# Estimating Cancer Risks at Low Doses and Dose Rates: Lessons from Dr. Land

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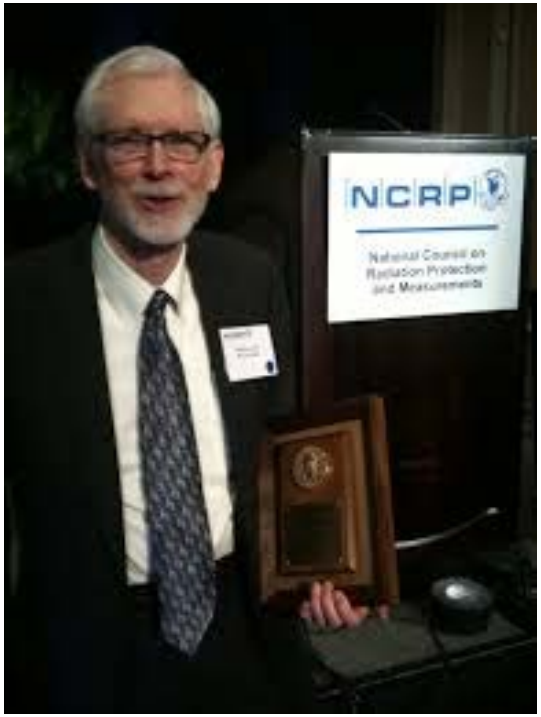
# Questions

- What is the Linear No-Threshold (LNT) model?
- How is it used to estimate risks at low doses and dose rates (LD/LDR)? Why?
- What could possibly go wrong?
- Should it still be used?
- What inferences are appropriate from statistical tests and P values from epidemiological data?

# Dr. Charles E. Land

(1937-2018)

- Statistician: co-founded (with Dr. Boice) NCI's Radiation Epidemiology Branch
- Studied radiation effects on atomic bomb survivors at RERF
- NCRP member, served on NAS, ICRP, NCRP committees
- "Estimating Cancer Risks at Low Doses of Ionizing Radiation"



# Terminology

- Risk: The probability of death or disease developing in a population in a specified interval of time.
- Excess Absolute Risk (EAR): $R_{exposed} - R_{unexposed}$
- Relative Risk (RR):

  Rate of disease/death in an exposed population divided by the rate in an unexposed population

- Excess Relative Risk: ERR = RR - 1

# What is the LNT Model?

I can’t remember what we’re arguing about, either. Let’s keep yelling, and maybe it will come back to us.

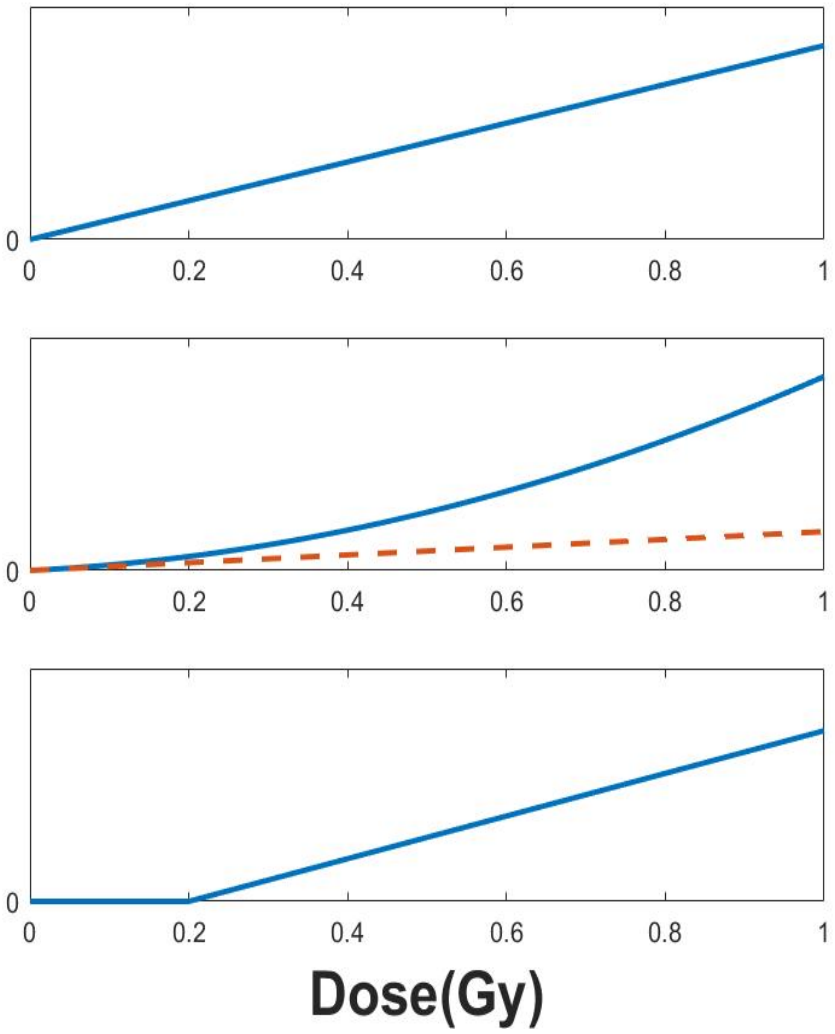
David Sipress, New Yorker Magazine (from Condé Nast collection)


*“I can’t remember what we’re arguing about, either. Let’s keep yelling, and maybe it will come back to us.”*

# Linear No Threshold (LNT) Model

- Excess risk of cancer at low doses is (approximately) proportional to dose
- There is no threshold
- Dose response models which satisfy the LNT hypothesis include
  - Models that are linear over a range of doses and with no threshold !!!!
  - Linear-quadratic (LQ) models

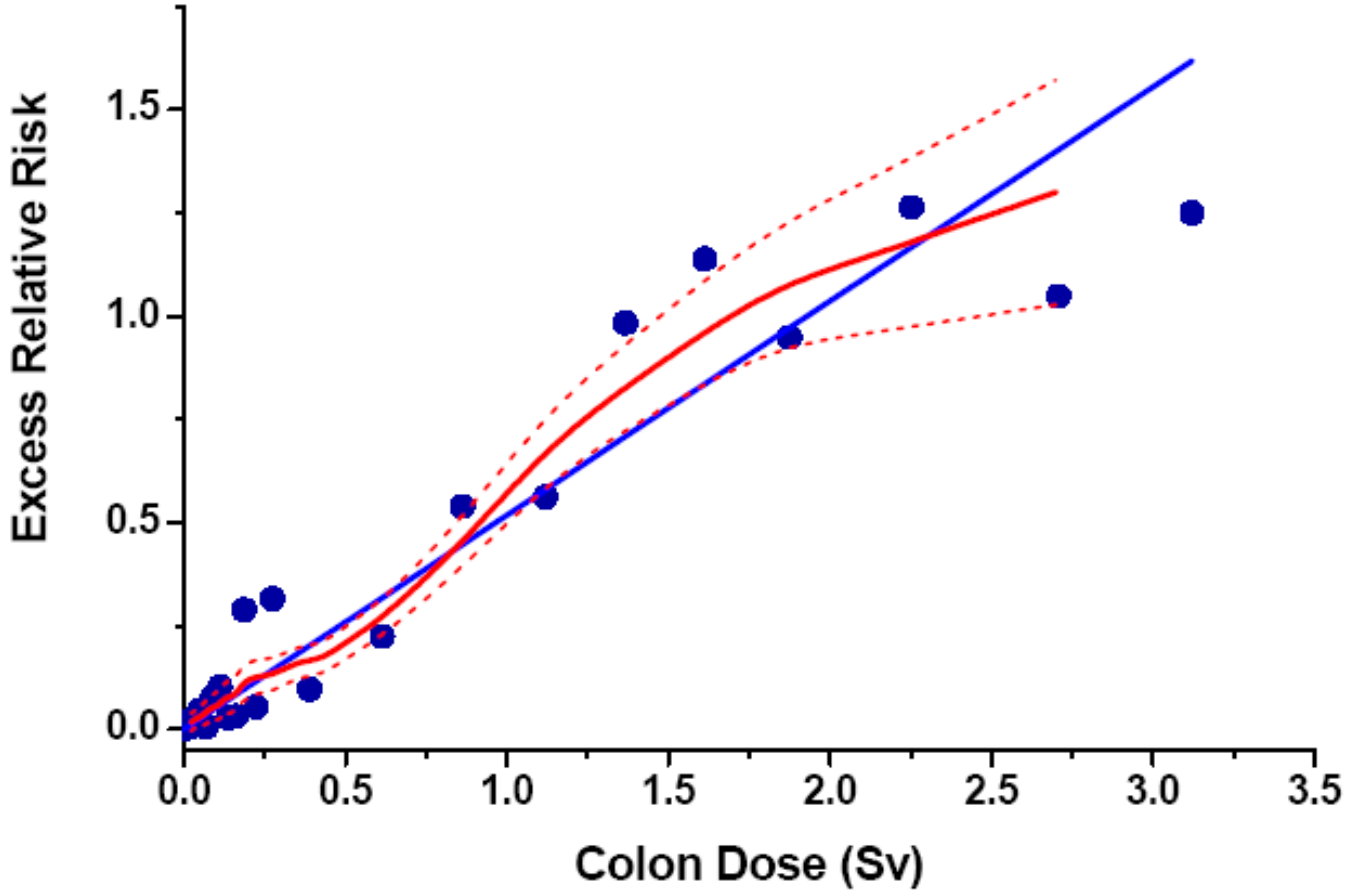
# Which Satisfy the LNT Model?



# How is LNT Used to Estimate Risks for LD/LDR Exposures?

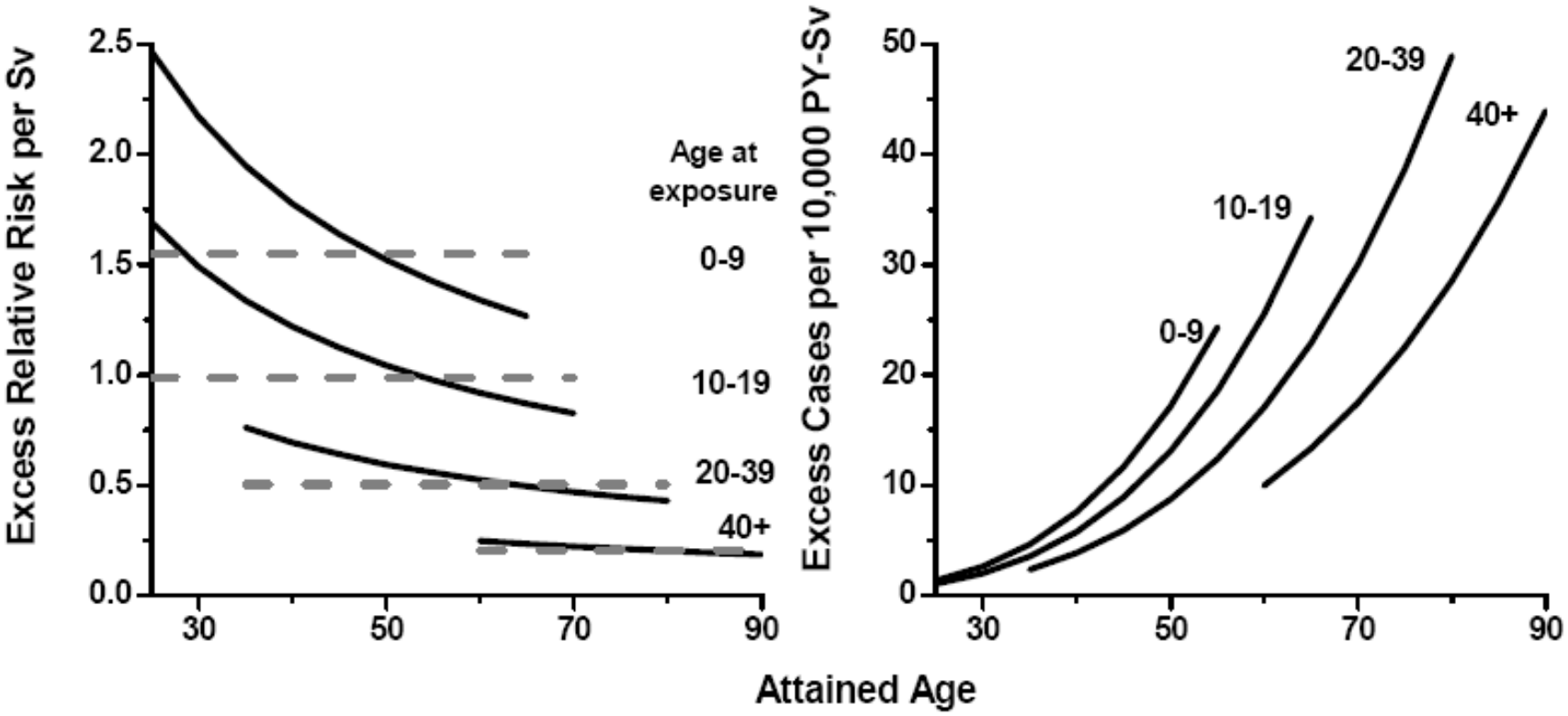
- Current LD low-LET risk projections (UNSCEAR, BEIR VII, EPA) are based on extrapolations.
- Risk models fit to Atomic Bomb Survivor data
  - Assume LQ dose response (sometimes with additional term(s), e.g., for cell killing
  - In theory can use other type of parametric models
  - Most models considered satisfy LNT

# Solid Cancer among Atomic Bomb Survivors




(LSS Report 13, Preston et al, 2003)

# ERR and EAR Depend on Age

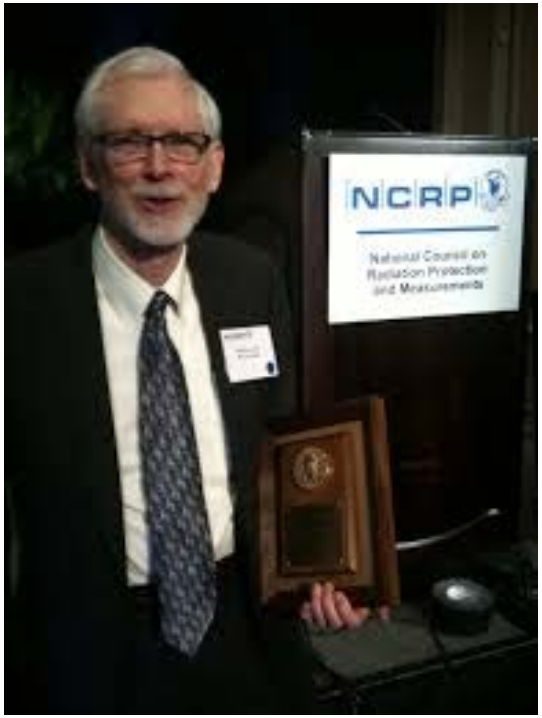



(LSS Report 13, Preston et al, 2003)

# WHY DO WE USE THIS APPROACH?

# Sample Size (and other!) Requirements

- Estimating Cancer Risks from Low Doses of Ionizing Radiation: “Precise direct estimation of small risks requires impracticably large samples.”
  - Land (1980)



# Some "Impracticably Large" Sample Requirements

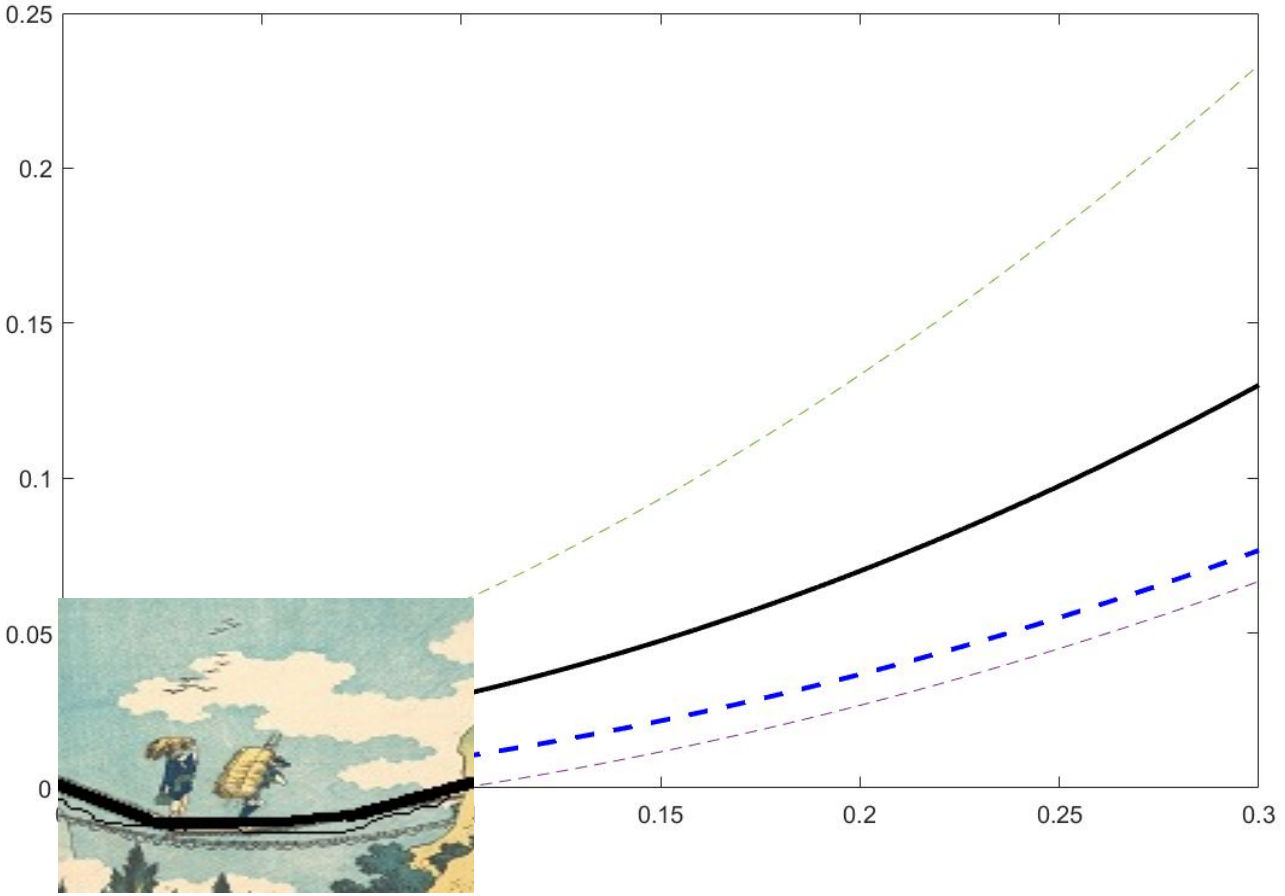
- Does the radiation from mammography (about 10 mGy) cause breast cancer?
  - Cohort study: about 100 million (20 y follow-up)!
  - Case-control: about 1 million cases (4:1 ratio)
  - at 100 mGy, 1 million (cohort); 10K (case-control)
- Does radiation cause leukemia?
  - Much smaller baseline rate
  - About 1300 cases (assume 1 rad to bone-marrow)

# Is Sample Size the Whole Story?

- **NO!***
- "Subtle sources of bias … may be comparable in effect to exposure. Increasing sample size cannot compensate for such bias, and may in fact add to difficulties … On the other hand, when the excess risk due to radiation is high, such biases often can be ignored." (Land 1980)

***Marcel Marceau, "Silent Movie"**

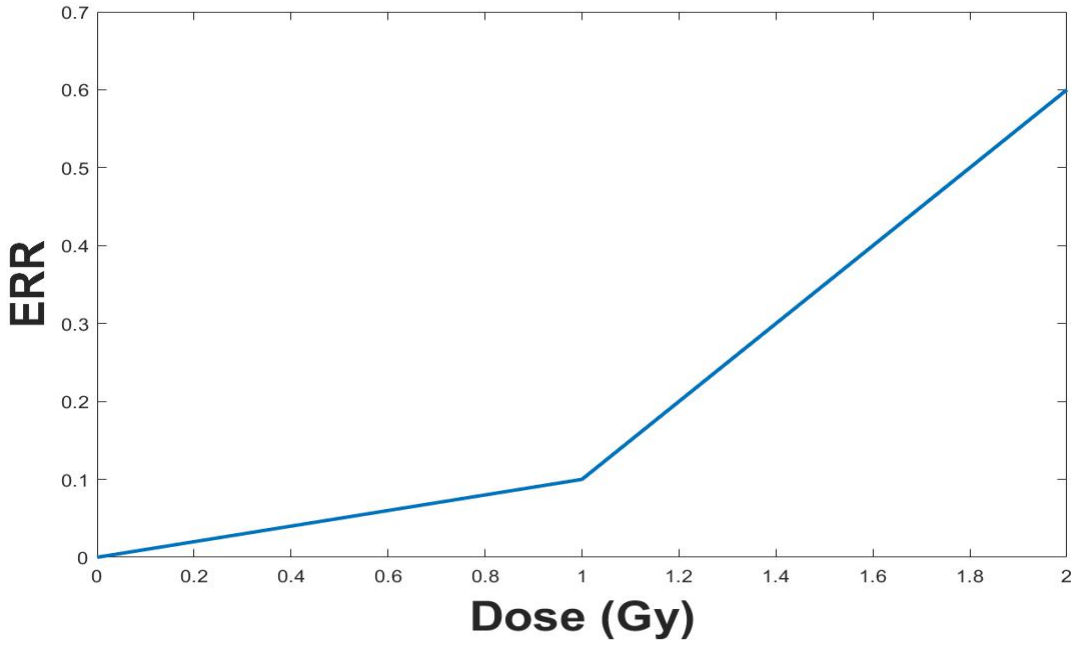
# What Could Possibly Go Wrong?



# Model Misspecification

## The REAL Issue

How does misspecification of models used for extrapolating to low doses and dose rates affect our projections of risk?



# No Better Alternative?

- Dr. Land (1980): “There seems to be no way to evade the problem of curve fitting and extrapolation from high-dose estimates of excess risk.”

  “We do not have the resources for adequate epidemiologic studies of populations exposed to low doses of radiation …”

- *But NOW with technological advances such as computerized medical record keeping …*

# Recent Studies with Sufficient Power

- Higher doses, lower dose rates
  - Techa River, Mayak, Chernobyl, …
- Large low dose studies
  - CT studies (Great Britain, Australia …)
  - Childhood leukemia natural background studies
- Pooled analyses
  - Nuclear workers (INWORKS)
  - Radon residential case/control
  - “Stay Tuned”: Million Person Studies

# For Future (UNSCEAR, BEIR) Reports on Radiation Risk

- What epidemiologic data should new risk projections be based on?

  LSS, Subset of low dose rate studies, or Both

- What type of approach might be used for deriving the projections?

  Pooled, Meta, or …

- *But what about that problem of bias?*

# What is the Lowest Dose at Which Cancer Risk is Shown in the LSS?

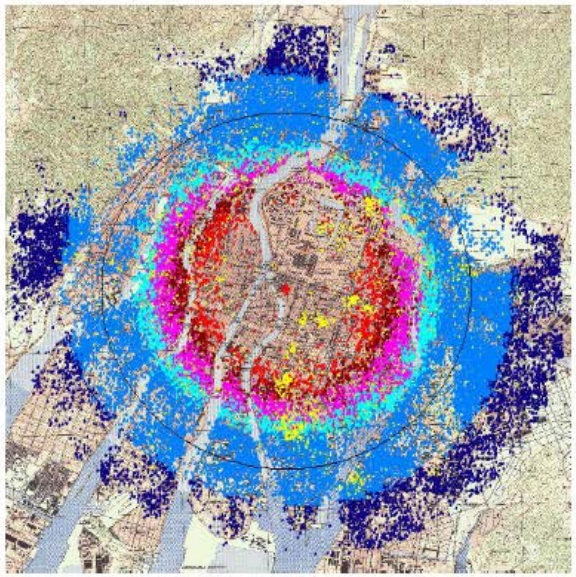
- LSS (Grant et al 2017): “The lowest dose range that showed a statistically significant dose response … was 0-100 mGy (p=0.038).”

  Estimated ERR at 0.1 Gy is about 0.05.

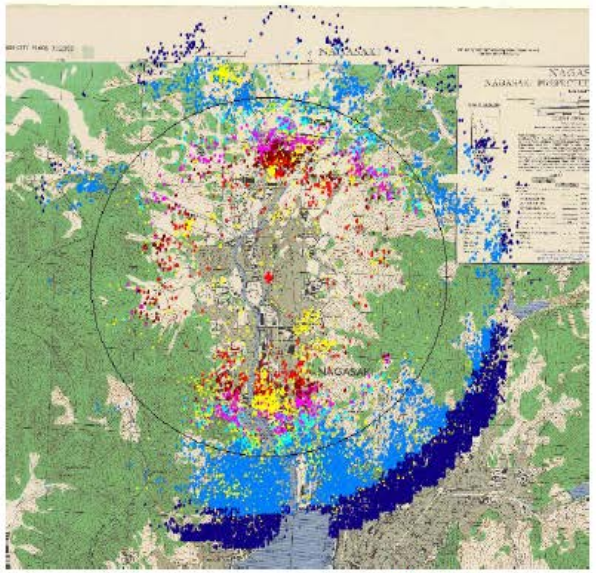
- Are these slightly elevated cancer rates evidence of radiation risk or something else?

# Survivors within 3 km

Hiroshima



Nagasaki



Dose (mSv)

- < 5
- 5 – 100
- 100 – 200
- 200 - 500
- 500 – 1000
- 1000 +
- unknown

✚ Hypocenter

* LSS: Life Span Study Cohort

Courtesy of Dale Preston

# What if Baseline Cancer Rates are Correlated with Dose?

- Suppose survivors with doses ≤ 0.1 Gy were exposed (at 0.1 Gy) or not exposed (0 Gy).
- Suppose the ERR at 0.1 Gy is about 0.05.
- In Hiroshima, the “non-exposed” live closer to the edge of the city. If the baseline cancer risk is just 2% higher at these locations, the “corrected” P-value would be about 0.2.
  - more on P-values later!

# Low Dose vs. Low Dose Rate Studies

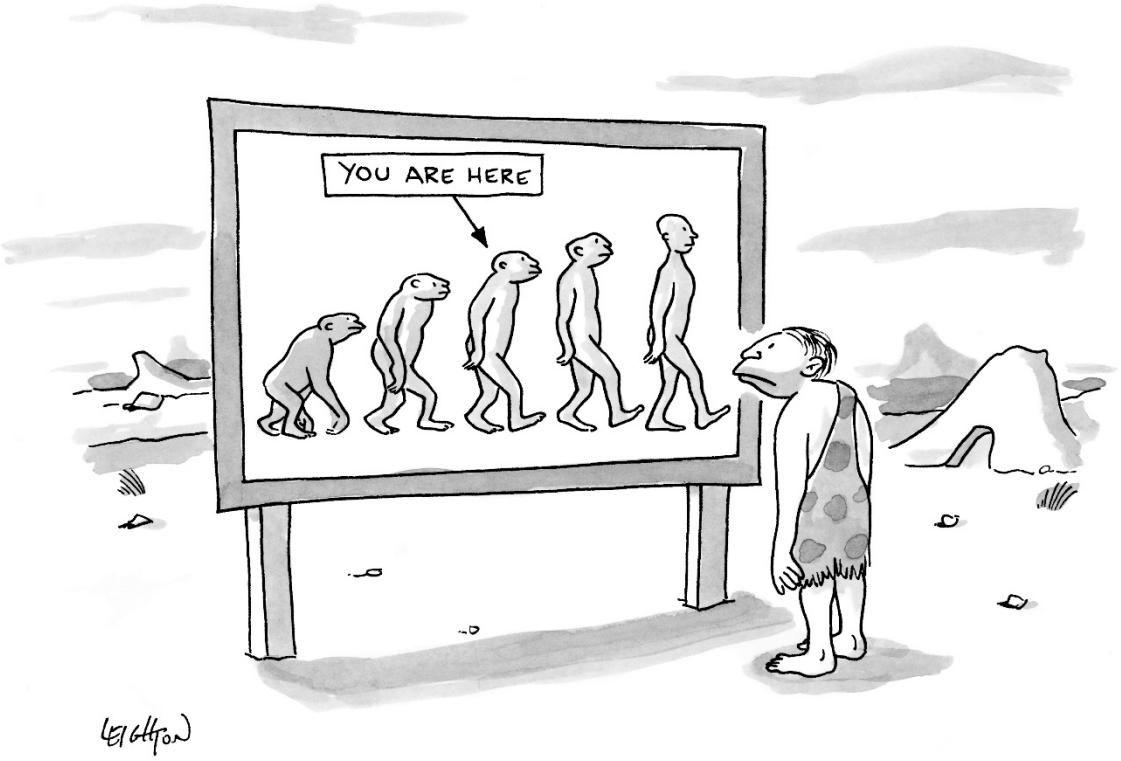
- Assertion: Low dose studies have the potential for large bias in radiation cancer risk estimates
  - ***Exception***: Radiosensitive cancers/subpopulations
- Pooling/meta analyses increase precision but, in general, not bias
- Prefer low dose rate studies that include subjects with moderate to large doses
  - Risks at low doses vs. risks at low dose rates?

# NCRP (2018): *Implications of Recent Epidemiological Studies for the LNT Model*

- "The most recent epidemiologic studies show that the assumption of a dose-threshold model is not a prudent pragmatic choice for radiation protection purposes. The consistency of the better-designed and larger studies with dose-response functions that are essentially linear or LQ, argues for some risk at low doses."

# Interpreting Statistical Test Results and *P*-values

(from epidemiological data)




Robert Leighton, New Yorker magazine (from Condé Nast collection)

# Statistical Hypothesis Testing Basics

Greenland et al. (2016) *Statistical tests, ..., guide to misinterpretations*

- ***Statistical testing***: one assumption in the model is a "test" hypothesis that a particular effect has a specific size, e.g.,

  $H_0$: β = 0 (β = ERR per unit dose for colon cancer)

- Inferences about the test hypothesis are based on a ***test statistic***, which measures the distance between the model and the data, e.g.,

  (Estimate of β)/(Standard deviation of estimate)

# *P*-value

- ***P*-value** is the ***probability*** that the test statistic is ***as large*** (extreme) as its observed value if ***every*** model assumption is correct, including the test hypothesis.
- "It can be viewed as a continuous measure of the compatibility between the data and the entire model used to compute it, ranging from 0 for complete incompatibility to 1 for perfect compatibility …"
- *P*-value is typically compared to 0.05
  - Why 0.05? R.A. Fisher (smart man) suggested it.

# Misinterpretations of *P*-values (I)

- ***A nonsignificant (NS) test result (P > 0.05) means that the test hypothesis should be accepted*** 
  - "To be scientifically sound compelling evidence must be provided that the valid null (no effect at low doses) should be rejected in favor of an alternative hypothesis, e.g., … LNT, …hormesis …"
  - "No detectable health effects below 100 mGy …"
- Note: It is simply false to claim that statistically NS results support a test hypothesis … even if power is high for alternatives

# Misinterpretations of *P*-values (II)

- A significant test result ($P \leq 0.05$) means the test hypothesis is false or should be rejected 
- The P-value is the probability that the test hypothesis is true; for example, if a test of the null hypothesis gave $P = 0.01$, the null hypothesis has only a 1 % chance of being true; if instead it gave $P = 0.40$, the null hypothesis has a 40 % chance of being true. 

# American Statistical Association (ASA) Statement on P-Values (2016)

1. P-values can indicate how incompatible the data are with a specified statistical model.
2. P-values do not measure the probability that the studied hypothesis is true, or the probability that the data were produced by random chance alone.
3. Scientific conclusions and business or policy decisions should not be based only on whether a p-value passes a specific threshold.
4. Proper inference requires full reporting and transparency.

# ASA Statement on P-values

(continued)

5. A p-value, or statistical significance, does not measure the size of an effect or the importance of a result.

6. By itself, a p-value does not provide a good measure of evidence regarding a model or hypothesis.

# Conclusions

- LNT model: Excess risk of cancer ***at low doses*** is proportional to dose.
- Land: “Precise direct estimation of small risks requires impracticably large samples.”
  - Also warned about bias in low dose studies
  - Still? Prefer “low dose rate” studies to low dose” studies
- Read Greenland et al. (2016) !!!!!

# Radon

- EPA (2003) estimated about 20K annual lung cancer deaths attributable to radon (about 3K among never smokers)
  - BEIR VI analysis of underground miner cohorts
- Pooled analyses of residential case-control studies in Europe, North America, and China provide “direct” evidence of substantial risk from radon in homes.