National Cancer Institute

Low-Dose Extrapolation of Radiation-Related Risk

Epidemiological Overview and Quantitative Uncertainty Analysis

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Introduction

- Ionizing radiation (IR) is a known, and well-quantified, human cancer risk factor
- But estimation of radiation-related cancer risk is uncertain
  - Statistical uncertainty
  - Transfer between populations
  - *Extrapolation to low doses*
    - Possibility of a threshold?
- Uncertainty considerations are important
  - Is there really a risk? How strong is the evidence?
  - How high could the risk plausibly be?

We know as much as we do about radiation-related risks mainly because we can (often) estimate organ-specific doses with some precision

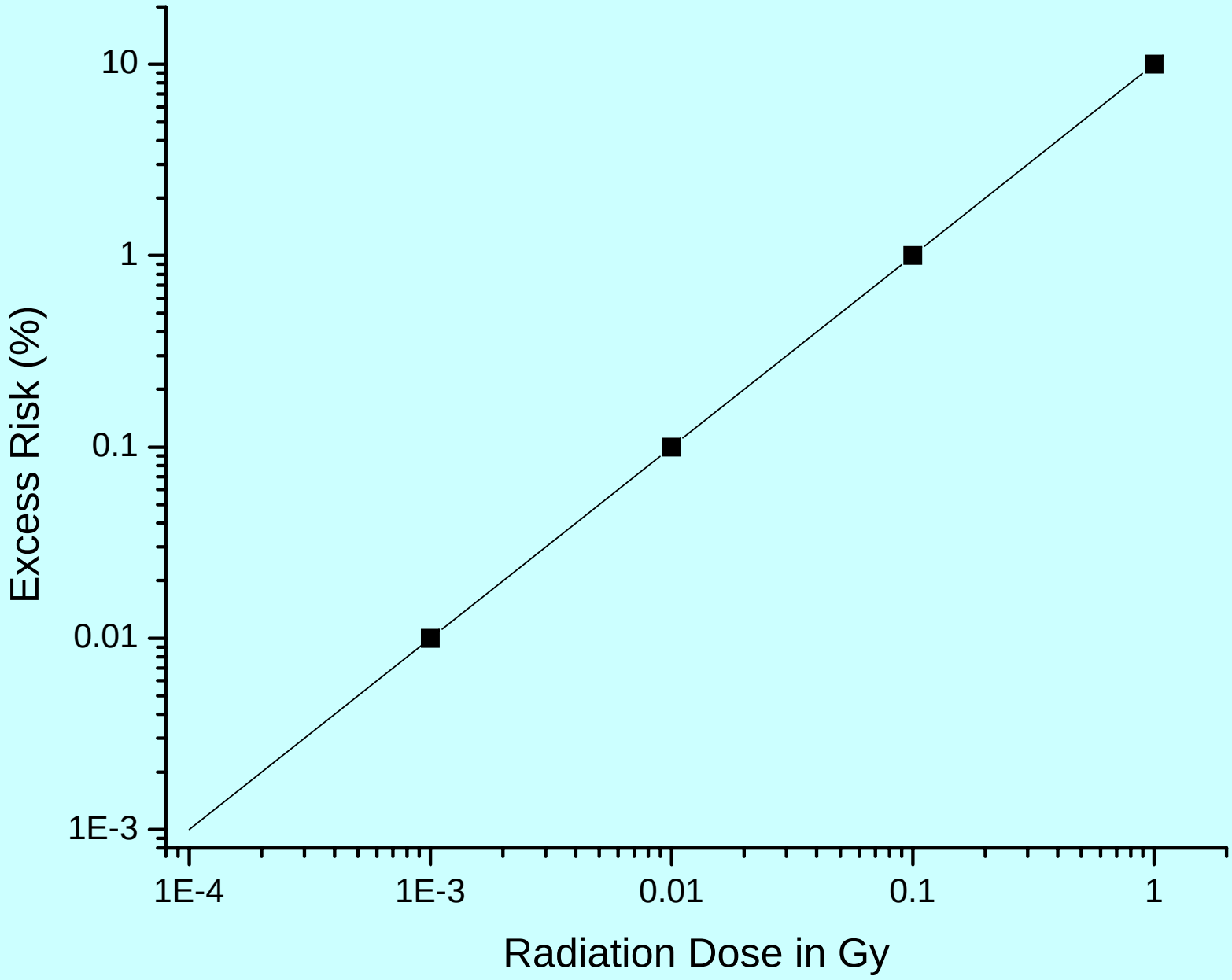
Even in human populations

Even when the doses are low

Estimating low-dose cancer risks directly is one of the most difficult tasks there is in epidemiology

An overly simple example

- Suppose a *known* population baseline cancer risk of 10% over a 30-year period (i.e., no need to estimate it)
- Suppose a uniform exposure, to dose D
- Suppose also that excess risk is proportional to dose, for $0 \leq D \leq 1$ Gy
- And that risk is doubled for D = 1 Gy


Excess Risk (%)
10
1
0.1
0.01
1E-3
1E-4
1E-3
0.01
0.1
1
Radiation Dose in Gy

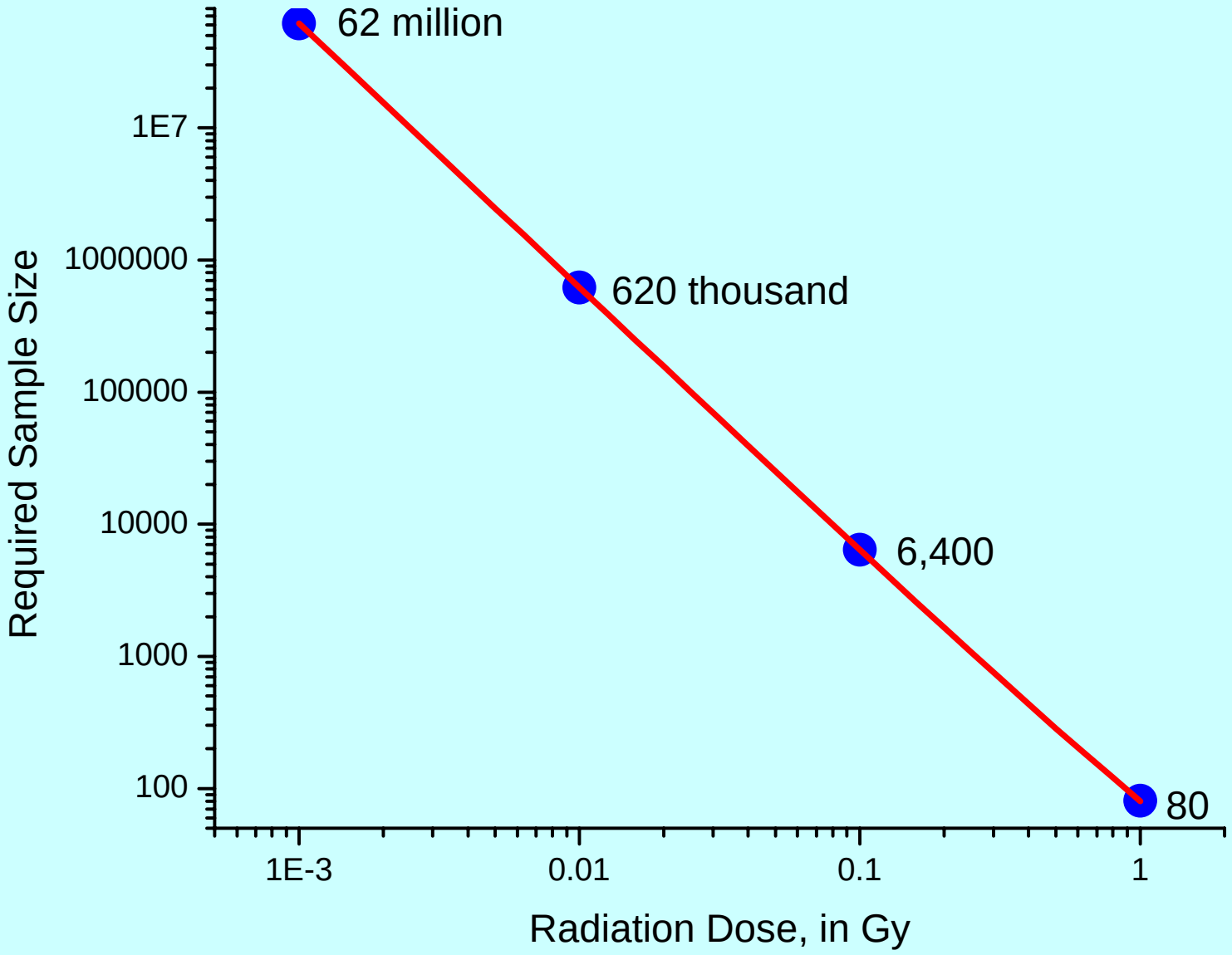
Statistical power and sample size

- Consider statistical tests of the null hypothesis of no excess risk at dose D
  - vs. the one-sided alternative that there is an excess
  - for tests at the 5% significance level
- How large a sample size, N, is needed to have an 80% probability of rejecting the null hypothesis when it is false?

Example (cont.)

- Number of cancers: binomial (N, p), $p = 0.1 \times (1+D)$
- Est. *excess* risk, ER = (number of cancers) / N - 0.1
  - Approx. normally distributed
  - mean = $0.1 \times D$
  - variance = $0.1 \times (1+D) \times [1 - 0.1 \times (1+D)] / N$
- If no dose response, ER has mean = 0, variance = 0.09/N (standard deviation = $0.3/ N^{½}$)
- We reject the null hypothesis if $N^{½} \times ER / 0.3 > 1.645$
- *How large must N be for statistical power $\geq$ 80%?*

Overly simplified example: sample size for 80% power at 5% significance level

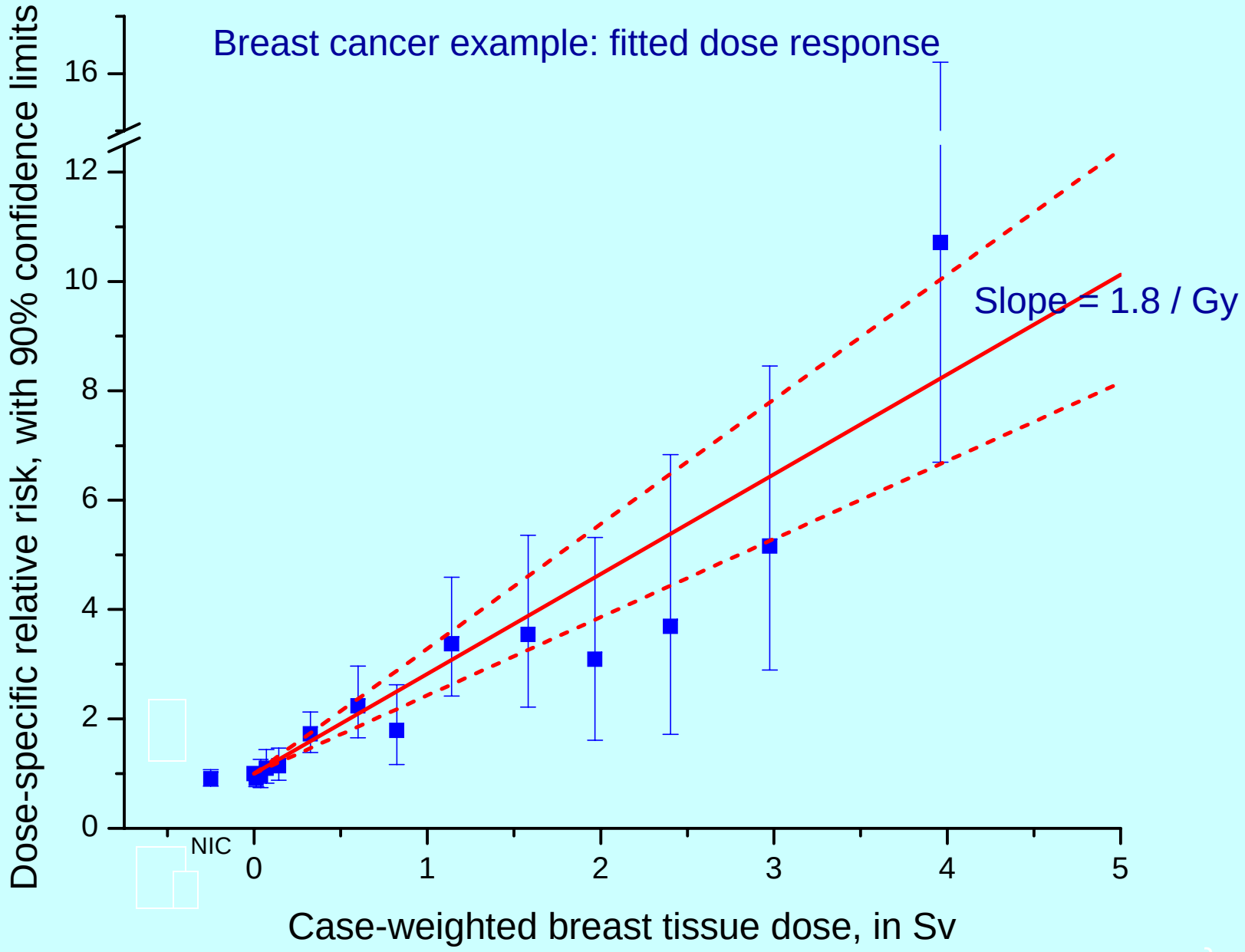


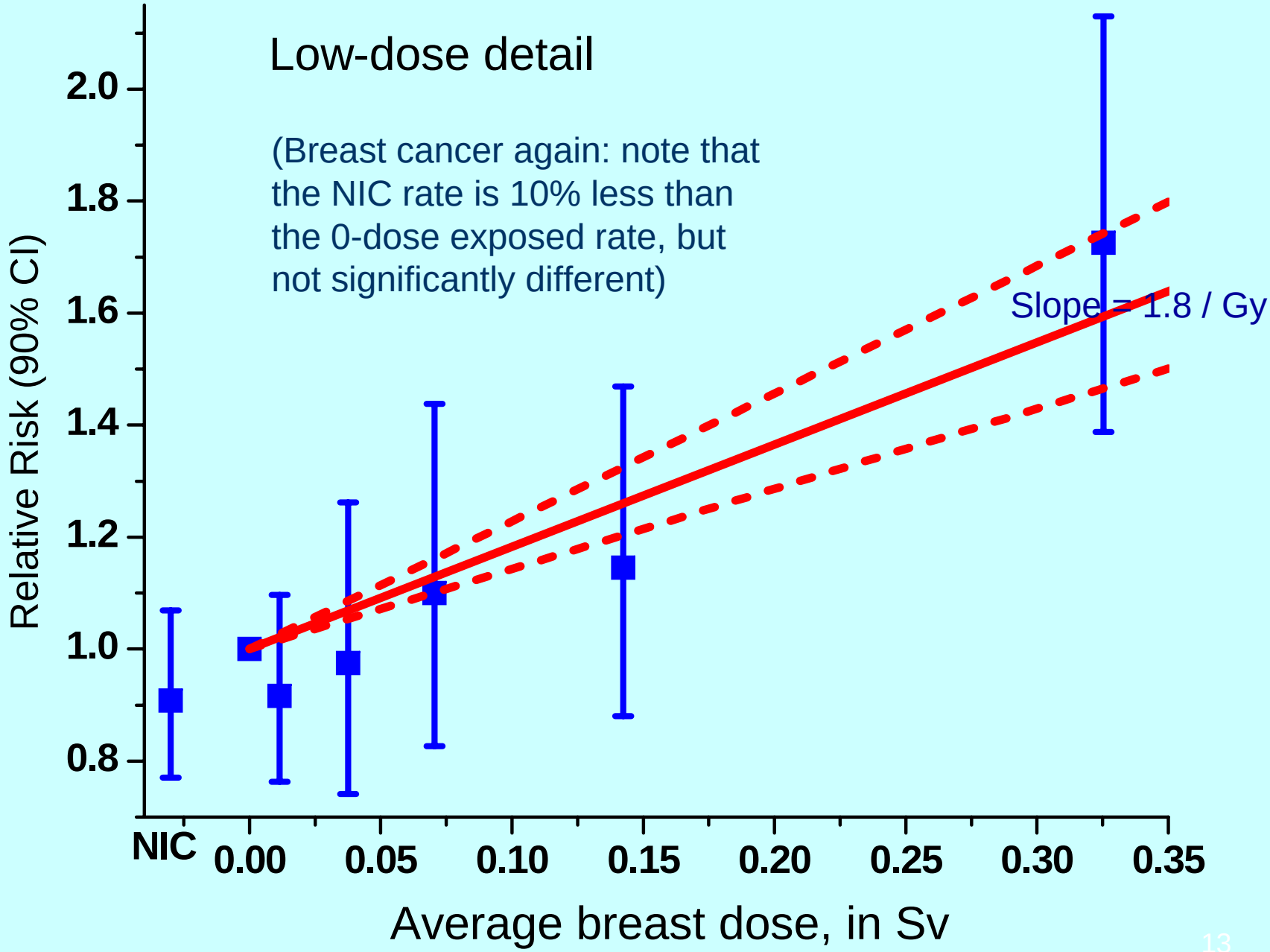
Suppose N is too small

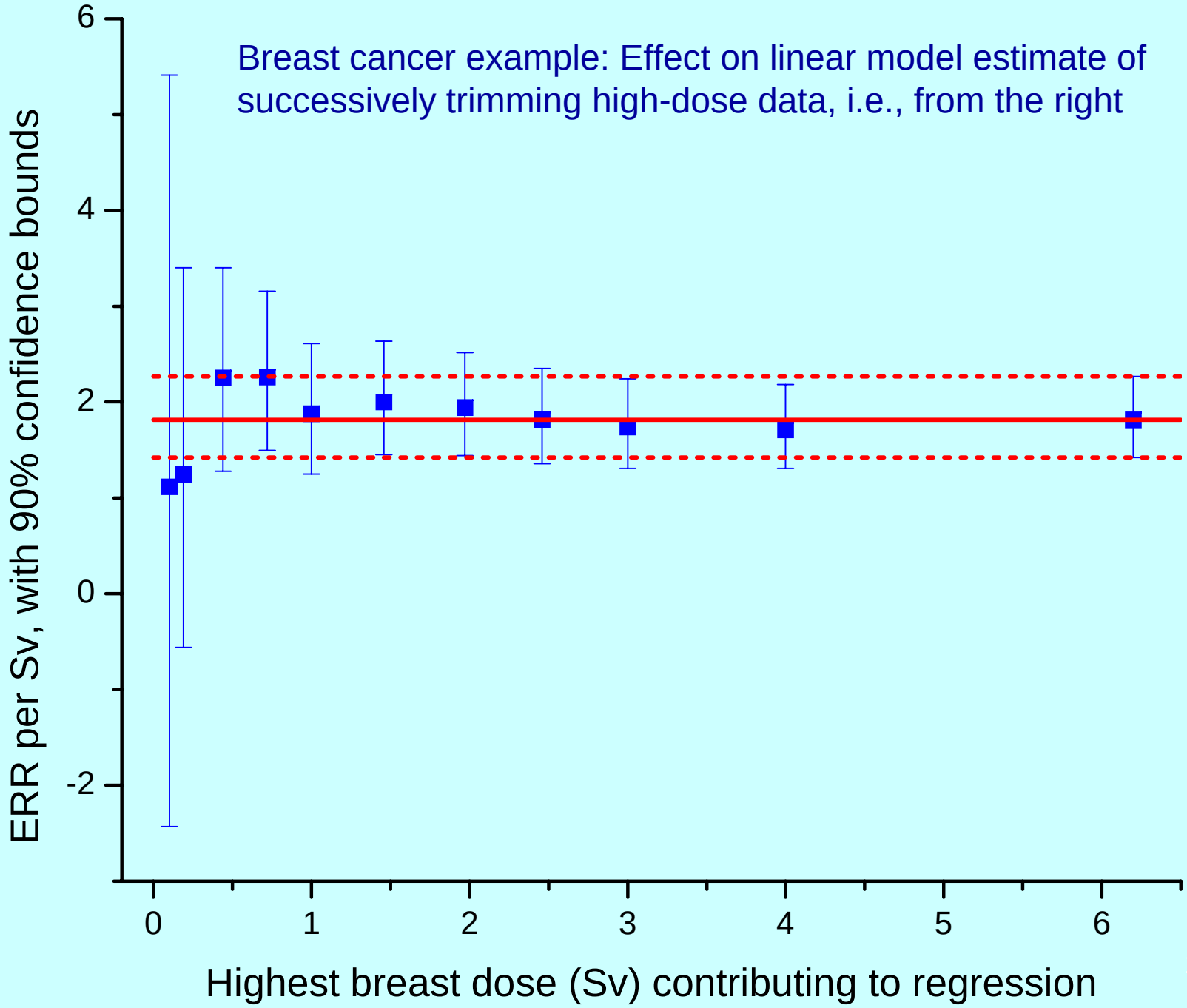
- For D = 0.01 Gy (i.e., excess risk = 0.1%) and N = 50,000, the probability of rejecting the null hypothesis is 19%
  - Under the null hypothesis, it is 5%
  - Failure to reject would be predicted by both null and alternative hypotheses
- Thus, (in the example) even a large study would be very unlikely to yield conclusive results
  - In fact, a significant result would be misleading, because the estimated excess risk would be biased upward:
  - If the lower 95% confidence limit > 0 for N=50,000, the estimate must be > 0.22%, over 2 times the true value of 0.1%

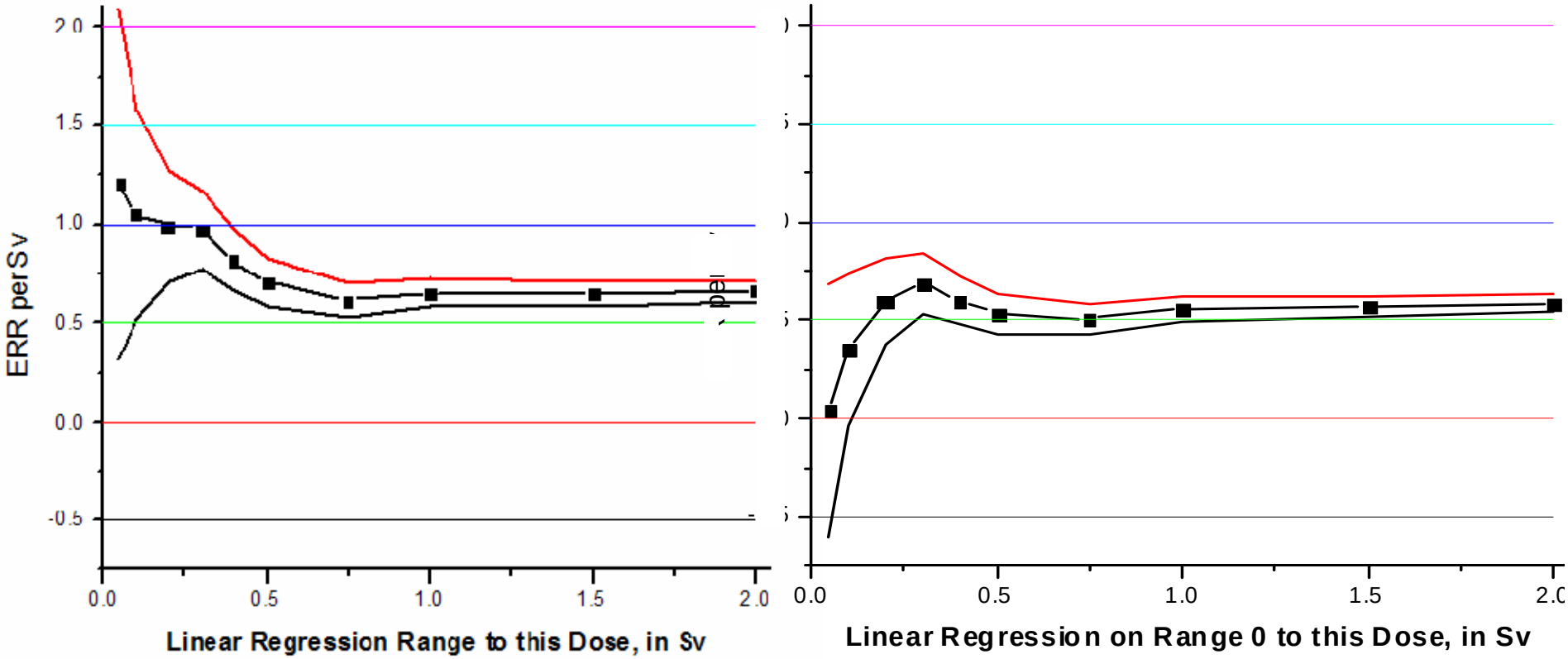
It's actually worse than that:

- We don't "know" the baseline; we have to estimate it, which requires about twice as many subjects
- Are we estimating the "right" baseline?
  - How could we possibly control for every non-radiation risk factor that might increase risk from 10% to 10.1%, or decrease it to 9.9%?
  - How many such factors are known?
  - How many are unknown?
- **Low-dose extrapolation of estimates is unavoidable**


Breast cancer example: fitted dose response
Slope = 1.8 / Gy
Dose-specific relative risk, with 90% confidence limits
Case-weighted breast tissue dose, in Sv
NIC
0
2
4
6
8
10
12
16
0
1
2
3
4
5


Low-dose detail
(Breast cancer again: note that the NIC rate is 10% less than the 0-dose exposed rate, but not significantly different)
Slope = 1.8 / Gy
Relative Risk (90% CI)
2.0
1.8
1.6
1.4
1.2
1.0
0.8
NIC
0.00
0.05
0.10
0.15
0.20
0.25
0.30
0.35
Average breast dose, in Sv


Breast cancer example: Effect on linear model estimate of successively trimming high-dose data, i.e., from the right
ERR per Sv, with 90% confidence bounds
6
4
2
0
-2
0
1
2
3
4
5
6
Highest breast dose (Sv) contributing to regression



Regarding the baseline:

Linear regression estimates (± 1 s.d.) after trimming of high-dose data from the right.

Left-hand panel based on proximal (<3000m) survivors only; in right-hand panel the distal (>3000m) survivors also contribute, resulting in a higher zero-dose baseline

Based on data of Pierce & Preston, Radiation Research, 2000; 154:178:86

With all these problems, why do we study populations exposed to low radiation doses?

- Suppose our extrapolated estimates were badly wrong? (especially, way too low?)
- *We would need to know*
- Except for that, we rely on low-dose extrapolation
  - And not on low-dose studies

The linear, no-threshold (LNT) theory

- Currently, radiation protection philosophy is based on the LNT model
- The theory states that, at low doses and low dose rates, excess risk is proportional to dose
- That doesn’t require linearity of dose response over the entire dose range, just at low doses

The LNT theory (continued)

- **For radiation protection, the ICRP posits a "dose and dose rate effectiveness factor" (DDREF) of 2 for low-LET radiation at low doses and dose rates**
  - **(BEIR VII recommends a DDREF of 1.5)**
- **Where the DDREF applies, we divide the linear-model risk based on high-dose data by the DDREF**
  - **In the statistical power example, with a DDREF of 2, excess risk at 10 mGy would be 0.05% instead of 0.1%**
- **A DDREF of 2 is implicit in the linear-quadratic model for leukemia**

Implications of the LNT theory: Collective dose

- If the estimated risk from 100 mGy to 10,000 people is 50 excess cancers,
  - The estimated risk from 10 mGy would be 5 excess cancers,
  - But the risk to 100,000 people would be 50 excess cancers
  - And the estimated risk from 1 mGy to 1,000,000 people would also be 50 excess cancers

- Of course, you'd never be able to prove it
- It might be expensive to reduce the dose, and the million people might not want to pay for it
- They might feel that someone else should pay for it
- But probably "someone else" would insist on proof

The low-dose threshold theory

- If we could agree that there is ***no*** radiation-related cancer risk associated with doses below (say) 2 mGy, the 1 million people exposed to 1 mGy could relax
- Radiation protection might be cheaper and easier than it is today
- It might be even easier with a threshold at 10 mGy
- Unfortunately, a low-dose threshold at 10 mGy or 2 mGy would be difficult to prove, for the same reasons that make it difficult to demonstrate the opposite

A long-standing issue*

- Leukemia risk associated with 90-Sr in global fallout from nuclear weapons testing during the 1950s & early 60s
  - Very small doses to very large populations
  - Leukemia risk had been demonstrated from higher-dose exposures:
    - A-bomb survivors, ankylosing spondylitis patients, thymic irradiation patients, **US radiologists (compared to non-radiologist physicians)**

*J Caron, undergraduate thesis
http://resolver.caltech.edu/CaltechETD:etd-03292004-111416

- Fruit fly geneticists found linear dose response for drosophila mutations down to 250 mGy
- Moreover, radiation doses to US radiologists were estimated to have accumulated at rate of ~ 1 mGy per day
  - And they had been shown to have a higher cancer risk than non-radiologists
  - Thus, presumably, dose-related risk accumulated daily

Edward Lewis and Austin Brues

- Edward Lewis (1957) used available data on leukemia in radiation-exposed populations to fit a linear dose-response model
  - Argued for a mutational factor in radiation leukemogenesis
  - Estimate: 2 excess leukemias per million per cGy per year
  - Argued that there was no experimental or epidemiological basis for radiation threshold

- Austin Brues, for AEC: toxicology model argues for radiation threshold – why should radiation be different?
  - Clearly there was a leukemia risk at high doses
  - But no direct proof of excess leukemia risk at very low doses
- Eventually, the LNT model prevailed in radiation protection policy
  - But we are still in the same debate, and using many of the same arguments

Quick review of radiobiology

- Unique type of DNA damage by ionizing radiation involves multiple lesions in close proximity (clustered damage)
  - ~ 70% for high-LET, ~30% for low-LET
- Can be induced by single electron track
- Can compromise repair machinery
- Processing and misrepair can lead to chromosome aberrations and mutations
  - Damaged or altered cells can escape cell cycle checkpoint and apoptotic pathways

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Radiobiology Review (cont)

- Roles of radiation-related adaptive response, genomic instability, & bystander effects not well understood; may not be relevant to threshold question
- Critical radiation events in tumorigenic process are mostly early events involving DNA losses and critical genes
- Mechanistic arguments support linear response in low-dose region

Evidence differs by tissue

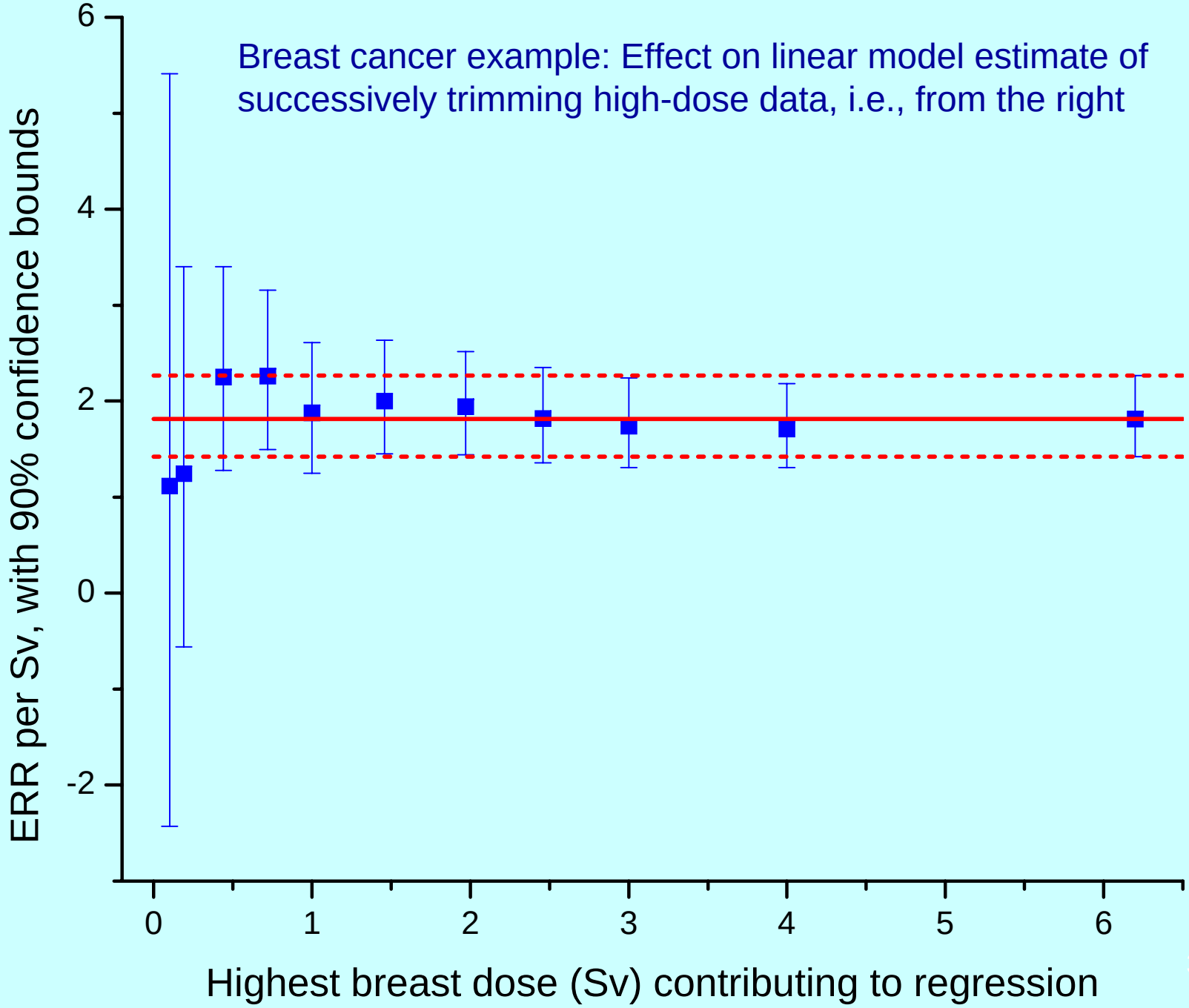
- Stem cells in the intestinal crypt of laboratory mouse: Selective retention of template DNA strands in stem cells, providing protection of the stem cell genome (Cairns 1975; 2002)
- But induction of small intestine cancer by high-dose radiation of exteriorized loop is a well-established experimental procedure
  - Threshold?
- Very different for colon, for which there is clearly a low-dose risk

Epidemiological evidence

- For threshold:
  - Shape of dose responses for basal cell skin carcinoma, bone, soft tissue sarcoma, rectum, small intestine
  - Apparent fractionation effect for lung cancer
- Against threshold:
  - X-ray pelvimetry studies (leukemia, solid cancers)
  - TB, scoliosis fluoroscopy studies (female breast)
  - Linear dose responses for female breast, thyroid, all solid cancers combined

- Experimental and epidemiological evidence doesn’t preclude tissue-specific thresholds
- But also, it doesn’t support existence of a universal threshold, operating in all tissues
- And a threshold has to be universal to have much influence on radiation protection policy

But estimates of low-dose risk are uncertain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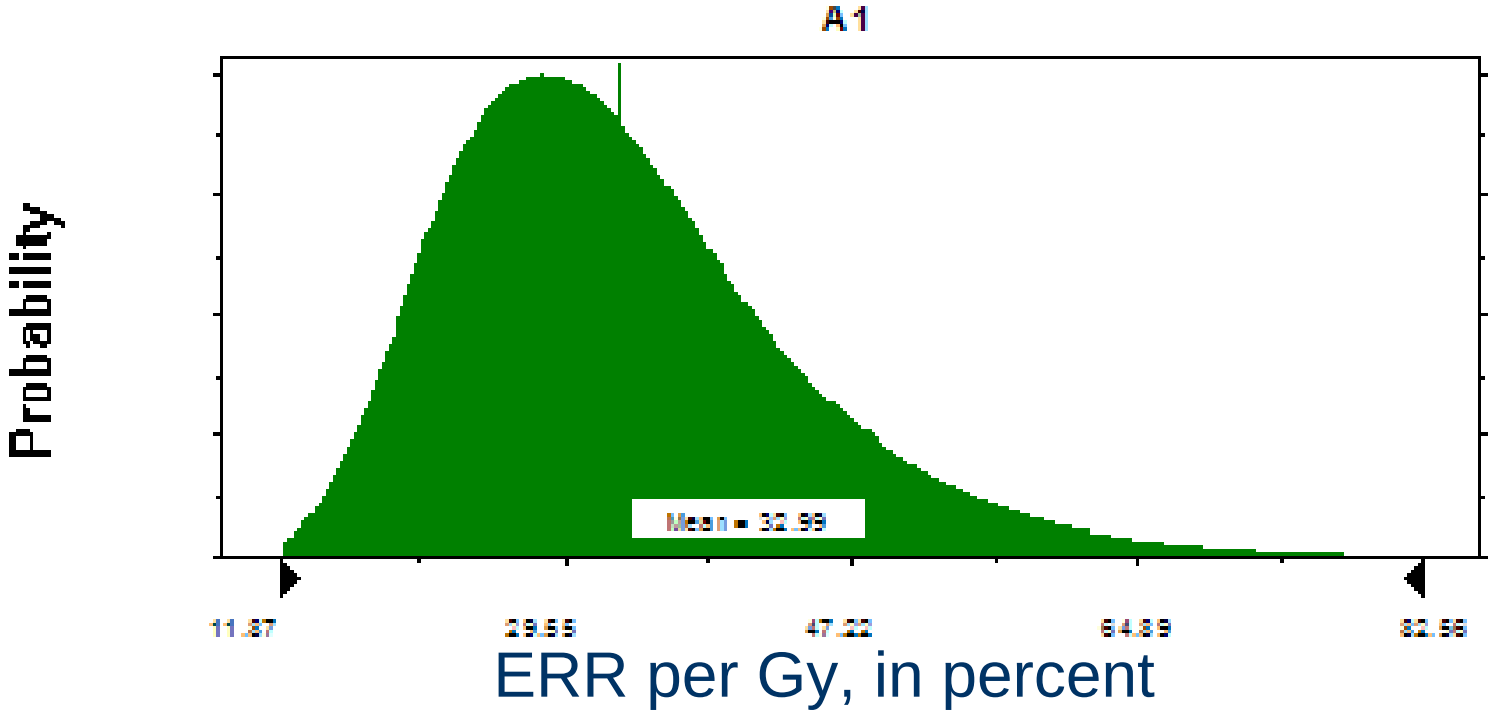
ERR per Sv, with 90% confidence bounds
6
4
2
0
-2
0
1
2
3
4
5
6
Highest breast dose (Sv) contributing to regression

Major uncertain components

- Linear model estimate of ERR at 1Gy
  - Note confidence limits in previous slide
- Correction for transfer from LSS to US population
- DDREF to be applied at low doses and low dose rates
- Possibility of a universal threshold at some dose above that of interest

Lognormal statistical uncertainty distribution for all solid cancers, LSS population. Sex-averaged ERR per Gy at age 50 following exposure at age 30.

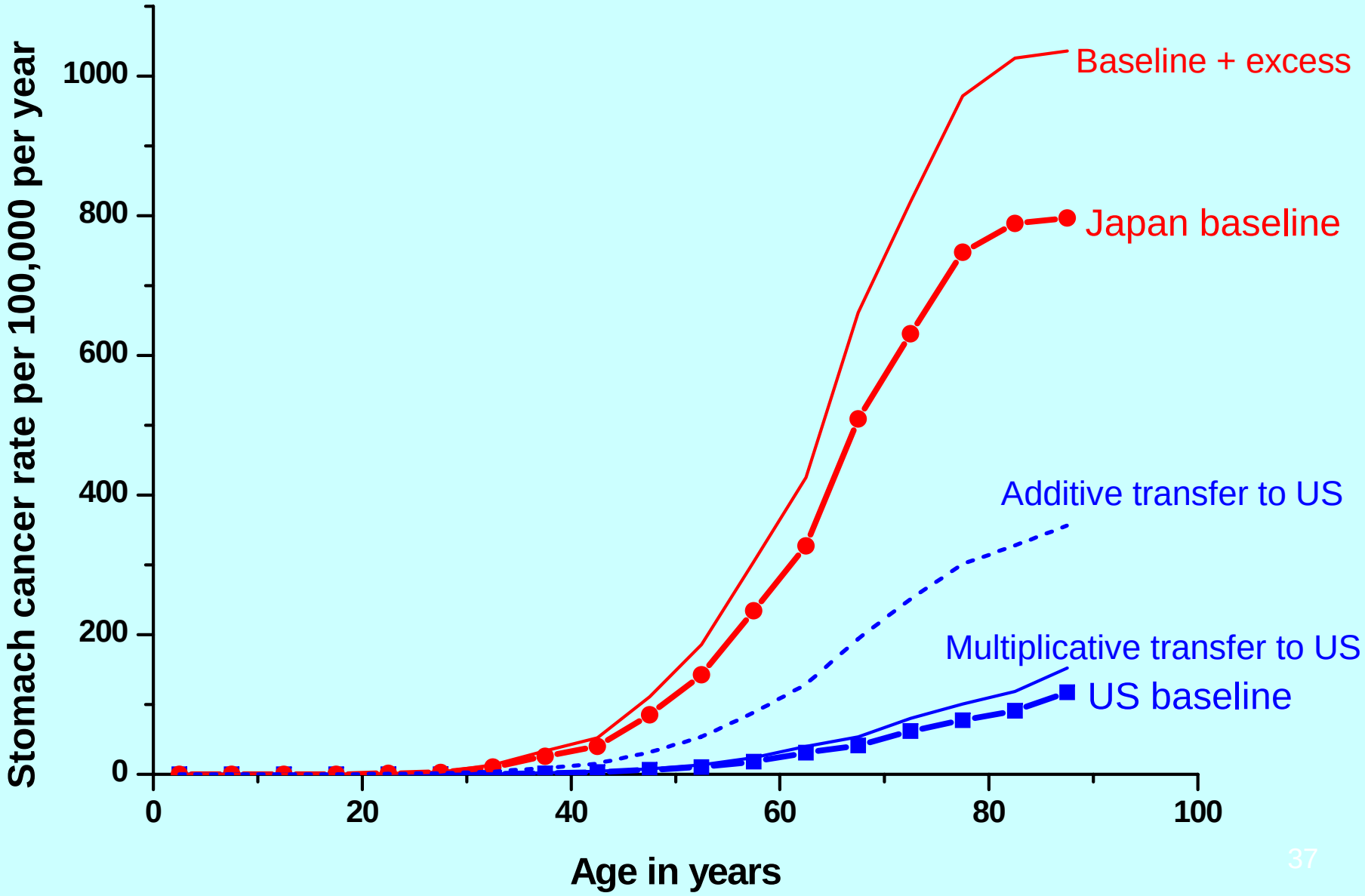
Mean 0.33, 90% probability limits 0.18 - 0.43.



Transfer to the U.S. population

- Baseline cancer rates differ between Japan and the U.S.
- This has uncertain implications for radiation-related risk in the US population
- For a few cancers, choice of a transfer model can really make a difference
- Example: for stomach cancer, Japanese rates are 12 times those in the United States

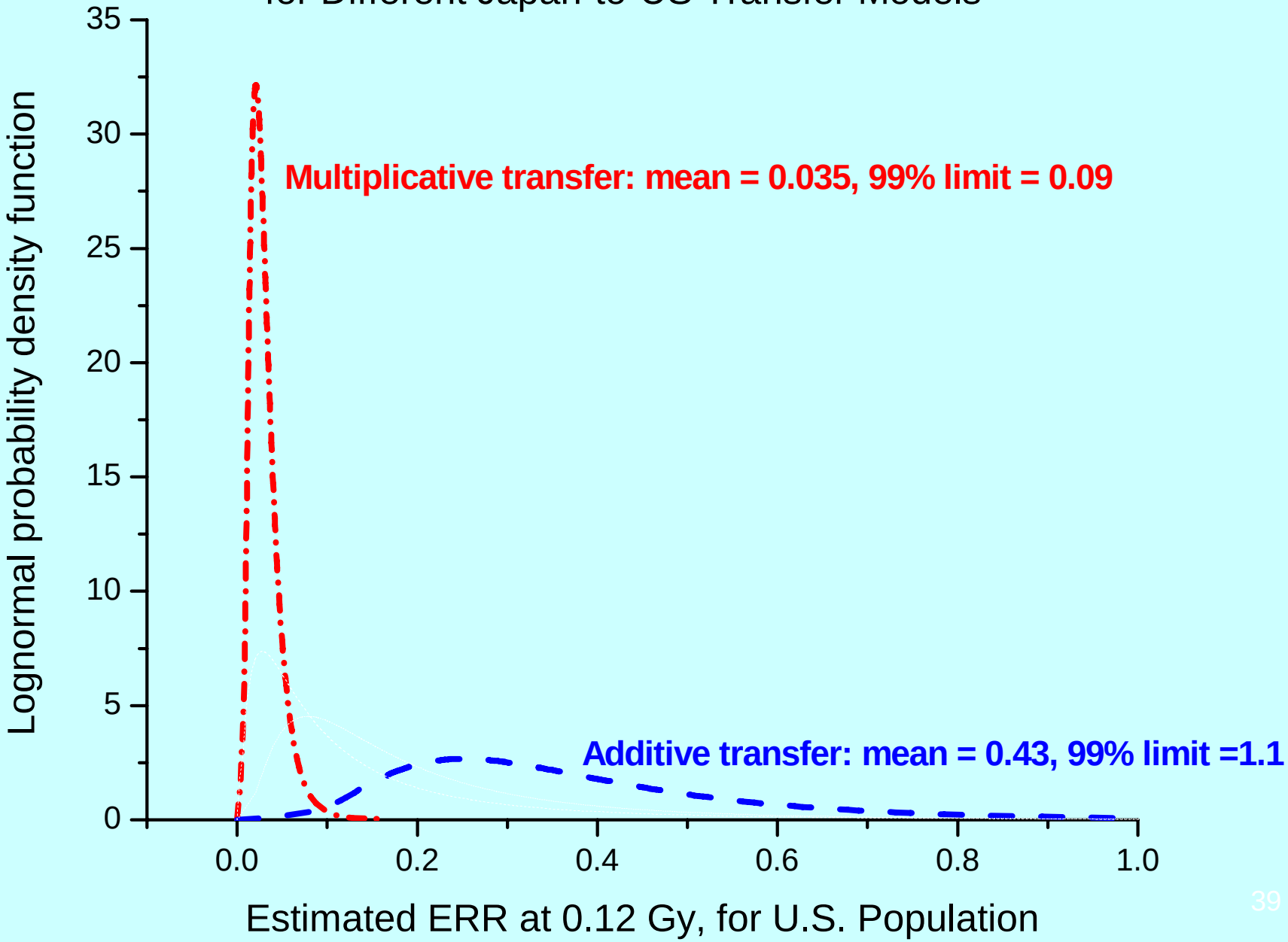
Comparison of U.S. and Japanese Stomach Cancer Rates (Males)

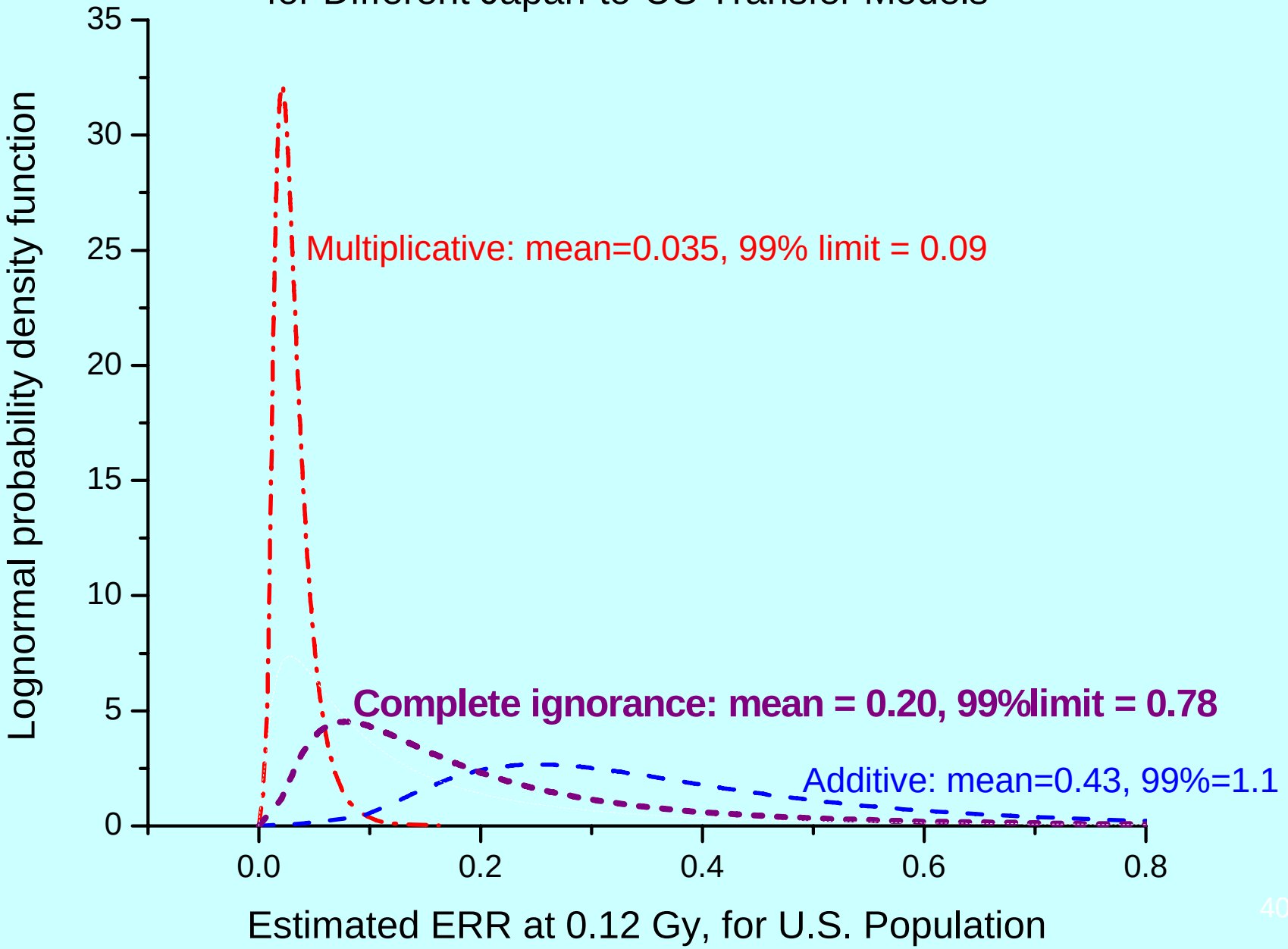


How to transfer ERR estimate from Japan to the US?

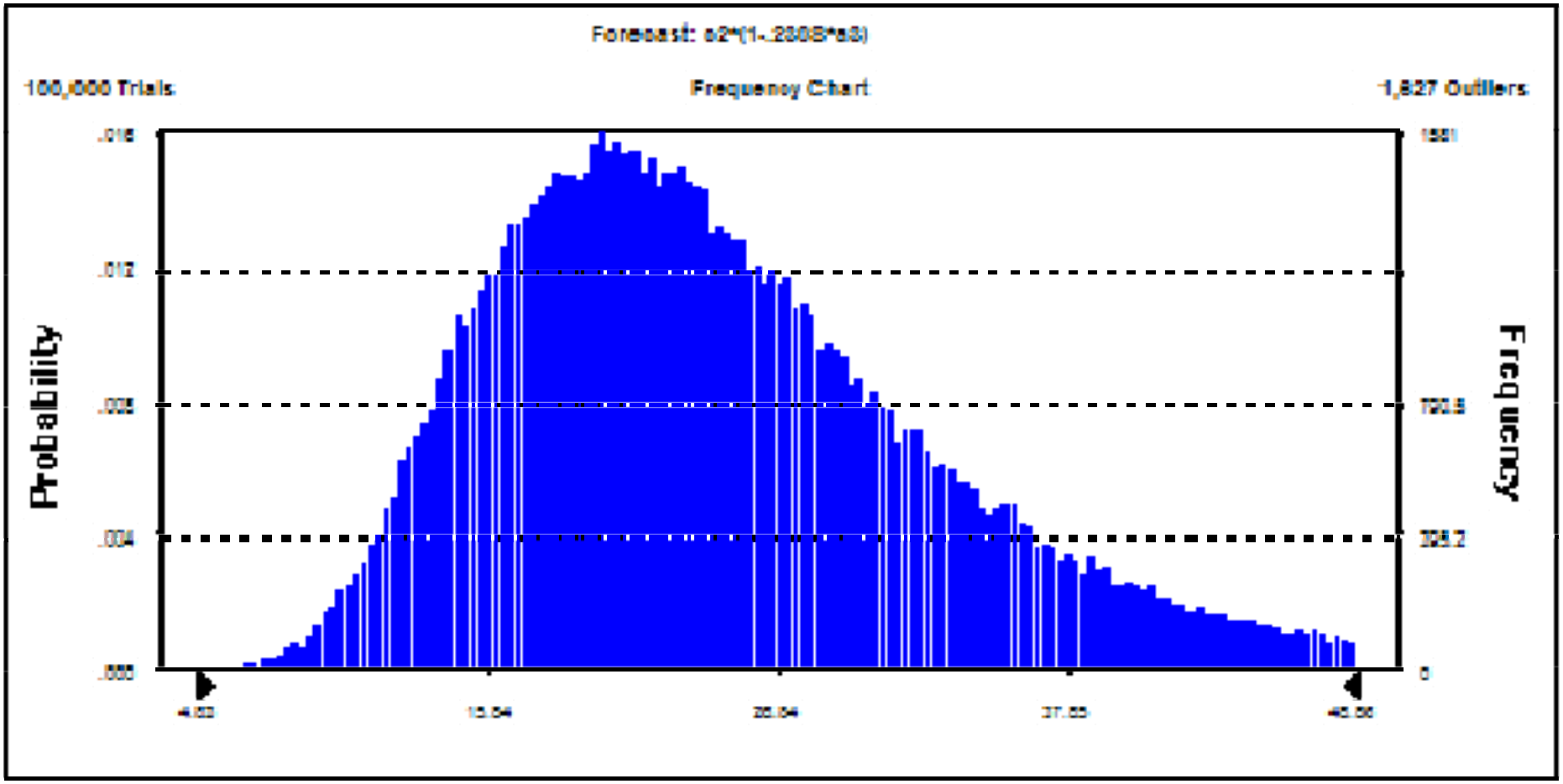
- Use the A-bomb survivor ERR
  - **Multiplicative transfer – assume ratio of excess to baseline doesn't change**
  - Biologically plausible if baseline rates differ because of differential exposure to promoters
- **Use the LSS excess rates** (ERR $\times$ baseline)
  - **Additive transfer**: **use the Japanese ERR, times 12**
  - Plausible if baseline rates differ because of differential exposure to competing cancer initiators

Stomach Cancer Example: Comparison of ERR Uncertainty Distributions for Different Japan-to-US Transfer Models




Stomach Cancer Example: Comparison of ERR Uncertainty Distributions for Different Japan-to-US Transfer Models
Lognormal probability density function
35
30
25
20
15
10
5
0
Multiplicative: mean=0.035, 99% limit = 0.09
Complete ignorance: mean = 0.20, 99%limit = 0.78
Additive: mean=0.43, 99%=1.1
0.0
0.2
0.4
0.6
0.8
Estimated ERR at 0.12 Gy, for U.S. Population

- For all cancers combined, the baseline rates are not very different between the US and Japan
  - So the difference between multiplicative and additive transfer is not very great
- In this case, “complete ignorance” about population transfer does not add much uncertainty to the estimate

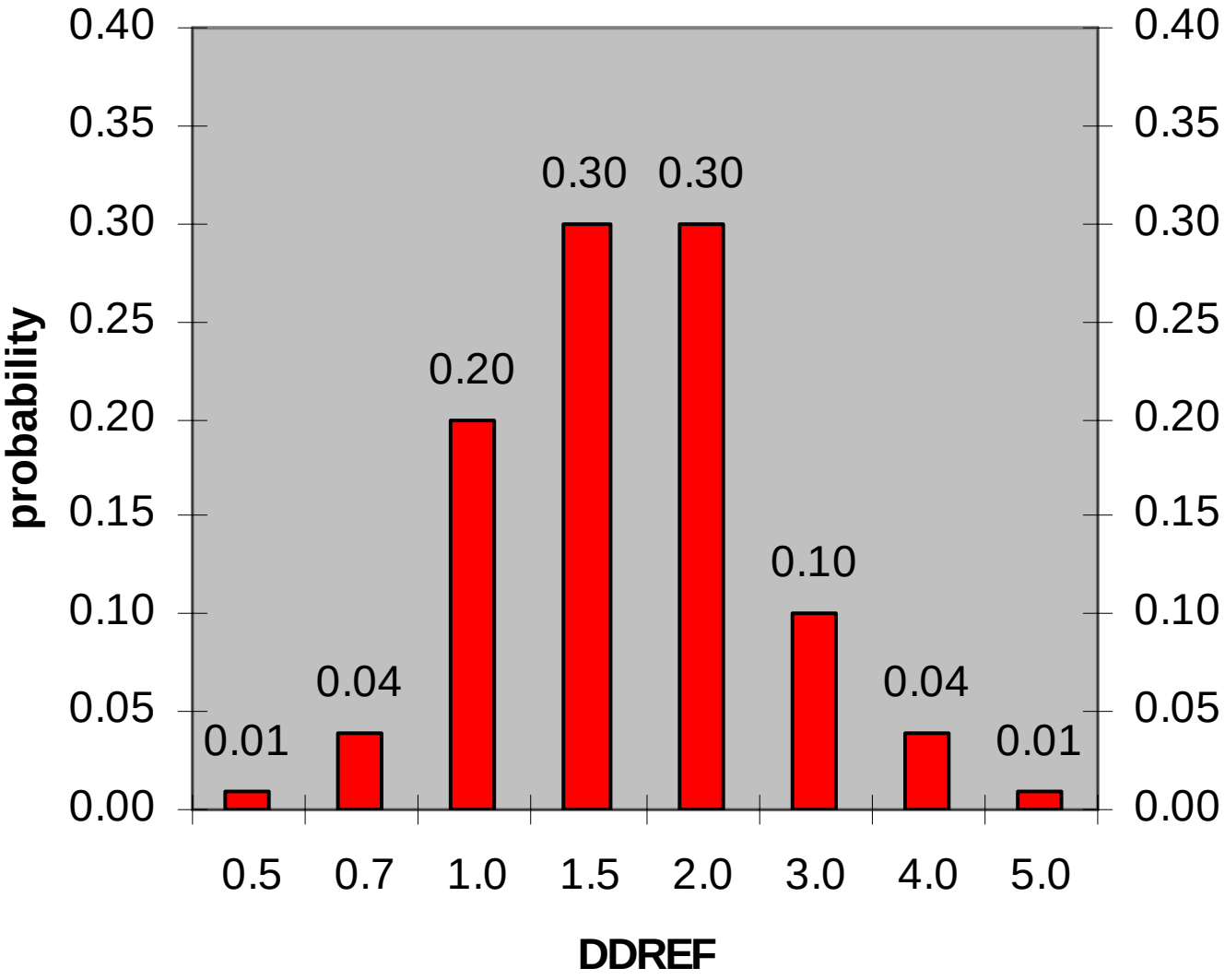


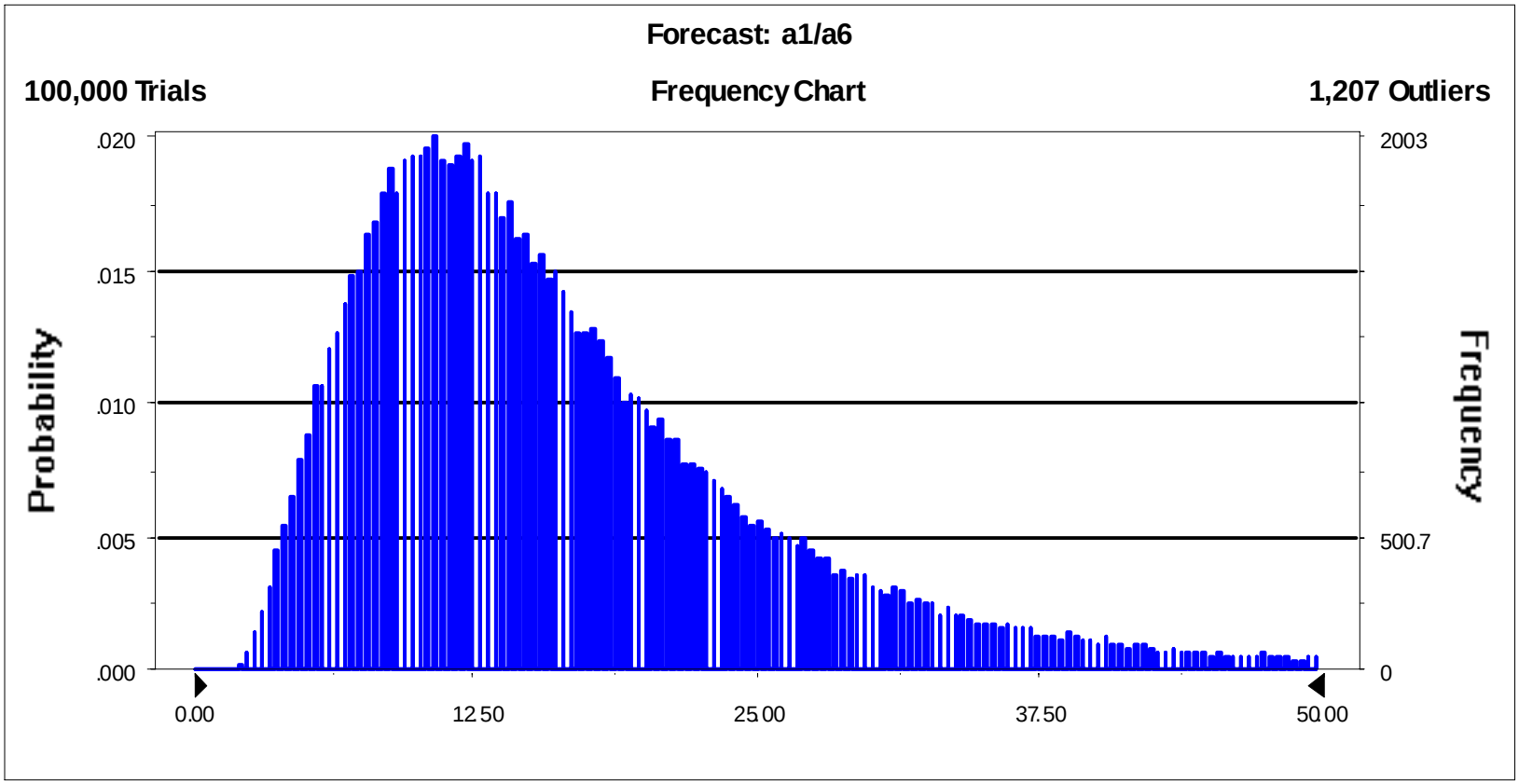
Monte Carlo simulation of the uncertainty distribution for cancer ERR at 1 Sv, after transfer to a U.S. population: the simulated distribution is approximately lognormal, mean 0.25 and 90% probability limits 0.13 – 0.41.

Uncertain DDREF

- Using a DDREF of 2 at low doses and low dose rates means dividing the linear-model estimate by 2
- Using an uncertain DDREF means dividing by an uncertain number
- Which adds uncertainty to the low-dose estimate

DDREF for solid tumors other than breast and thyroid





Monte Carlo simulation of the uncertainty distribution for low-dose cancer ERR per Sv, after division by an uncertain DDREF: the simulated distribution is roughly lognormal with

mean 0.17 and 90% probability limits 0.08 – 0.36.

Point of view:
Implications of an uncertain risk estimate

- It is widely recognized that risk estimation is uncertain
  - Uncertainty distributions like the one in the previous slide aren't a new idea

- Formally, radiation protection today is based on a single, central value, e.g., the mean

Point of view (cont.)

- But that ignores important information
- The uncertainty distribution summarizes all the *identified* information about risk
  - (We can't think of everything)
- The exposed population presumably is concerned with upper limits on risk
  - How bad might it be? Is the benefit really worth the risk?

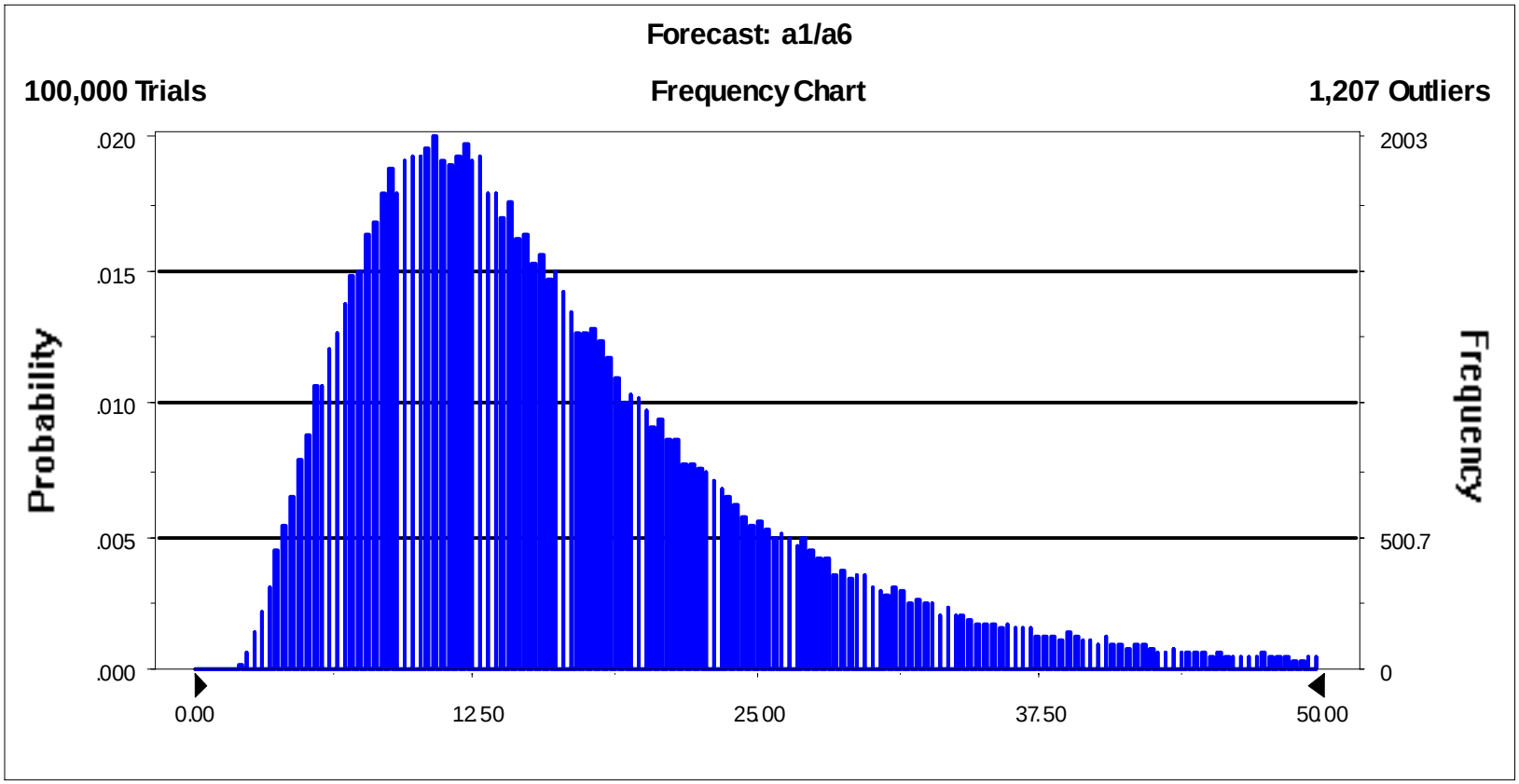
Point of view (cont.)

- Those liable for the expense of dose reduction tend to be more concerned with lower limits
  - Is there strong statistical evidence that there is a risk, or that the risk high enough to be of concern? (Can you prove it?)
- Radiation protection is a political process, which depends on the consent of those affected
  - If it is to work, the various points of view must be considered
  - And must be *seen* to be considered

- The process of estimation determines the final uncertainty distribution for excess risk
- That distribution summarizes all we know, think we know, or had to assume in order to get the estimate
  - That includes the uncertainties of the parts

Uncertain possibility of a threshold

- Consider a threshold somewhere above (say) 1 mGy as an uncertain possibility, with probability *p.*
- Then, with probability *p*, ERR for radiation-related cancer at 1 mGy would be zero
- And with probability *1-p*, ERR at 1 mGy would be distributed lognormally with
  - mean 0.00017
  - upper 95% probability limit 0.00036



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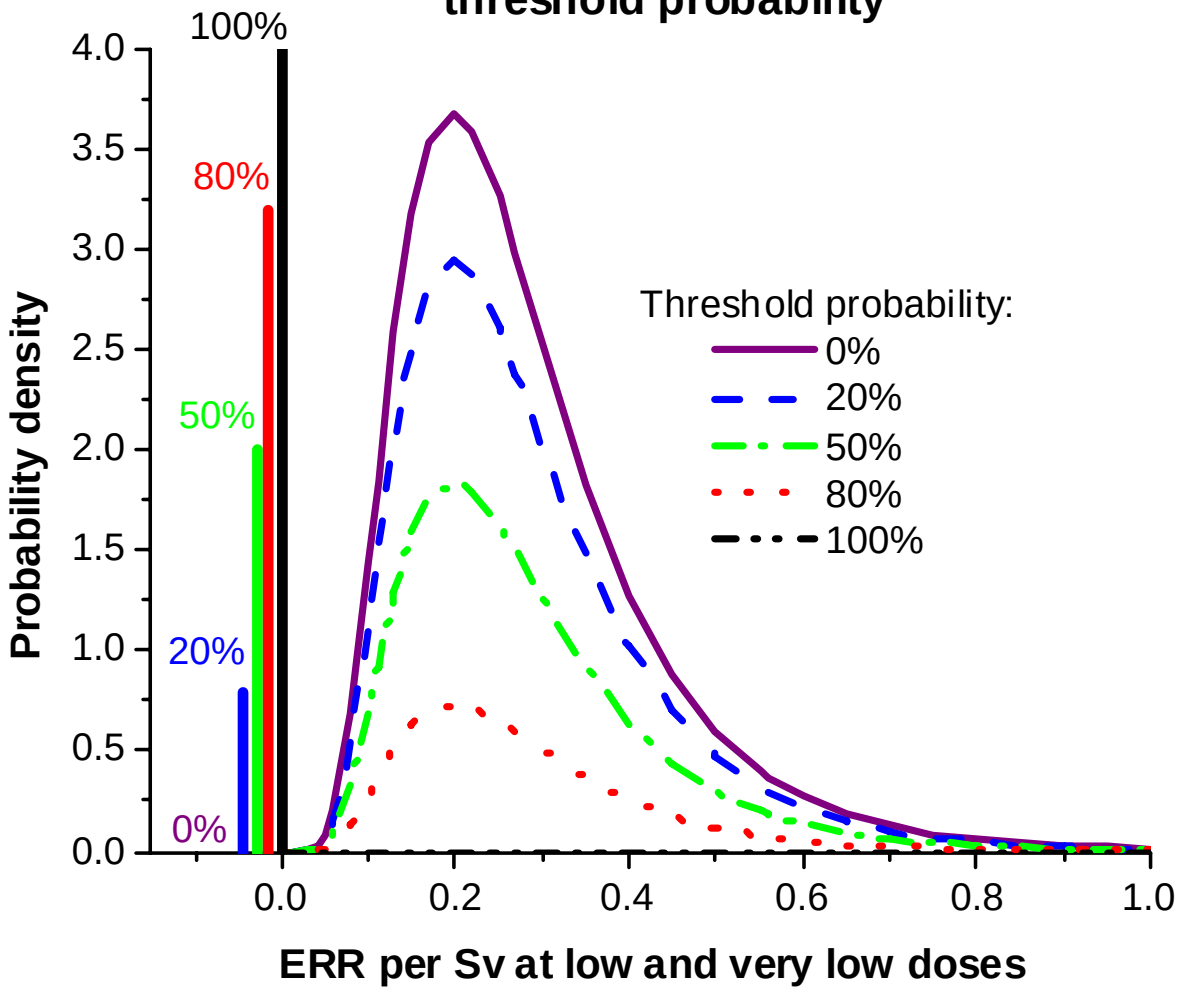
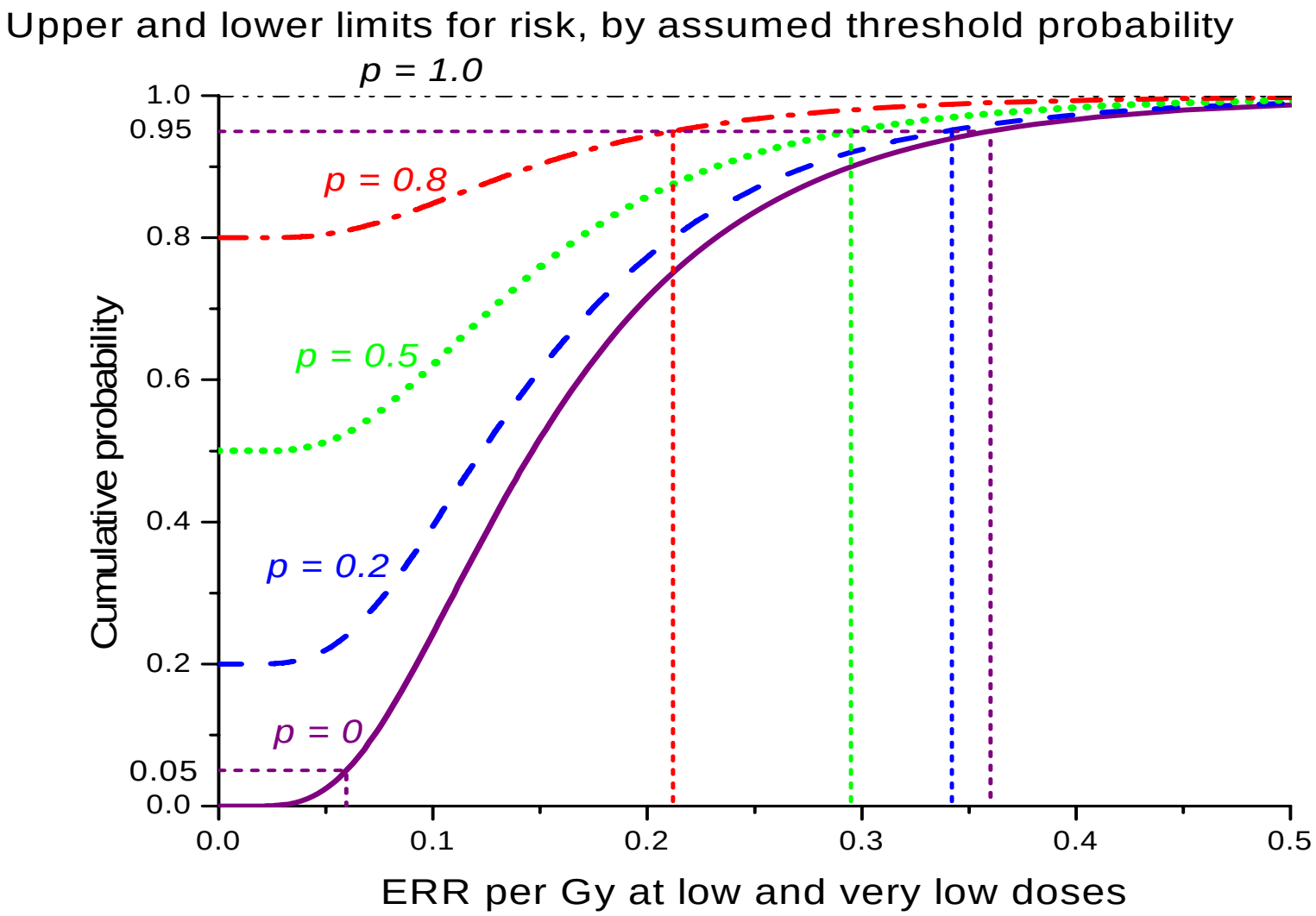
Uncertain possibility of a threshold

Figure 8. Credibility distributions for low-dose risk, by assumed threshold probability



Uncertain threshold possibility

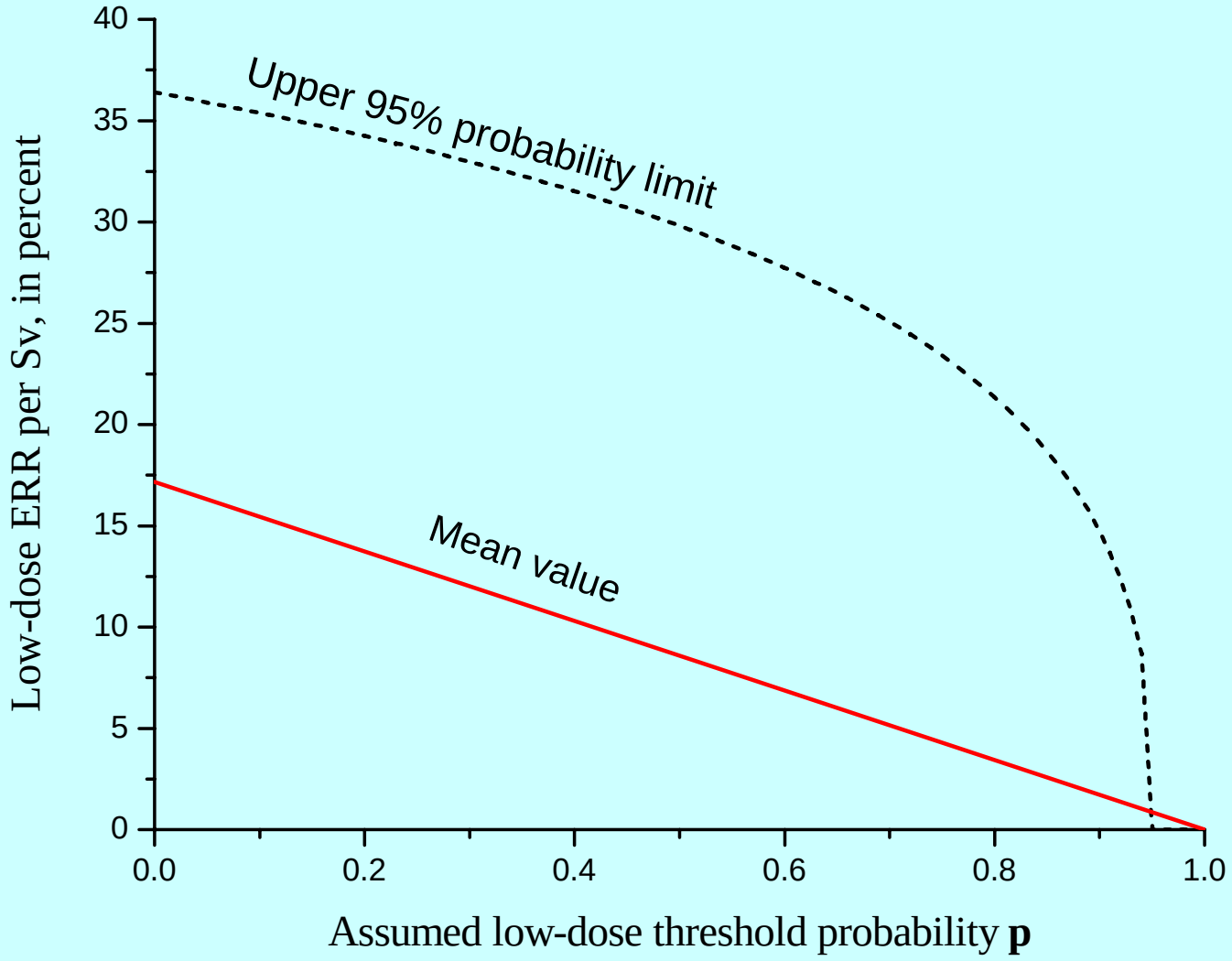


Assume uncertain threshold possibility, with probability *p*

- ERR at 1 mGy is estimated to be
  - zero with probability *p*
  - lognormal (0.00015, 1.73) with probability *1-p*

p	mean	5% limit	95% limit
0	0.00017	0.00006	0.00036
0.2	0.00014	0	0.00034
0.5	0.000085	0	0.00030
0.8	0.000034	0	0.00021
1	0	0	0

Effect of uncertain threshold assumption on a lognormal (mean 0.17, upper 95% limit 0.36) uncertainty distribution for ERR per Sv



Implications of an uncertain threshold for radiation protection

- For the simple case (threshold probability = *p*)
  - The mean of the uncertainty distribution for excess risk is multiplied by *1-p* and therefore decreases with increasing *p*
  - It doesn't disappear until *p* reaches 1
  - An upper uncertainty limit also decreases with increasing *p*, but the decrease is rather slow until *p* approaches the uncertainty level for the upper limit.
- The epidemiological and radiobiological information available does not suggest a high value for *p* at any dose level high enough to matter.
- Thus, allowing for the *possibility* of a threshold would make very little difference to radiation protection

Conclusions

- Unless the benefit of a low-dose exposure clearly outweighs the risks, most people would prefer not to be exposed
- So upper limits on risk are important.
- If a threshold is judged to be very likely, it would make sense to take that into account
- Otherwise, the threshold possibility should make very little difference to radiation protection
- LNT is an appropriate basis for radiation protection

The NIH radio-epidemiological tables – a real-life example

- In 1983 Congress passed a law directing the Secretary of the Department of Health and Human Services (DHHS) to compile “probability of causation” tables
- PC = ERR/(1+ERR) estimates the actuarial likelihood that a given cancer diagnosis could be attributed to a given prior history of radiation exposure
- The mandate specified that the tables be updated as new scientific information became available

- DHHS Secy directed NIH to respond, and a working group was put together
- WG (NIH, 1985) computed “radio-epidemiological tables” for estimating site-specific ERR as a function of exposure history, age at diagnosis, and other data
  - Uncertainty assessment included
- Tables used by the Dept. of Veterans Affairs (VA) to adjudicate compensation claims by military veterans
- VA asked CIRRPC (another govt. comm.) to help make the tables easier to use

- CIRRPC devised “screening” tables to screen out obviously unmeritorious claims
- CIRRPC tables screened out claims for which the 90^{th}, 95^{th}, or 99^{th} percentile of the uncertainty distribution for PC = ERR/(1+ERR) was < 50%
- VA decided to accept claims not screened out at the 99^{th} percentile, i.e., at the least stringent screening level
- In 1998 VA asked NCI to update the tables
- REB replaced tables by “Interactive Radioepidemiological computer Program” (IREP)
- Program computes uncertainty distribution for PC

Applications

- IREP easily modified to calculate yearly ERR for site-specific cancer risk for arbitrary exposure history
  - Lifetable-weighted sum estimates lifetime risk
- Example: Fallout and thyroid cancer risk calculator
- Example: Site-specific lifetime risk calculator
- Next version of IREP to reflect new RERF tumor registry data, BEIR VII report, etc.

2000 Energy Employee Occupational Injury Compensation Act (EEOICPA)

- Dept of Labor directed to use radioepi tables (& therefore IREP) to adjudicate claims by DOE & DOE contractor employees
- NIOSH to reconstruct doses
- Compensation claims to be awarded under 99th percentile rule
- NIOSH uses modified version of IREP to calculate PC & advises DOL on claims adjudication