 cases in 10^6 (chronic diseases $\underline{\sim}$ 650,000 per 10^6)
- Compare above to BEIR V (<2,400-5,300 per 10^6 F1 per Gy or 5 to 14% of baseline); [Note: BEIR V did not include chronic diseases]

Fetal Irradiation

No significant risk of adverse developmental effects below ~10 rem

Weeks After Fertilization	Period of Development
<2	Pre-implantation
2-7	Organogenesis
7-40	Fetal
All	

Effects

- Little chance of malformation.
- Most probable effect, if any, is death of embryo.
- Reduced lethal effects.
- Teratogenic effects.
- Growth retardation.
- Impaired mental ability.
- Growth retardation with higher doses.
- Increased childhood cancer risk. (~ 0.6% per 10 rem)

Overview of Radiation Effects on Embryo/Fetus

- Principle effects
  - Growth retardation
  - Embryonic, neonatal or fetal death
  - Congenital malformations
  - Functional impairment (i.e. mental retardation)
- Function of stage of gestation period, dose and dose rate
- Congenital abnormalities occur in the absence of radiation exposure > background

In Utero Effects based on animal data (rodents)

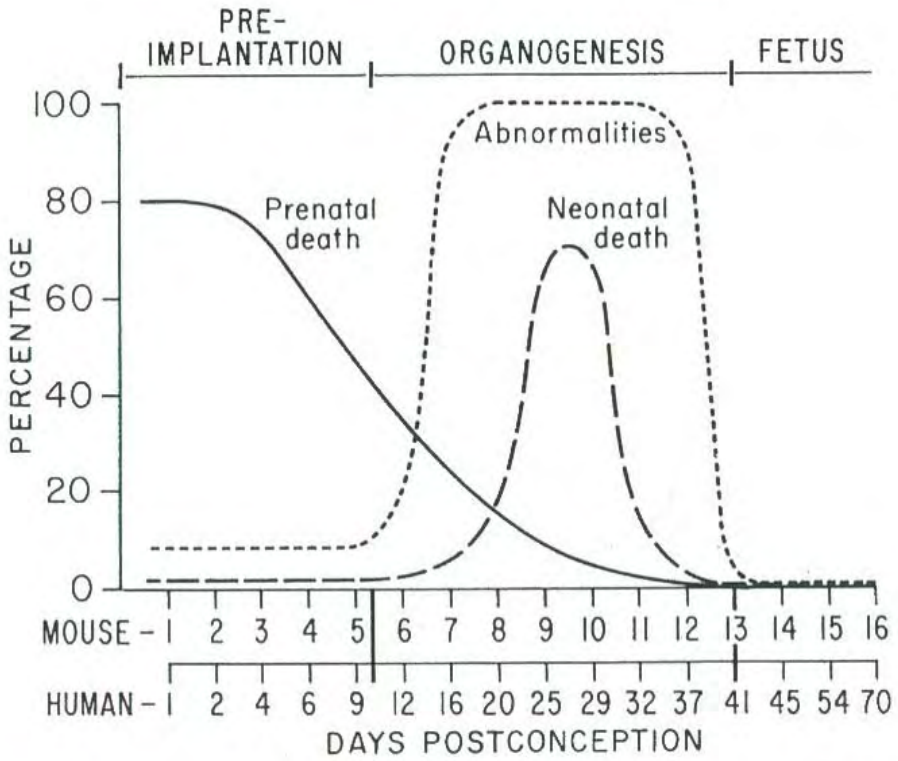


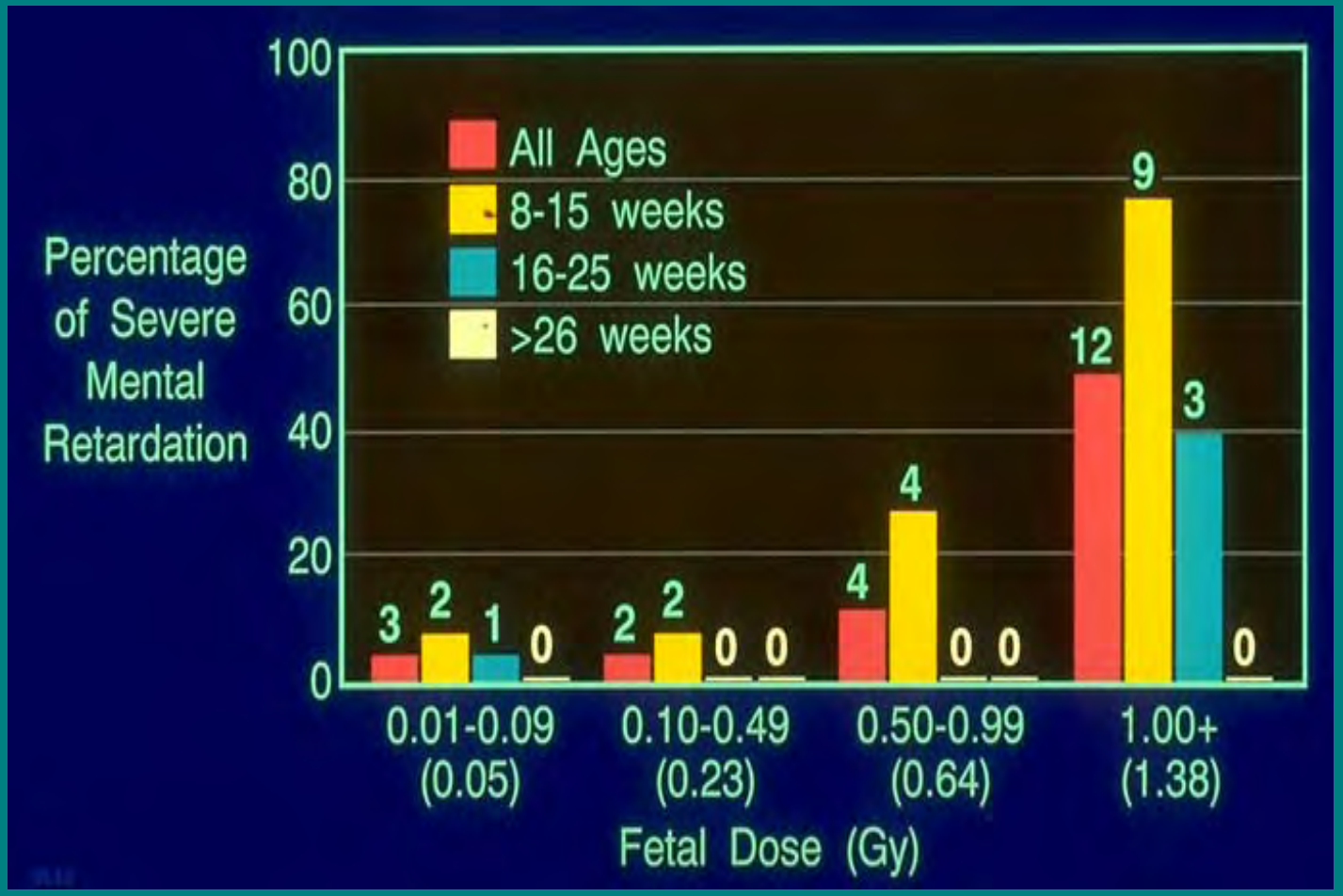
Figure 12.1. Incidence of abnormalities and of prenatal and neonatal death in mice given a dose of 200 R at various times after fertilization. The lower scale consists of Rugh's estimates of the equivalent stages for the human embryo. (Data from Russell LB, Russell WL: An analysis of the changing radiation response of the developing mouse embryo. J Cell Physiol 43[suppl 1]:1030–149, 1954.)

Hall, 2000

Experience in Humans

- A-Bomb Survivors
  - No birth defects observed for exposure up to 15 days post conception
  - Principle effects
    - Microcephaly (no recovery)
    - Mental retardation
- Medical Procedures
  - Microcephaly
  - Mental retardation
  - Congenital defects

Mental Retardation



- Most sensitive period – 8 to 15 weeks
- Less severe effect - fall in IQ (30 units per Gy)

Cancer in Childhood after Irradiation *In Utero*

- Stewart & Kneale (1970) suggested an association between cancer (principally leukemia) up to 15 years of age and exposure *in utero* to diagnostic x-rays
- Subsequent studies report similar associations

- Doll & Wakefield (1977)
  - Low dose fetal exposure (≥~ 10 mGy) particularly in the last trimester increases risk of childhood malignancies
  - Excess absolute risk ~6%/Gy

HEALTH EFFECTS FOLLOWING EXPOSURE TO RADIATION

- Tissue Injury (epilation, cataracts, ulcers)
- Acute Radiation Syndrome (nausea, leukopenia, GI symptoms, death)
- Non-cancer Diseases (RERF: stroke and heart, digestive, respiratory, and hematopoietic diseases; ERR/Sv = 0.14)

- Genetic Mutations
- Teratogenesis (exposure *in utero*)

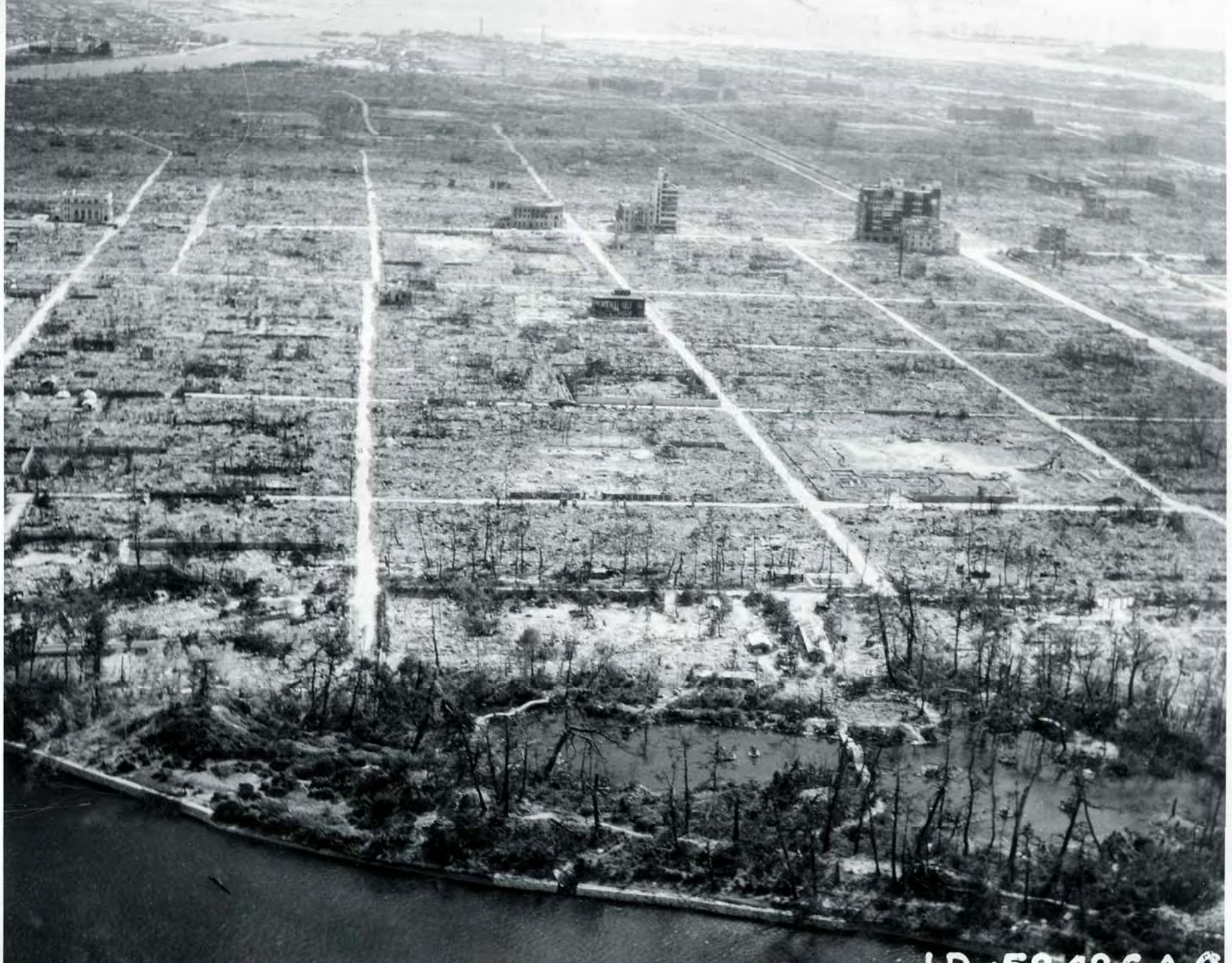
- Cancer (solid cancers and leukemia)

Chronic Health Effects from Radiation

- Radiation is a weak carcinogen at low doses
- No unique effects (type, latency, pathology)
- Natural incidence of cancer ~ 40%; cancer mortality ~ 25%
- Risk of fatal cancer is estimated as ~ 4% per 100 rem
- A dose of 5 rem increases the risk of fatal cancer by ~ 0.2%
- A dose of 25 rem increases the risk of fatal cancer by ~ 1%

EPIDEMIOLOGIC STUDIES

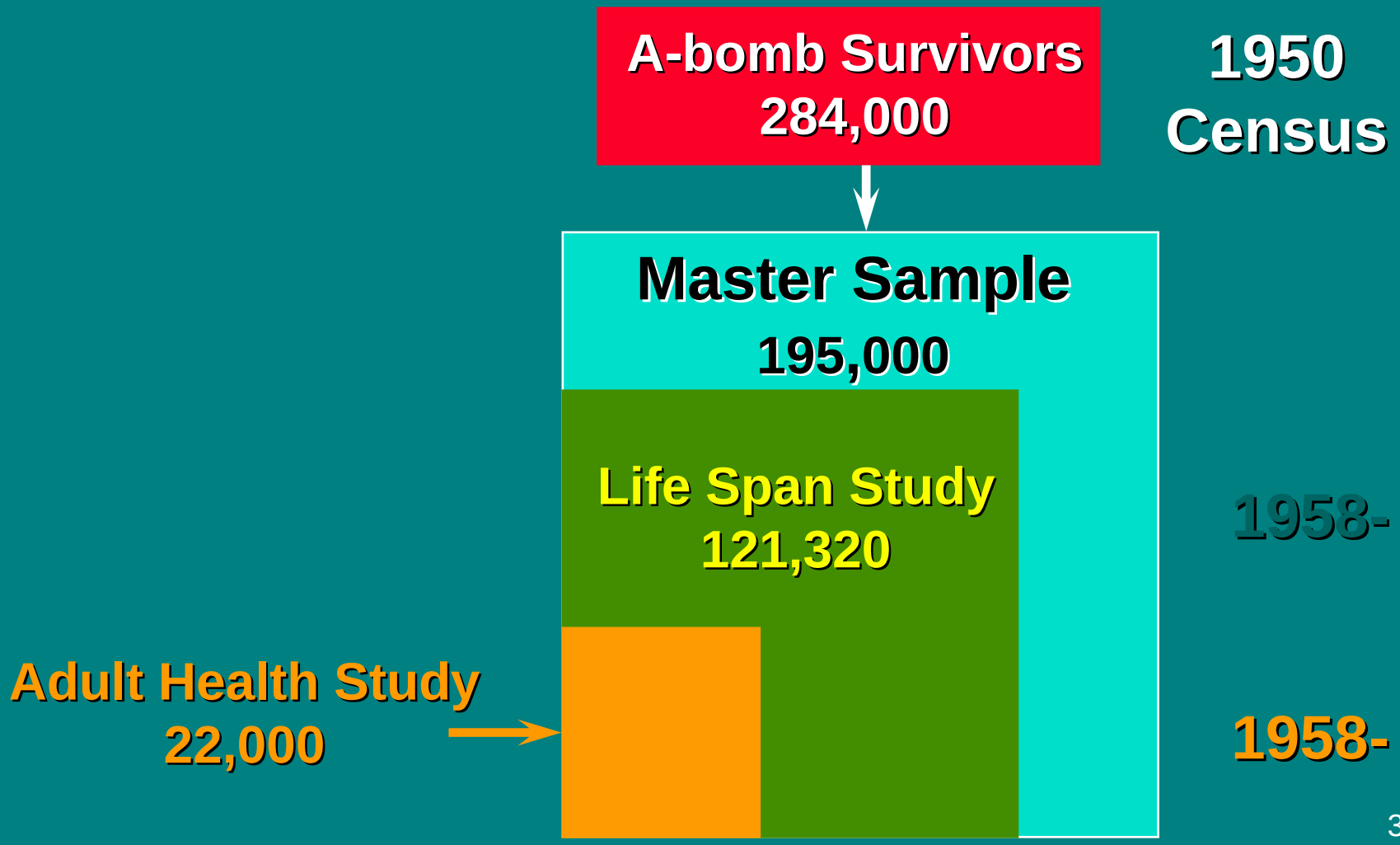
- **A-bomb survivors (Hiroshima & Nagasaki)**
- Occupational exposures (radiation workers)
  - 3-country study
  - UK National Registry of Radiation Workers
  - 15-country study of radiation workers
- Medical exposures
- Environmental exposures
  - Chernobyl
  - Semipalatinsk
  - Ural Mountains

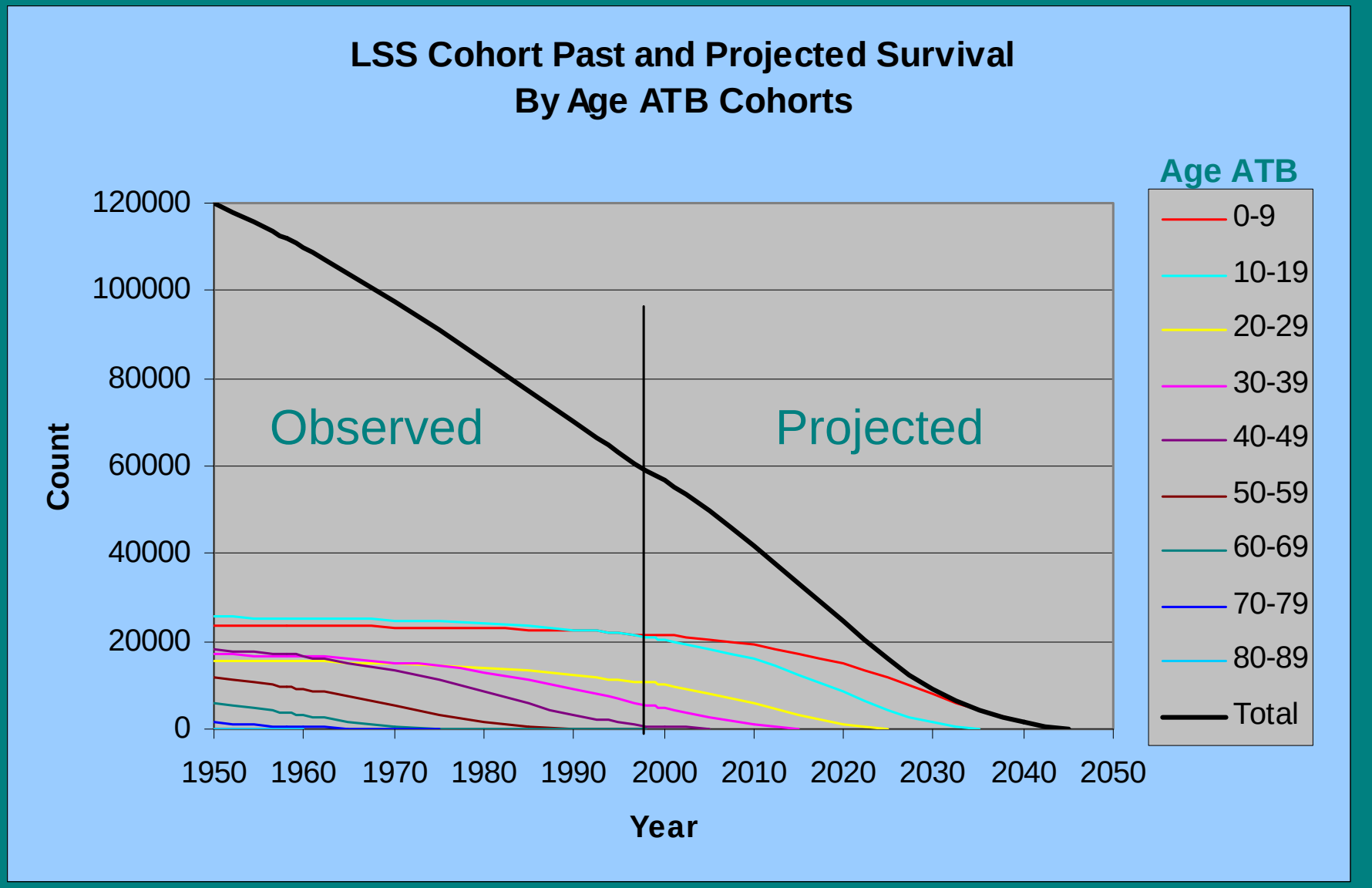


The Radiation Effects Research Foundation (RERF)

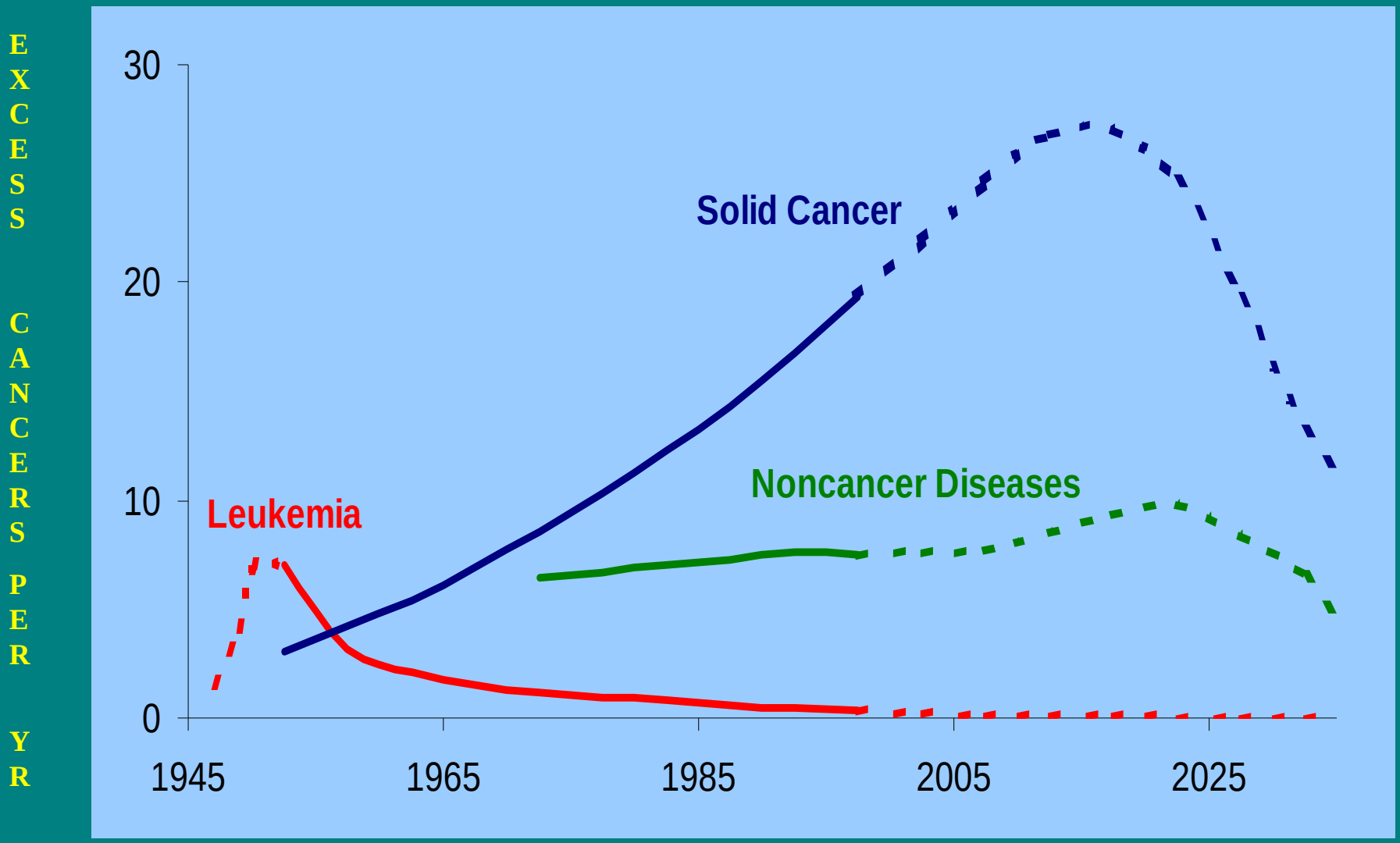
Hiroshima, Japan

ABCC/RERF COHORTS




LSS Cohort Past and Projected Survival
By Age ATB Cohorts
Age ATB
0-9
10-19
20-29
30-39
40-49
50-59
60-69
70-79
80-89
Total
Observed
Projected
Count
120000
100000
80000
60000
40000
20000
0
1950
1960
1970
1980
1990
2000
2010
2020
2030
2040
2050
Year

HEALTH EFFECTS IN ATOMIC-BOMB SURVIVORS (RERF)



RADIATION-RELATED RISKS

- Excess Relative Risk (ERR)
  - Percentage change in risk for a given dose
  - Relative change in rate
- Excess Absolute Rate (EAR)
  - Absolute change in rates for a given dose
  - Rate difference
- ERR and EAR can vary with age at exposure, gender, attained age, and other factors
- ERR and EAR provide complementary information

LSS Cancer Mortality 1950 - 1997

Dose (Sv)	Subjects	Observed	Excess
< 0.005 Sv	37,458	3,833	1
0.005 - 0.05	**26,561**	**2,682**	**26**
0.05 - 0.1	**5,089**	**595**	**19**
0.1 - 0.2	**5,732**	**668**	**39**
0.2 - 0.5	6,332	763	98
0.5 - 1	3,299	438	110
1-2	1,613	274	103
2+	488	82	48
Total	***86,572***	***9,335***	***443***

1950 –1990 follow-up 334 excess deaths among 7,578 cases

LSS SOLID CANCER INCIDENCE

1958 - 1998

Dose (Gy)	Subjects	Person Years	Observed	Excess	AR%
< 0.005 in city	35,545	918,200	5,603	3	0.1%
0.005 - 0.1	27,789	729,603	4,406	81	1.8%
0.1 - 0.2	5,527	145,925	968	75	7.6%
0.2 - 0.5	5,935	153,886	1,144	179	15.7%
0.5 - 1	3,173	81,251	688	206	29.5%
1-2	1,647	41,412	460	196	44.2%
2+	564	13,711	185	111	61.0%
In city total	***80,180***	***2,083,988***	***13,454***	***853***	**6.3%**
Not in city	25,247	680,744	3,994	-	-
Total	***105,427***	***2,764,732***	***17,448***	***853***	4.9%

Since 1987 follow-up:

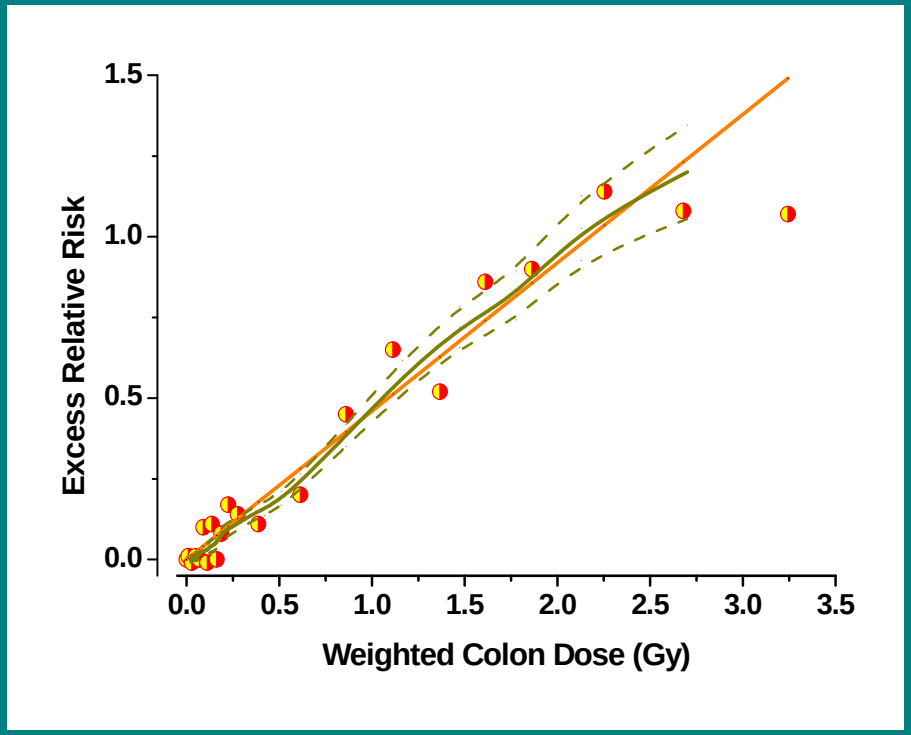
Person years	+24%
Cases	+56%
Excess	+68%

Preston et al. 2004

CANCER INCIDENCE (ERR) Dose Response

- No evidence of non-linearity in the dose response
- Statistically significant trend on 0 – 0.15 Gy range
- Threshold estimate: 0.06 Gy 95% CI (0; 0.14)
- Low dose range trend consistent with that for full range

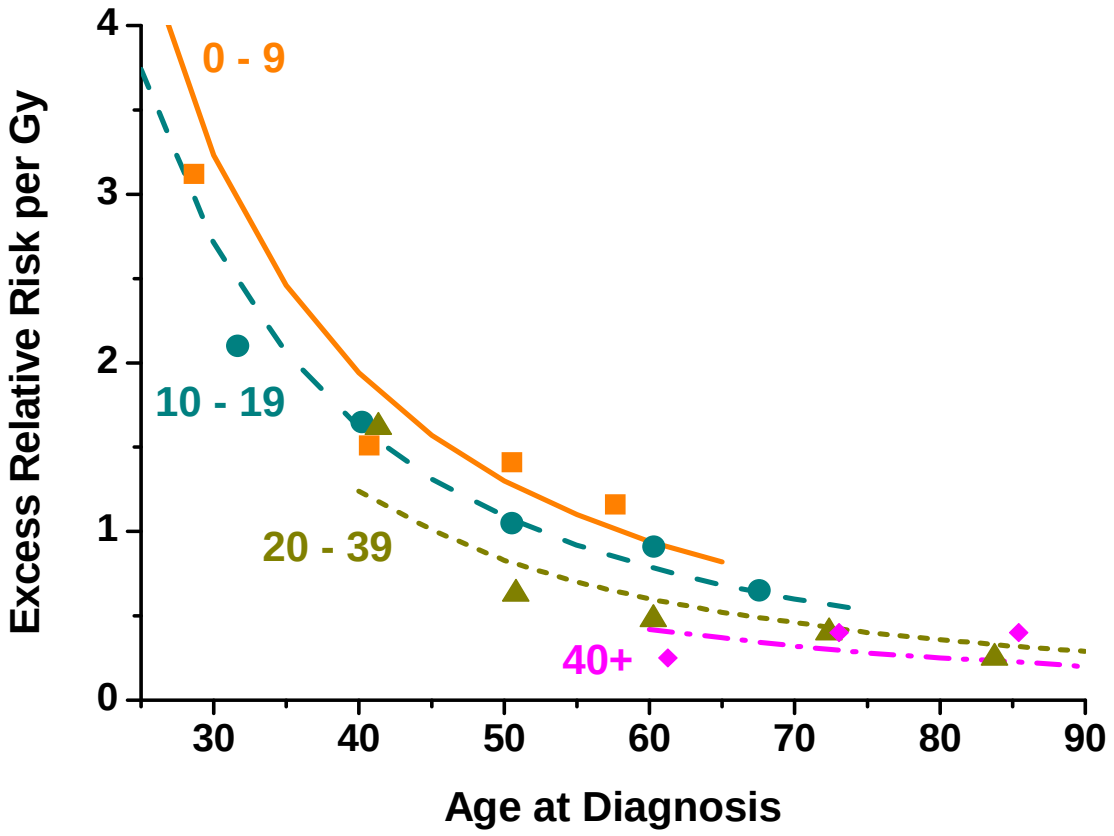
Preston et al. 2004



ERR/Gy * **0.47**
90% CI **(0.40; 0.54)**

* Sex-averaged at age 70 for exposure at age 30

SOLID CANCER ERR Temporal Patterns

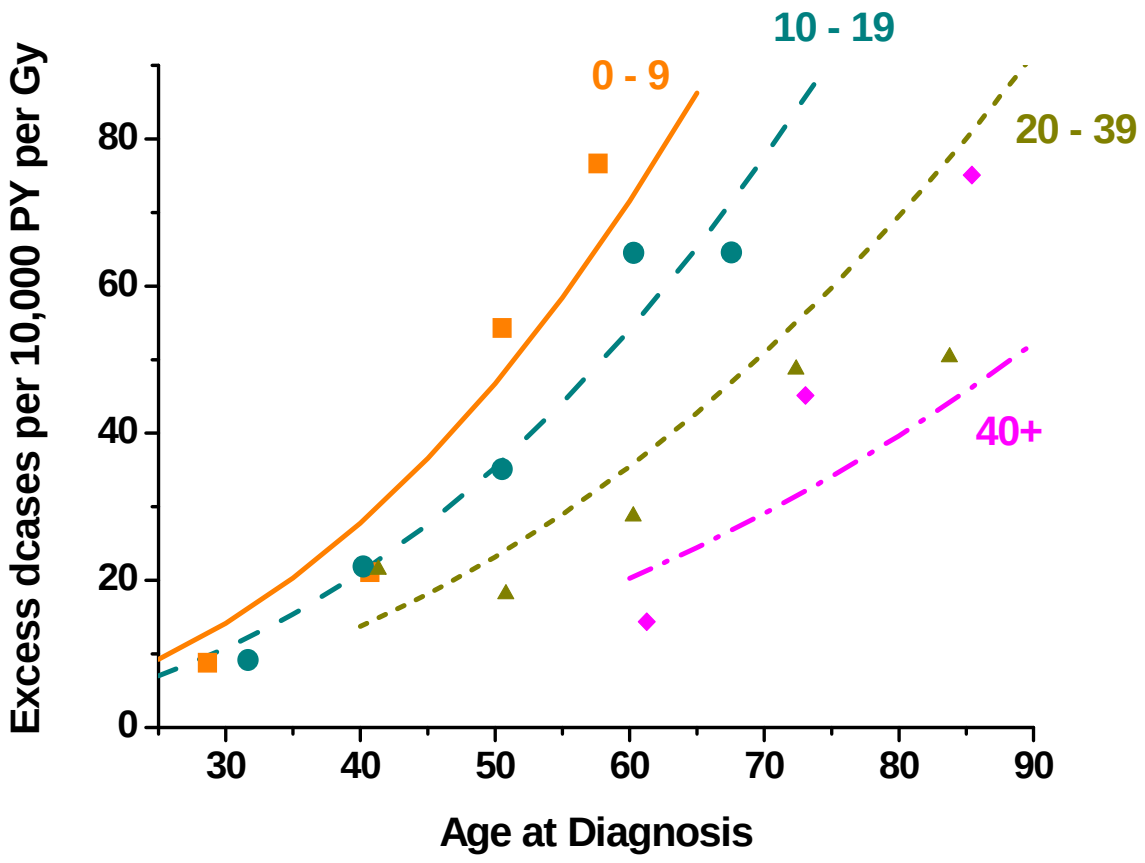


Age at exposure
-17% per decade *90% CI -25%; -7%*
Attained age
Age$^{-1.7}$ *90% CI -2.1; -1.2*
Gender *
M: 0.35 *(90%CI 0.28; 0.43)* F: 0.58 *(90% CI 0.43; 0.69)* F:M: 1.6 *(90% CI 1.3; 2.1)*

- ERR per Gy at age 70 for exposure at age 30

Preston et al. 2004

SOLID CANCER EXCESS RATE -Temporal Patterns



Age at exposure
-24% per decade *90% CI -32%; -16%*
Attained age
Age$^{2.4}$ *90% CI 1.9; 2.8*
Gender *
M: 43 *(90%CI 33; 55)* F: 60 *(90% CI 51; 69)* F:M: 1.4 *(90% CI 1.1; 1.8)*

- Excess cases per 10,000 PY at age 70 for exposure at age 30

Preston et al. 2004

CONCLUSIONS: Solid Cancer Incidence

- Excess rates increase throughout life for all ages at exposure
- Linear dose response
- ERR
  - Decreases with age at exposure and age
- EAR
  - Increases with age
  - Age-specific excess rates decrease with age at exposure
- Continued follow-up will continue to clarify age/time patterns

NEW EPIDEMIOLOGY STUDIES

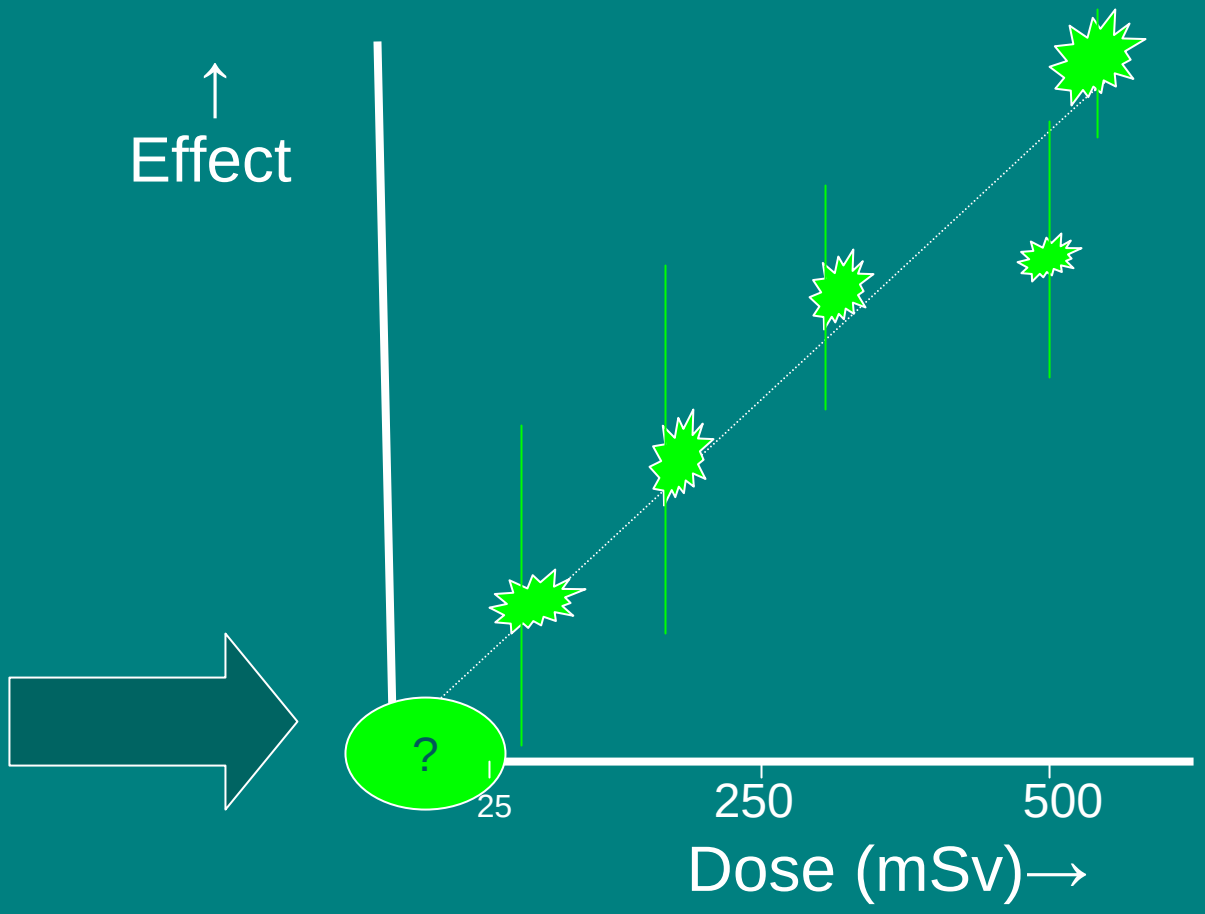
- **External exposure at low doses or low dose rates**
  - **Nuclear workers (most countries; low doses)**
  - **Mayak workers**
  - **Techa River cohort**
  - **Chornobyl clean-up workers**
- **Internal exposure to radionuclides**
  - **Mayak workers (plutonium)**
  - **Techa River cohort (strontium)**
  - **Mayak offspring, Semipalatinsk, Hanford, Chornobyl (I-131)**

LARGE WORKER STUDIES

- International Agency for Research on Cancer (IARC) 3-country study
  - Cardis et al. *Radiation Research* 1995
- National Registry of Radiation Workers (NRRW)
  - Muirhead et al. *J Radiol Protection* 1999
- IARC 15-country study
  - Cardis et al. *British Medical Journal* 2005

LOW-DOSE RESPONSE CURVE

While moderate doses cause well-documented effects, one cannot measure significantly effects at the doses where real doses or regulated doses occur



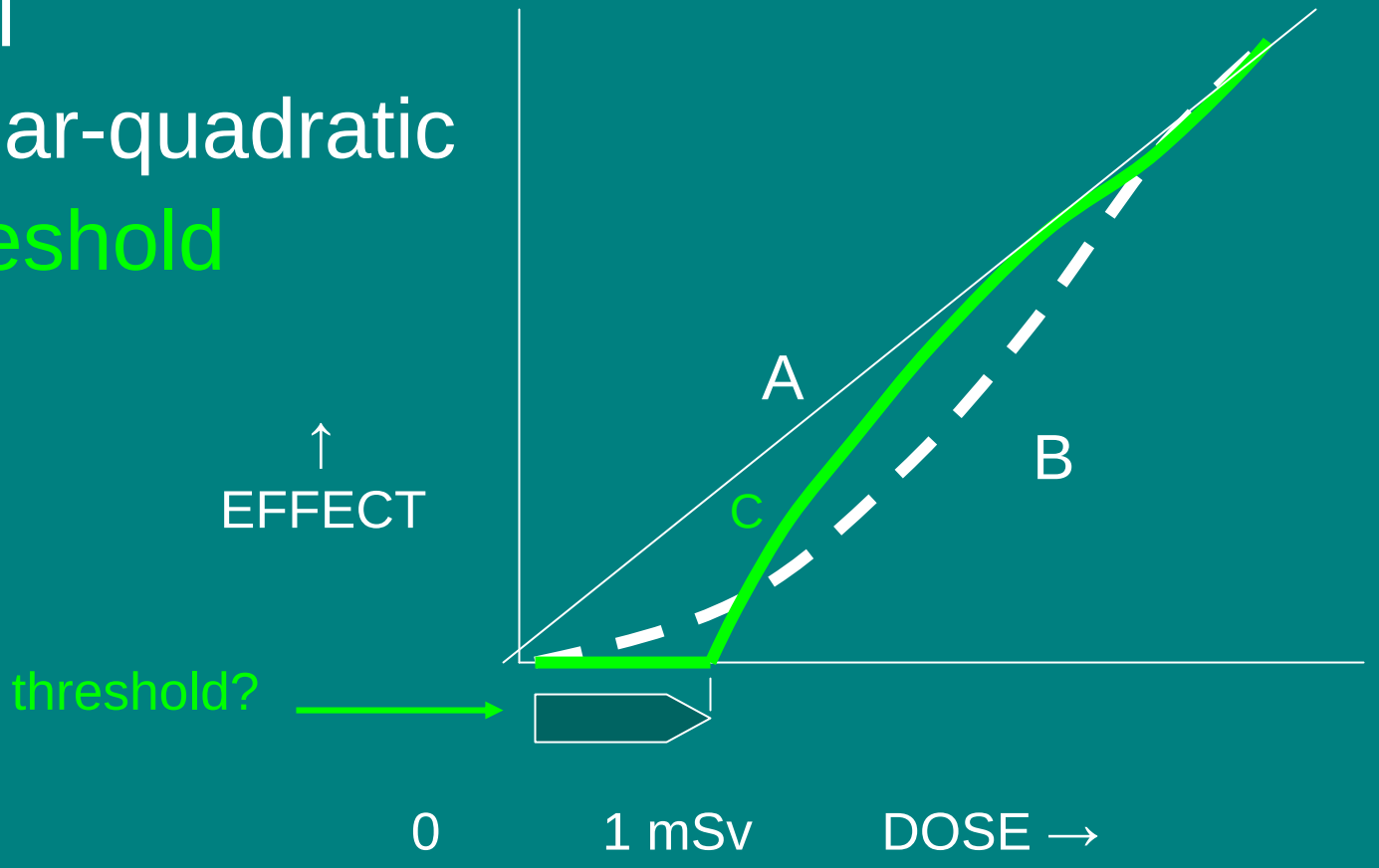
WHAT IS A “LOW-DOSE”?

- On the order of background (2.5 mSv)?
  - ~1.5 mSv/y from radon (high-LET; α)
  - ~1.0 mSv/y (low-LET; β and γ)
  - Approximately 18% is “man-made radioactivity” (of which 79% is medical exposures and 1% is related to the nuclear fuel cycle)
- On the order of protective standards?
  - 1 mSv/y to general public
  - 50 mSv/y whole-body to worker (100 mSv/5 y)
- < 0.1 Sv (or <100 mSv)

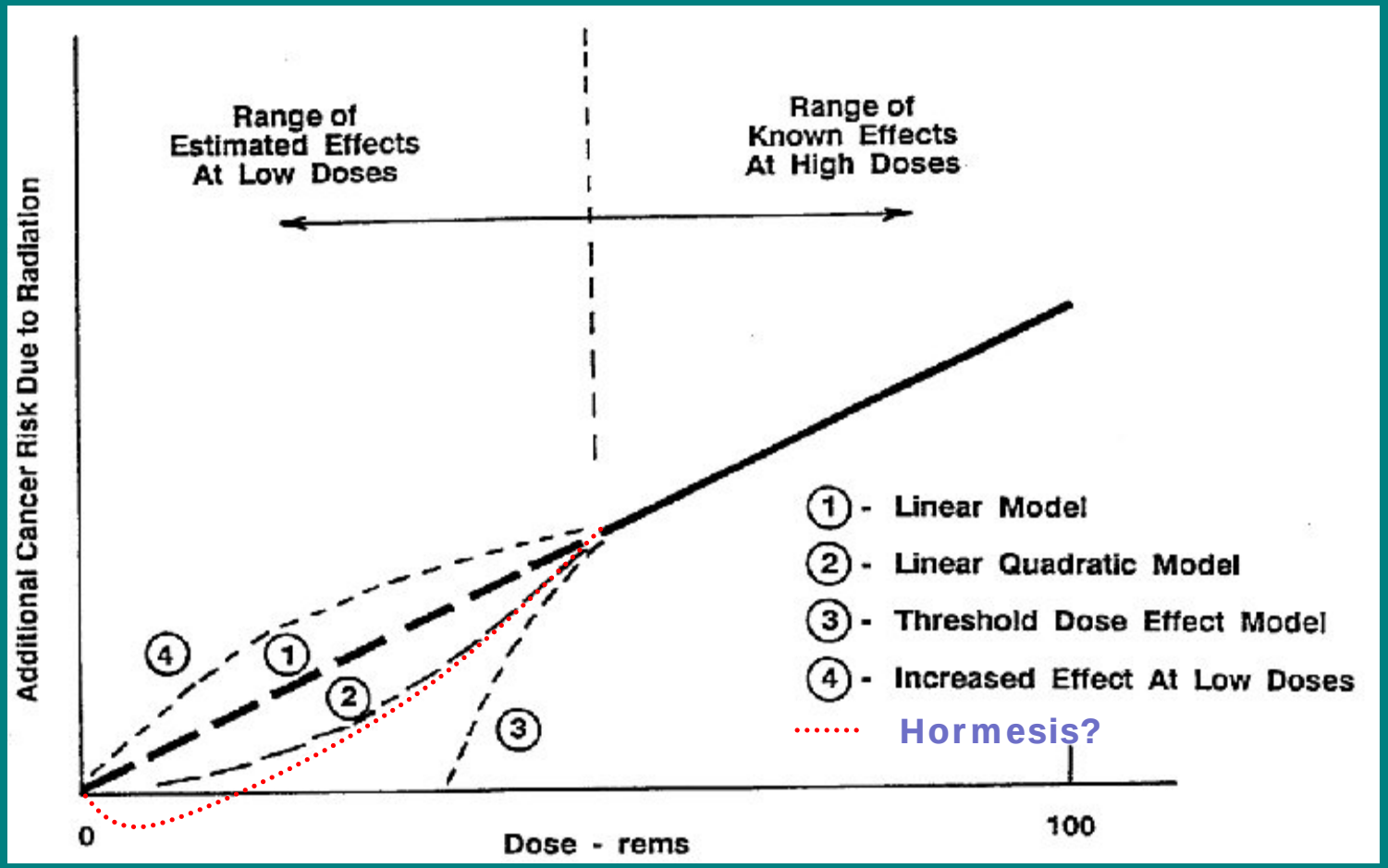
LOW-DOSE RESPONSE CURVE?

3 models:

- A = LNT
- B = linear-quadratic
- C = threshold



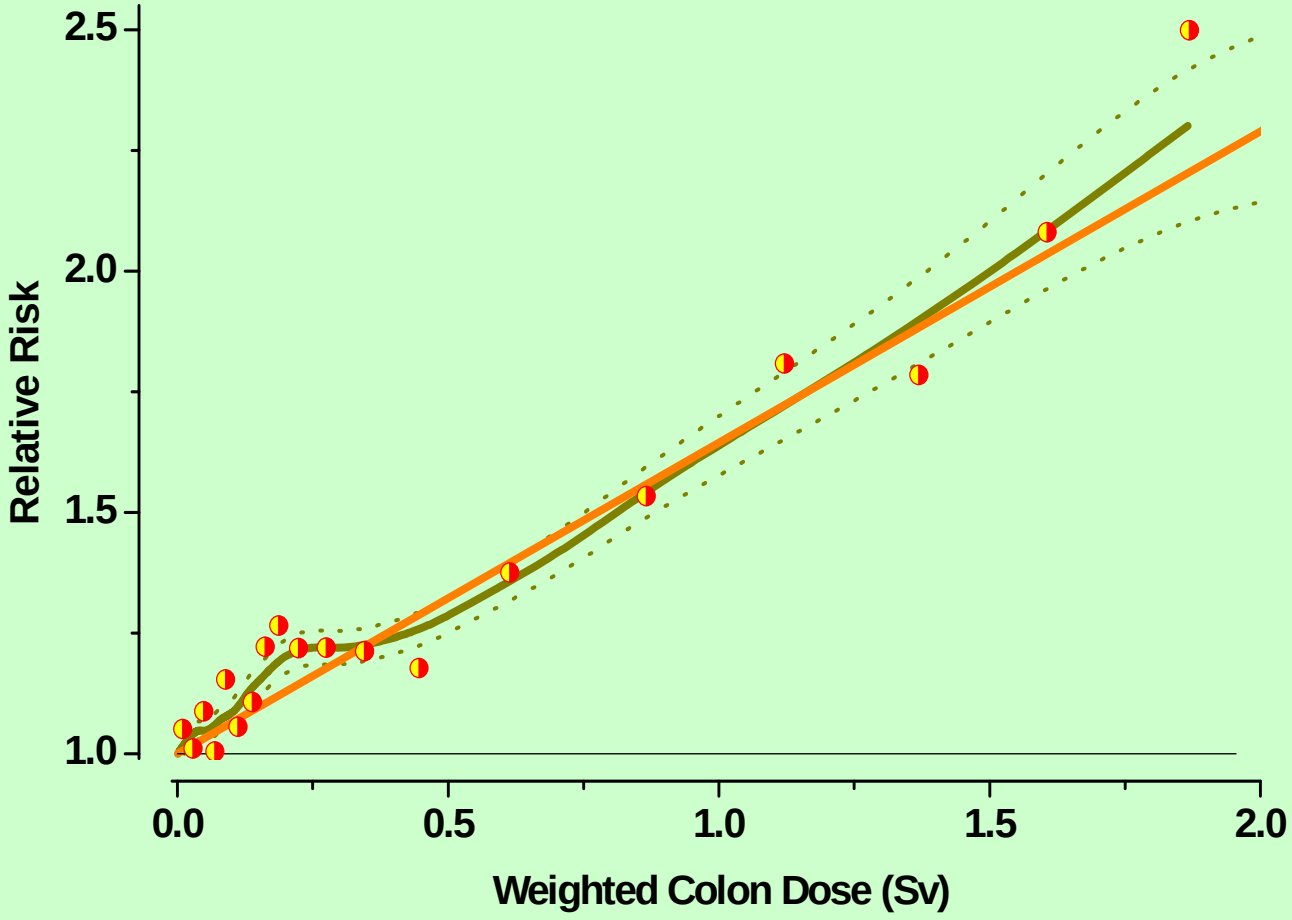
Extrapolation of Acute Dose



BIOLOGICAL OBSERVATIONS

- Bystander effects – effect extends to unirradiated cells thereby increasing the "target" cell population or activating repair enzyme expression (+/-)
- Genomic instability – puts all genes at higher risk for mutagenesis and impacts carcinogenesis when mutations arise in certain critical genes (+)
- Adaptive responses – radiation priming dose protects cells from subsequent radiation doses (-)
- Threshold and/or hormesis – anecdotal evidence but usually in ecological studies with low power (-)

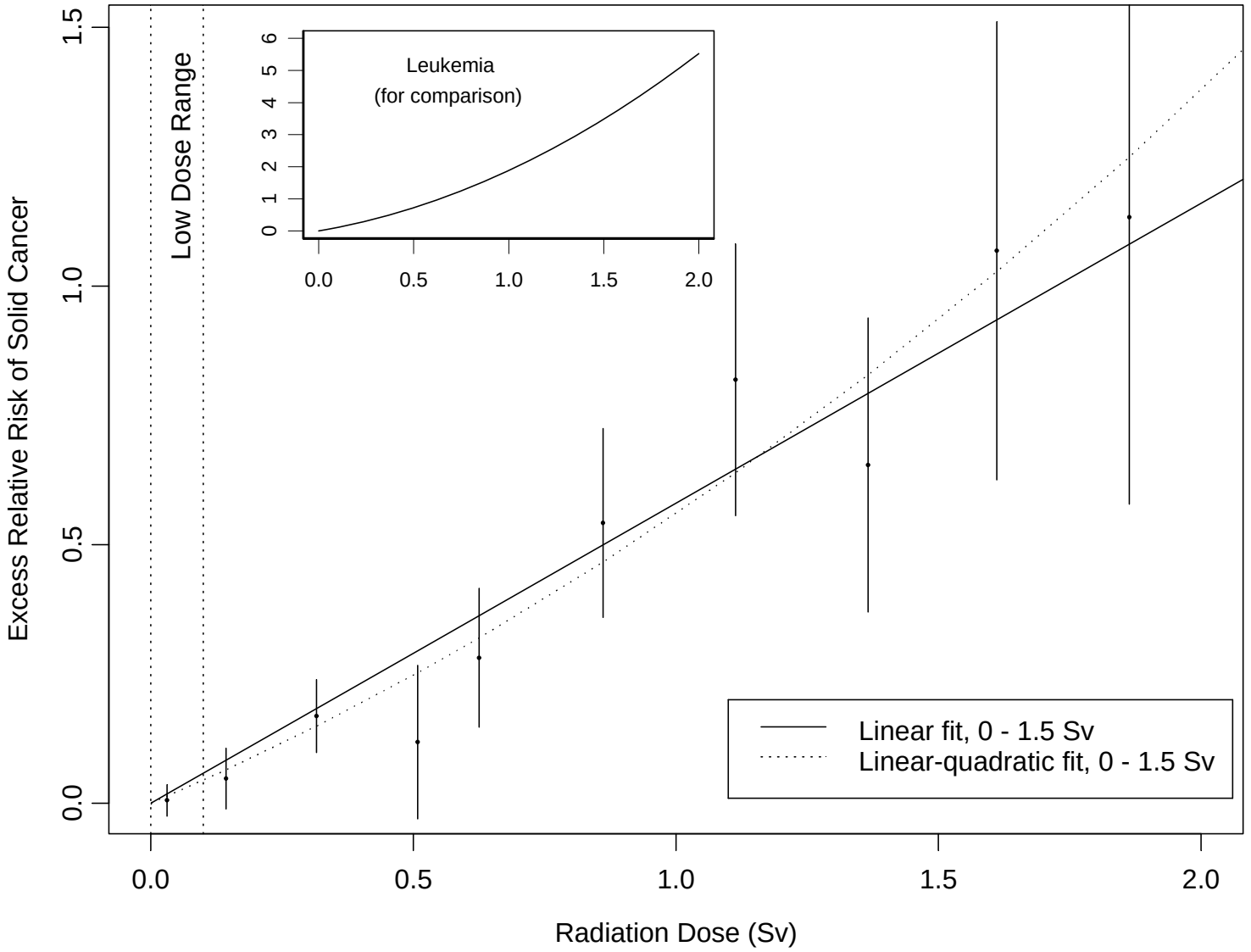
SOLID CANCER INCIDENCE
Dose Response



CONCLUSIONS – OTHER, NON-CANCER

- Radiation appears to increase the risk of diseases other than cancer, particularly cardiovascular disease, following high doses in therapeutic medicine and modest doses in A-bomb survivors.
- However, there is no direct evidence for increased risk at low doses and data are inadequate to quantify this risk if it exists.

Solid cancer incidence: Excess relative risk



BEIR VII, Fig. ES-1

Excess Lifetime Cancer Mortality Estimates (per 100,000 exposed)

TABLE ES-1 The Committee's preferred estimates of the lifetime attributable risk (LAR) of incidence and mortality for all solid cancers and for leukemia with 95% subjective confidence intervals. Number of cases or deaths per 100,000 exposed persons.

	All solid cancer		Leukemia	
	Males	Females	Males	Females
Excess cases (including non-fatal cases) from exposure to 0.1 Gy	800 (400, 1600)	1300 (690, 2500)	100 (30, 300)	70 (20, 250)
Number of cases in the absence of exposure	45,500	36,900	830	590
Excess deaths from exposure to 0.1 Gy	410 (200, 830)	610 (300, 1200)	70 (20, 220)	50 (10, 190)
Number of deaths in the absence of exposure	22,100	17,500	710	530

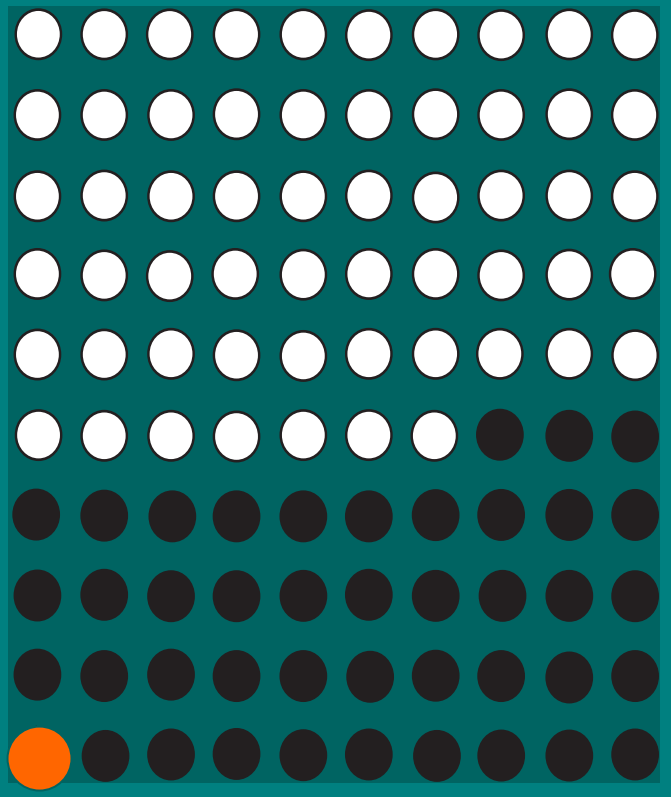
Health Effects of Exposure to Low Levels of Ionizing Radiation - BEIR VII, 2006

Lifetime risk for incidence of solid cancer and leukemia

If 100 people exposed to

0.1 Gy (100 mGy), expect:

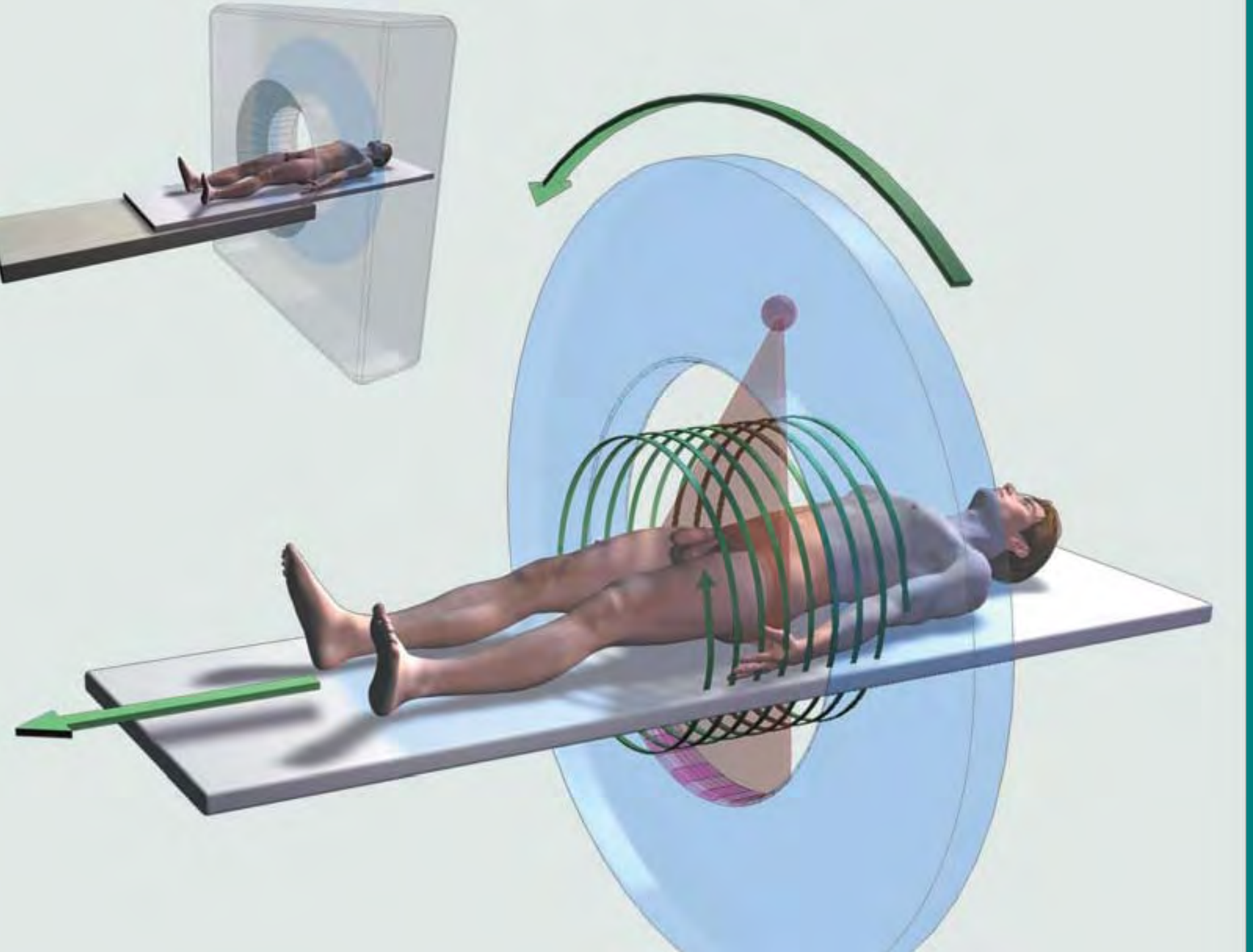
- 1 cancer from this exposure
- 42 cancers from other causes



CONCLUSIONS – CANCER

- Cancer is clearly significant at doses >100 mSv for adults in Hiroshima and Nagasaki
- Cancer is significant at doses >10 mSv for children exposed in utero*
- LNT represented a reasonable fit for solid ca; linear-quadratic for leukemia
- Risk of 100 mSv = 1 in 100 for cancer (vs 42)
- A DDREF from 1.1-2.3 was obtained; 1.5 used
- ERRs and EARs were estimated, including for incidence and with respect to sex, age, and attained age; also for 11 specific cancer sites

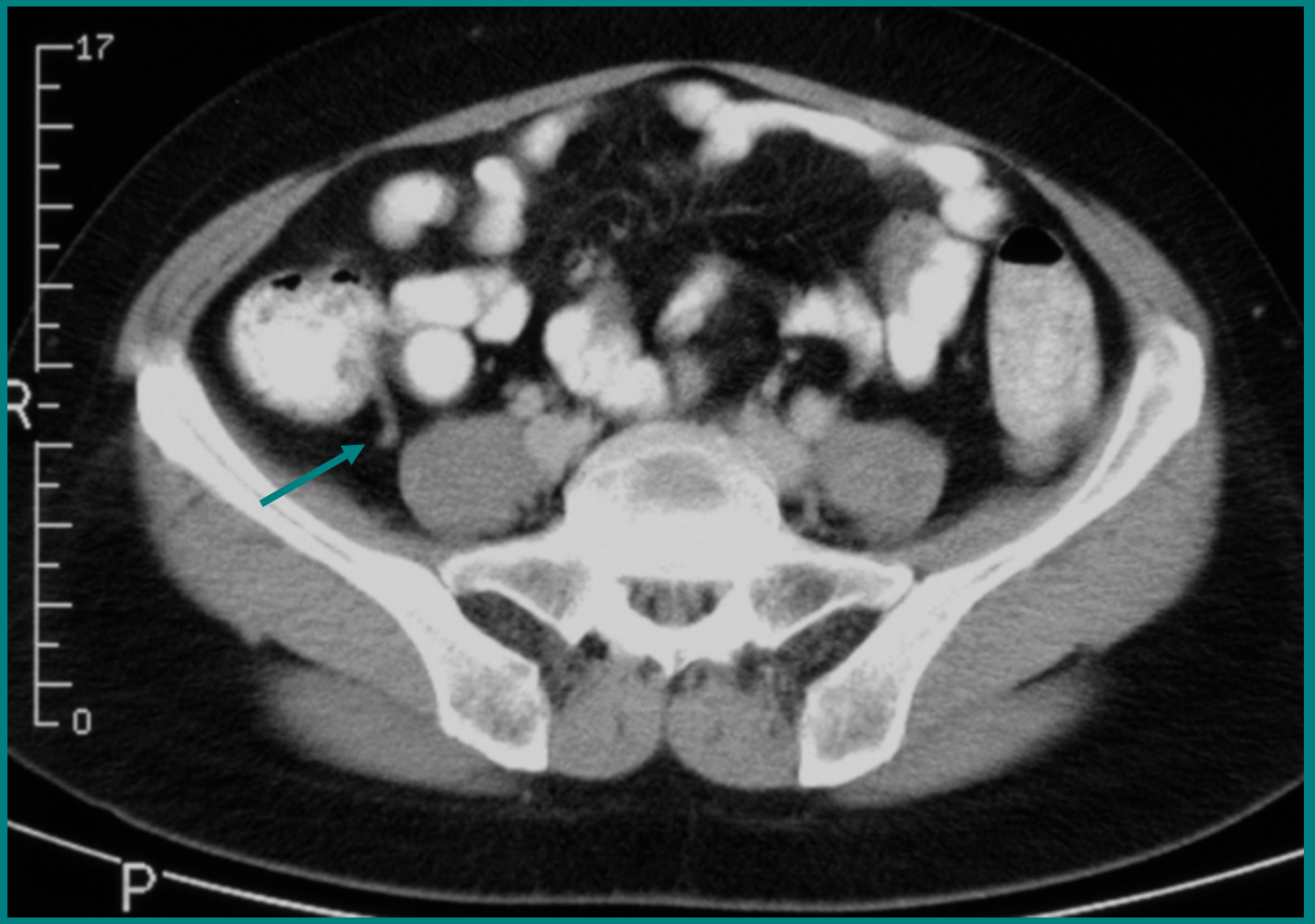
*Oxford Survey of Childhood Cancer found risk elevated 40% up to age 5 after 10-20 mSv exposures.



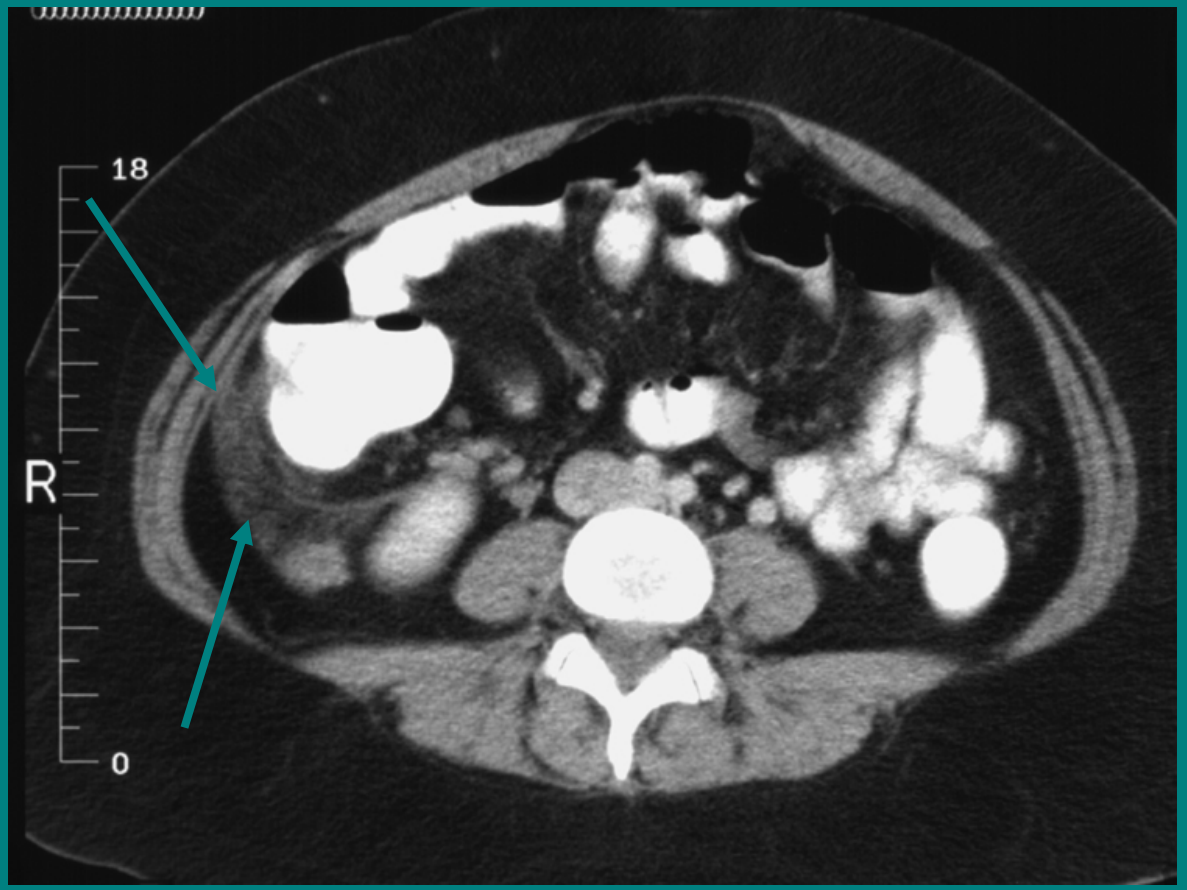
COMPUTERIZED AXIAL TOMOGRAPHY (CT)

- Has revolutionized diagnostic radiology since 1970
- Provides some of the largest doses in radiation medicine
  - Neonatal abdominal (20 mSv to stomach vs lung x-ray of 0.15 mSv or p-a chest film of 0.01 mSv or dental x-ray of 0.005 mSv to brain)
- New procedures continue to be introduced:
  - pre-surgical diagnosis of appendicitis (accurate and cost-effective)
  - CT colonography (virtual colonoscopy)
  - CT cardiac screening
  - Whole-body screening in asymptomatic patients

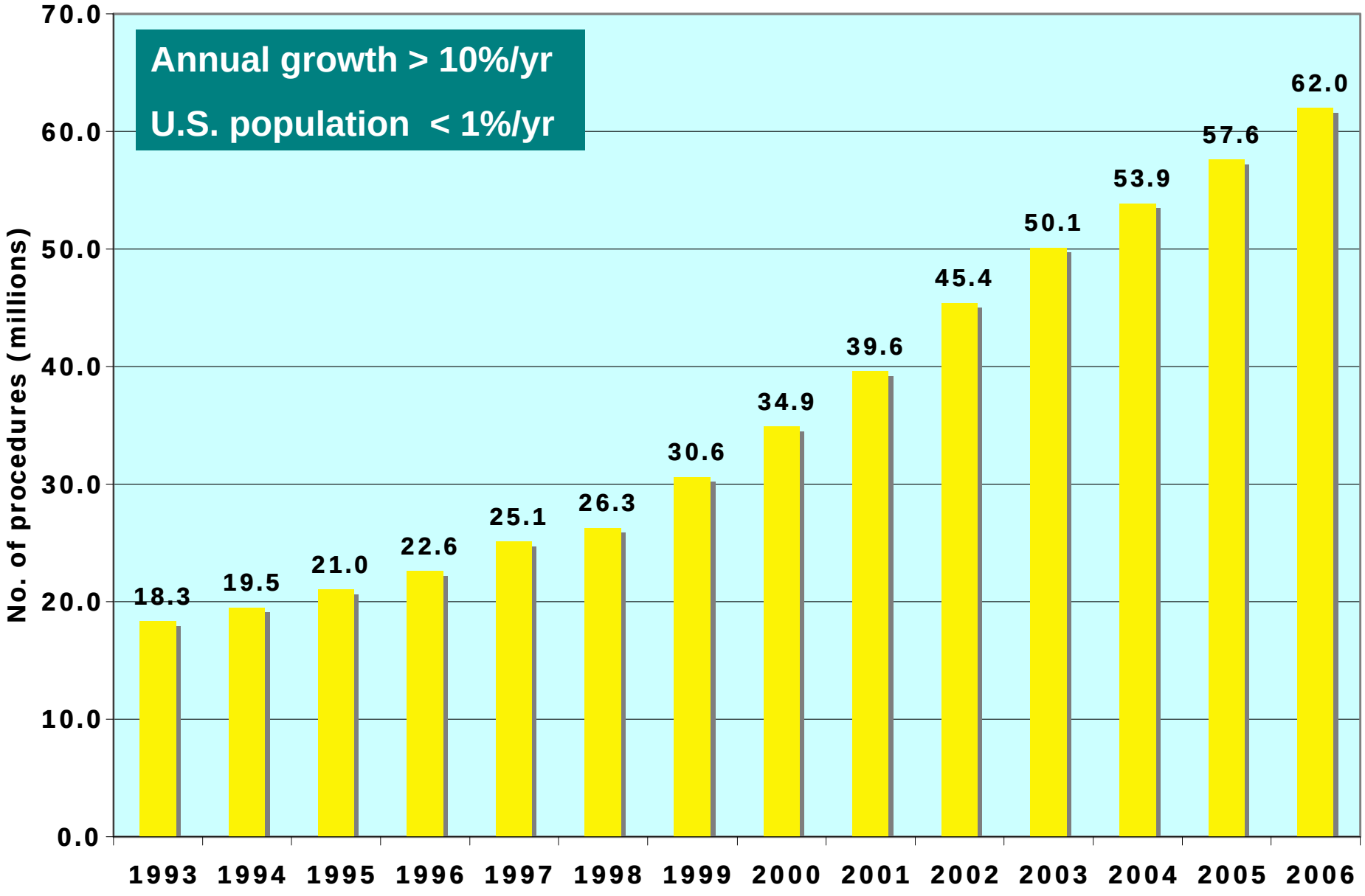
Normal appendix



Appendicitis: edema around cecum



CT procedures by year (millions)



DRAMATIC INCREASE IN CT USE

- 3 M/yr (1980) vs 62 M/yr (2006); 4 M/yr in children
- 0.54 mSv/person (1980) vs 3.2 mSv/person (2006) = 600% increase!
- 15 mSv (adult scan) vs 30 mSv (neonate)
- Scans are often repeated (2-3 scans/patient)
- Compare to:
  - 25,000 A-bomb survivors <50 mSv (m = 40 mSv)
  - 400,000 radiation workers (m = 20 mSv = 1 CT)

EFFECTS OF INCREASE IN CT USE

- CT represents 12% of procedures but 45 % of the dose
- Nuclear medicine represents 3 % of procedures but 23% (up 750% since 1980)
- Combined CT with nuclear medicine includes PET/CT and SPECT/CT
- It has been estimated that 0.4% of all cancer in US may be from CT scans in 1.5-2% of the population.

Medical radiation exposures to US population are increasing

- CT: 67 M (12% of procedures)

440,000 person-Sv (46% of dose) 1.45 mSv pc

- NM: 19 M (4% of procedures)

220,000 person-Sv (23% of dose) 0.7 mSv pc

- Total x-ray + NM: 535 M 960,000 person-Sv

3.2 mSv pc

Since 1980: per capita medical dose up 600%

collective annual dose up 750%

COMPARE COLLECTIVE DOSES

- ~600,000 person-Sv worldwide over all time from entire Chernobyl release*
- ~930,000 person-Sv ***annually*** from radiology and nuclear medicine in U.S.
- ~900,000 person-Sv ***annually*** from natural background radiation (assuming old NCRP 100 calculations)

* UNSCEAR

HOW DOSE CAN BE MINIMIZED

- Replace with alternate approach (1/3 could be replaced or not performed)
- Auto exposure controls and optimization of physical parameters (improve image quality)
- Ask: “Are they needed?” (20 M adult scans & >1 M children scans/yr may be unnecessary)
  - Ex. Abdominal pain —> abdominopelvic CT?
    cough —> chest CT?
- Avoid repeat scans

THE BOTTOM LINE

- The BEIR VII Committee concludes that the current scientific evidence is consistent with the hypothesis that there is a linear, no-threshold dose-response relationship between exposure to ionizing radiation and the development of cancer in humans, but notes that at low doses that risk will be small.
- While adverse health effects have not been observed in the children of exposed parents, extensive data in mice suggests that there is no reason to believe that humans would be immune to this sort of harm, but the risk is low.

SUMMARY

Investigators submitting to IRBs should:

- Factor in the relatively low but potentially real risk of fatal disease from proposed radiation procedures.
- Consider alternatives whenever possible and especially in young or pregnant patients.
- Minimize exposures and unnecessary retakes.
- Inform patients of a low risk and include in obtained informed consent.
- Include an estimate of risk in research protocol

Ex: 10 mSv ~ 1 in 2000 ca in child

REFERENCES

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