Low-Dose Extrapolation of Radiation-Related Risk

Epidemiological Overview and Quantitative Uncertainty Analysis

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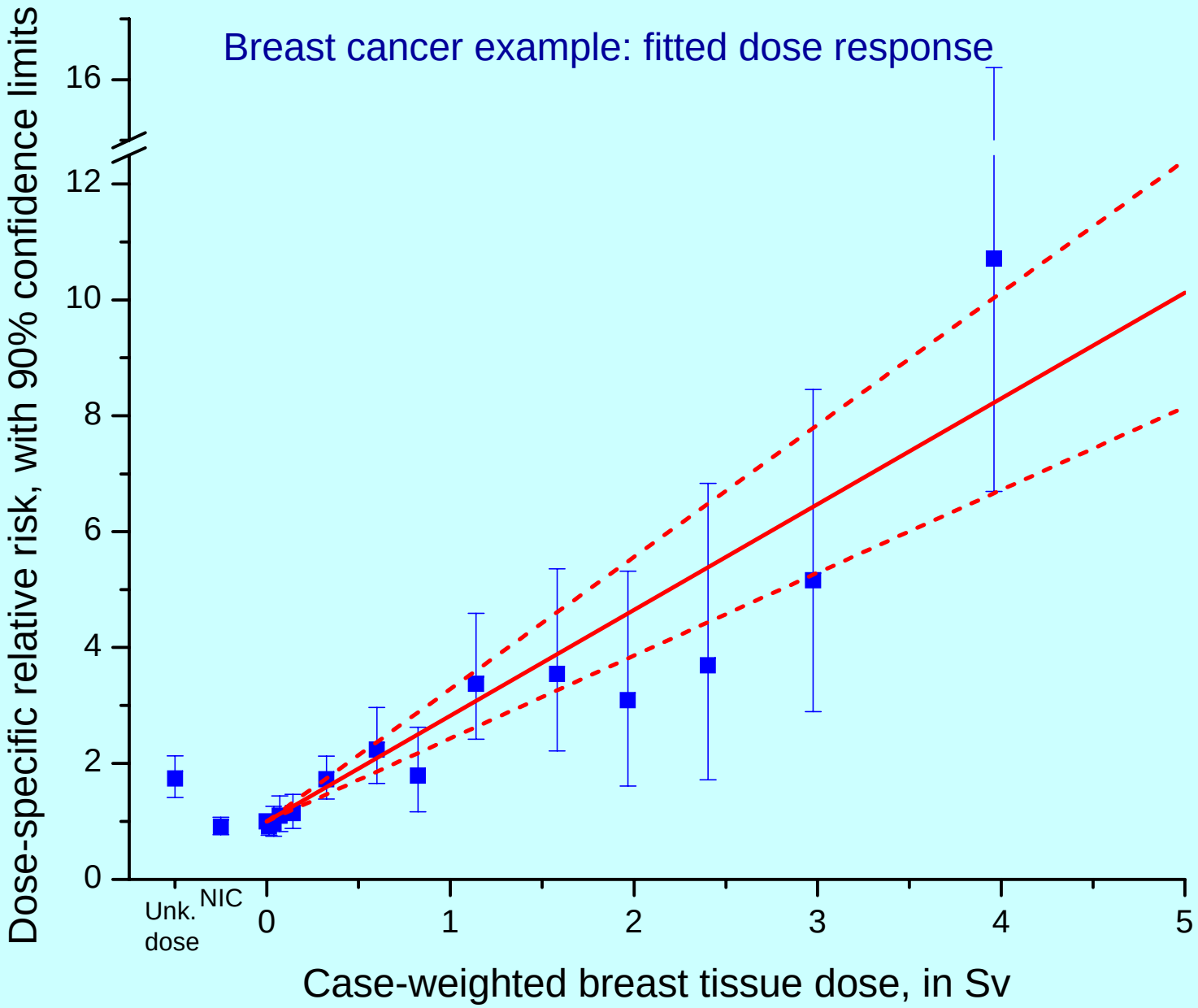
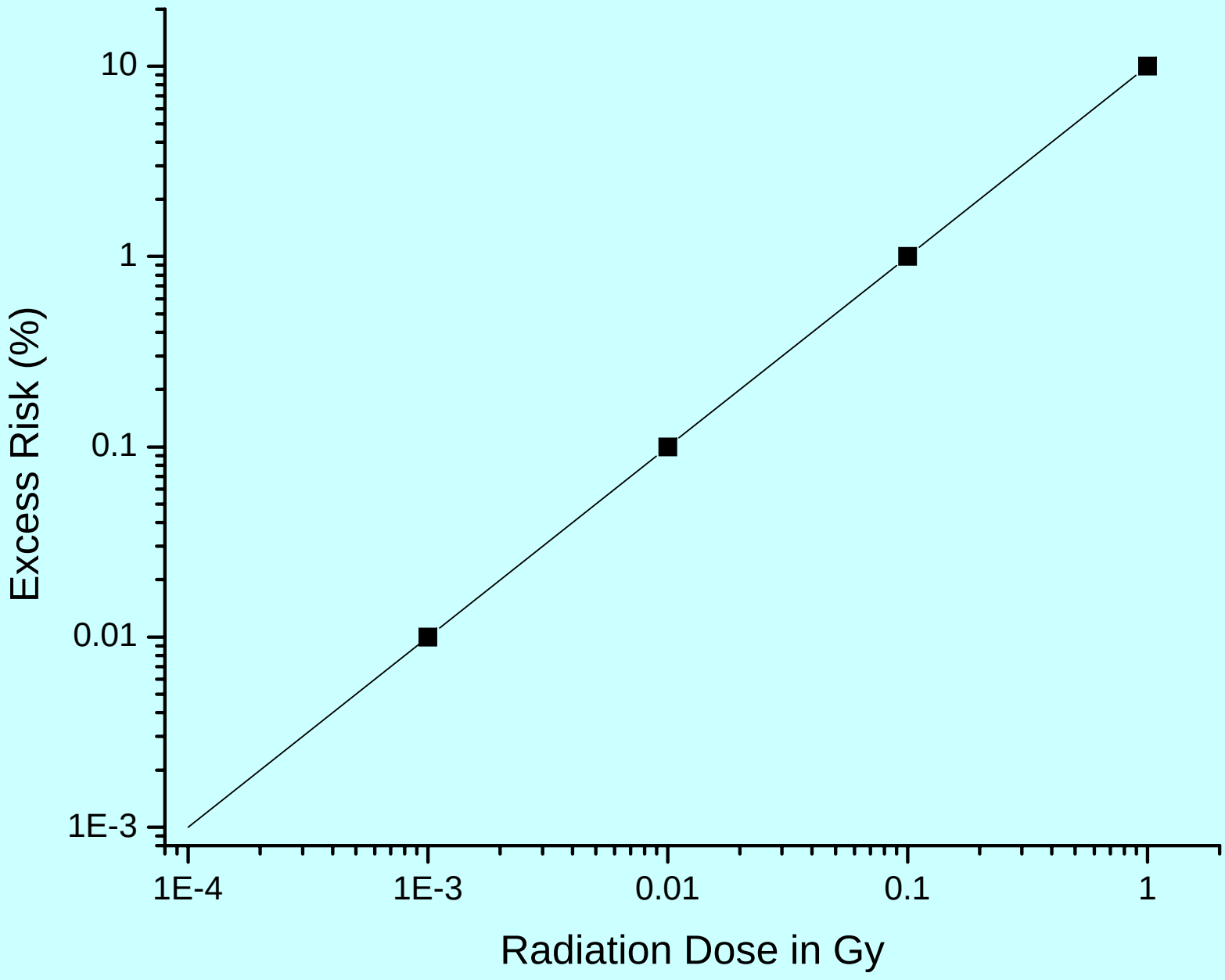
Introduction

- Ionizing radiation 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*


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

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 $0 < D < 1$ Gy
- And that risk is doubled for $D = 1$ Gy
- For a 1-tailed test of size .05, how large a sample size, N, would be required for an 80% chance of detecting the radiation-related excess for different values of D?


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

Example (cont.)

- Number of cancers is binomial (N, p), where p = 0.1 H (1+D)
- Estimated *excess* risk, E = (number of cancers) / N - 0.1, is approximately normally distributed with mean = 0.1 H D and variance = 0.1 H (1+D) H [1 - 0.1 H (1+D)] / N
- Under the null hypothesis of no excess, E has mean = 0 and variance = 0.09/N (standard deviation = 0.3/ $N^{1/2}$)
- Thus, we reject the null hypothesis if $N^{1/2}$H E / 0.3 > 1.645
- How large must N be for the probability of rejection to be $ 80%?

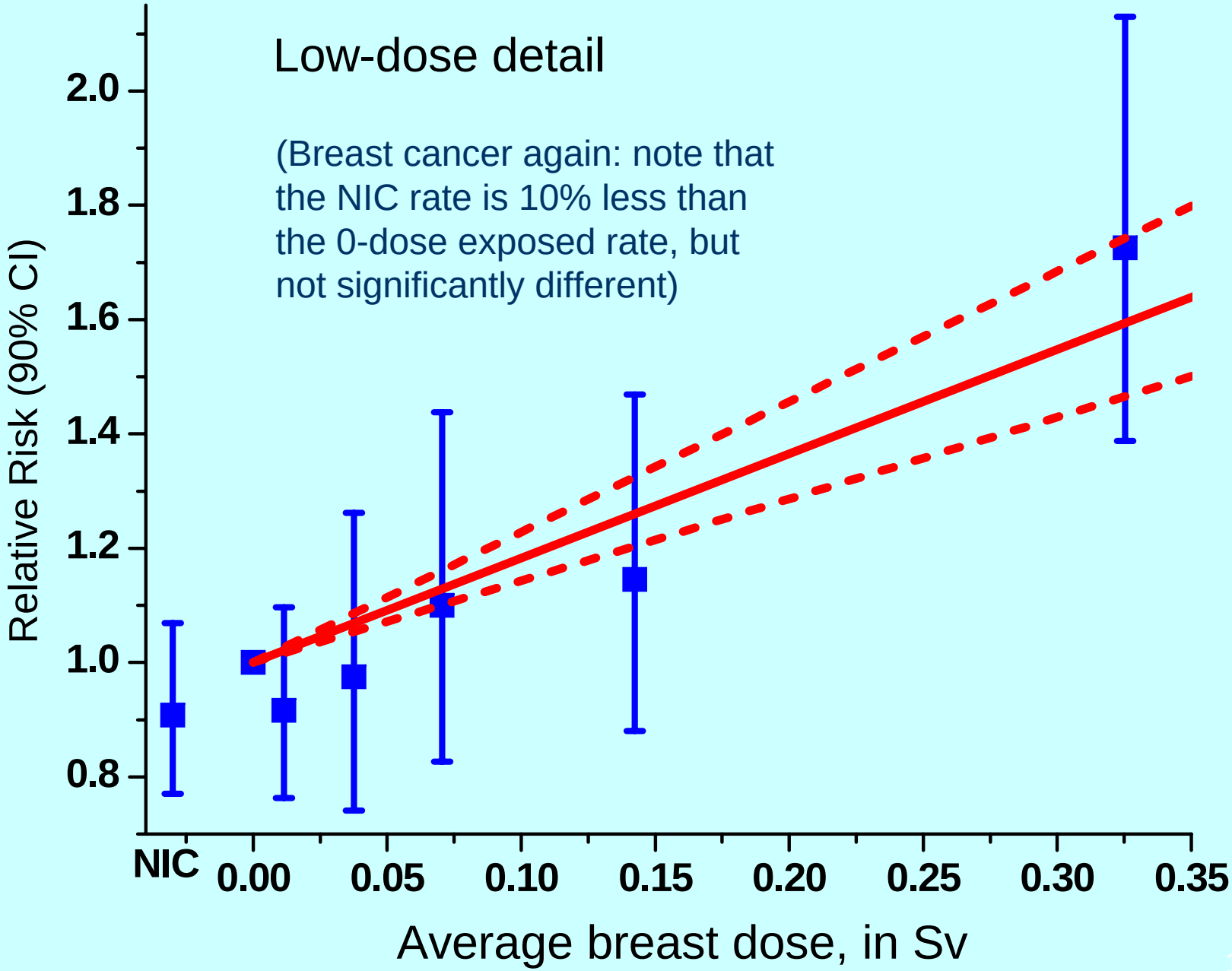
Dose D (Gy)	Excess Risk	Total Risk	$N^{1/2}$ × Standard Deviation of Estimate		Required Sample Size (N)
			Null Hypoth.	Alt. Hypoth.	
1.0	10%	20%	0.3	0.4	69
0.1	1%	11%	0.3	0.313	5728
0.01	0.1%	10.1%	0.3	0.301	558,000
0.001	0.01%	10.01%	0.3	0.300	55.7 million

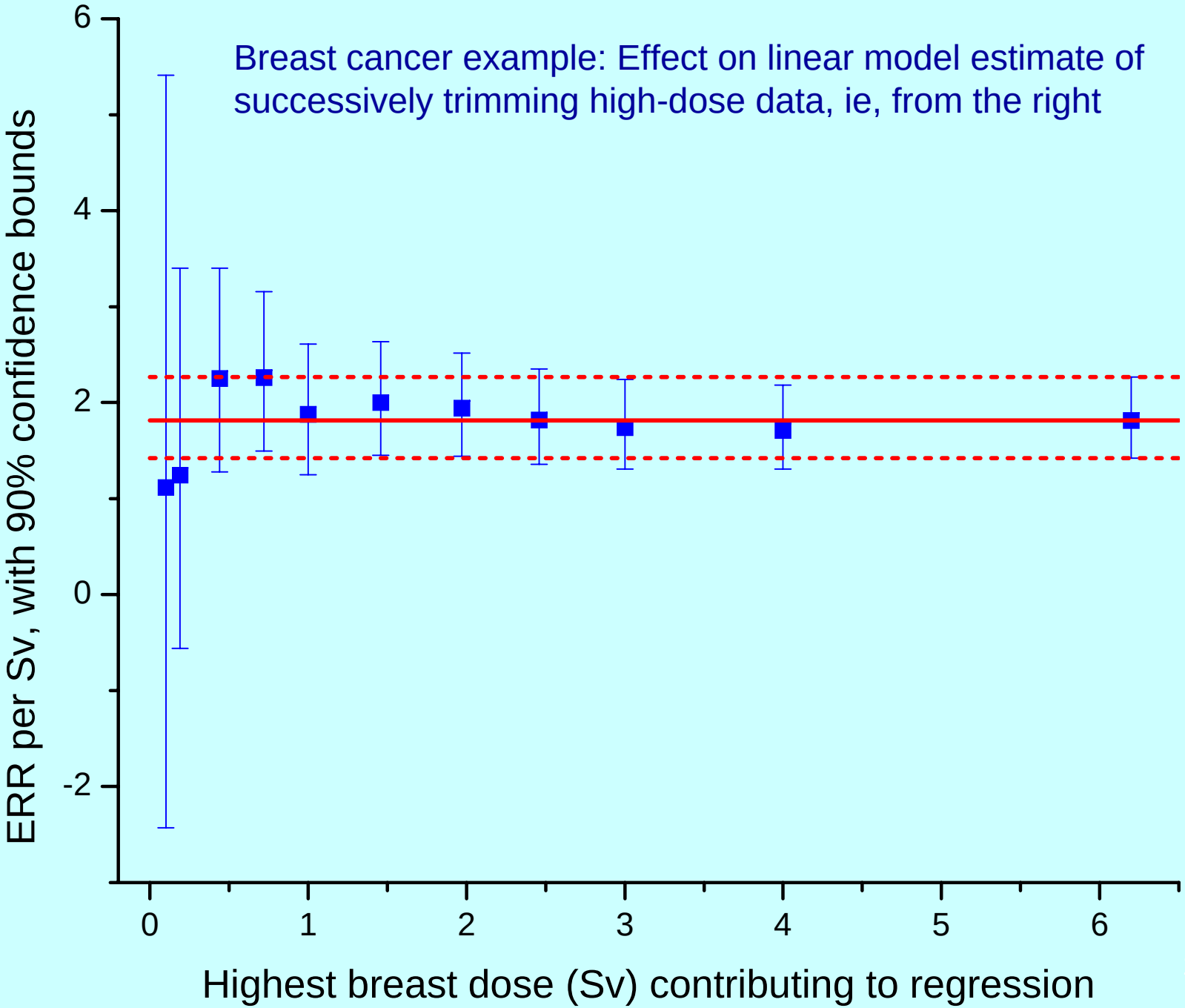
Example (cont)

- For D = 0.01 Gy (i.e., excess risk = 0.1%) and N = 50,000, the probability of rejecting the null hypothesis is .186
  - Under the null hypothesis, it is .05
  - 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, estimate must be > 0.22%, over 2 times the true value

More bad news:

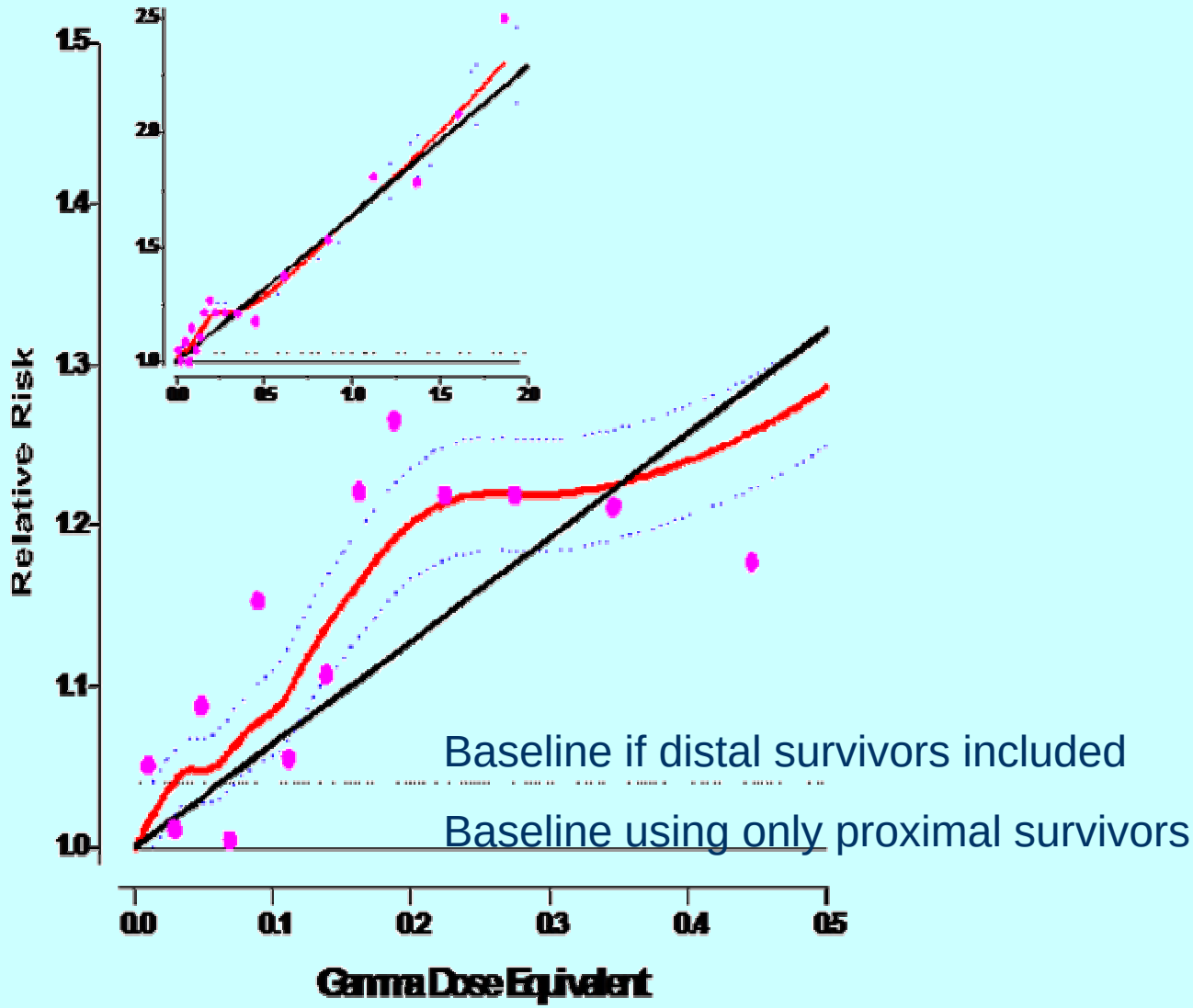
- In fact, sample size requirement is much more stringent
  - we don't "know" the baseline; we have to estimate it, which requires many more subjects
- And when we estimate the baseline,
  - Possibility of biased ascertainment of the baseline is serious when the predicted excess is low
  - How could we possibly control for every risk factor that might increase risk from 10% to 10.1%, or decrease it to 9.9%? How many such factors are known?
- Bottom line:
  - Stick to studies with reasonable power, judging by information from higher-dose studies
  - Low-dose extrapolation of estimates is unavoidable;
  - Direct estimation is likely to be either uninformative or misleading

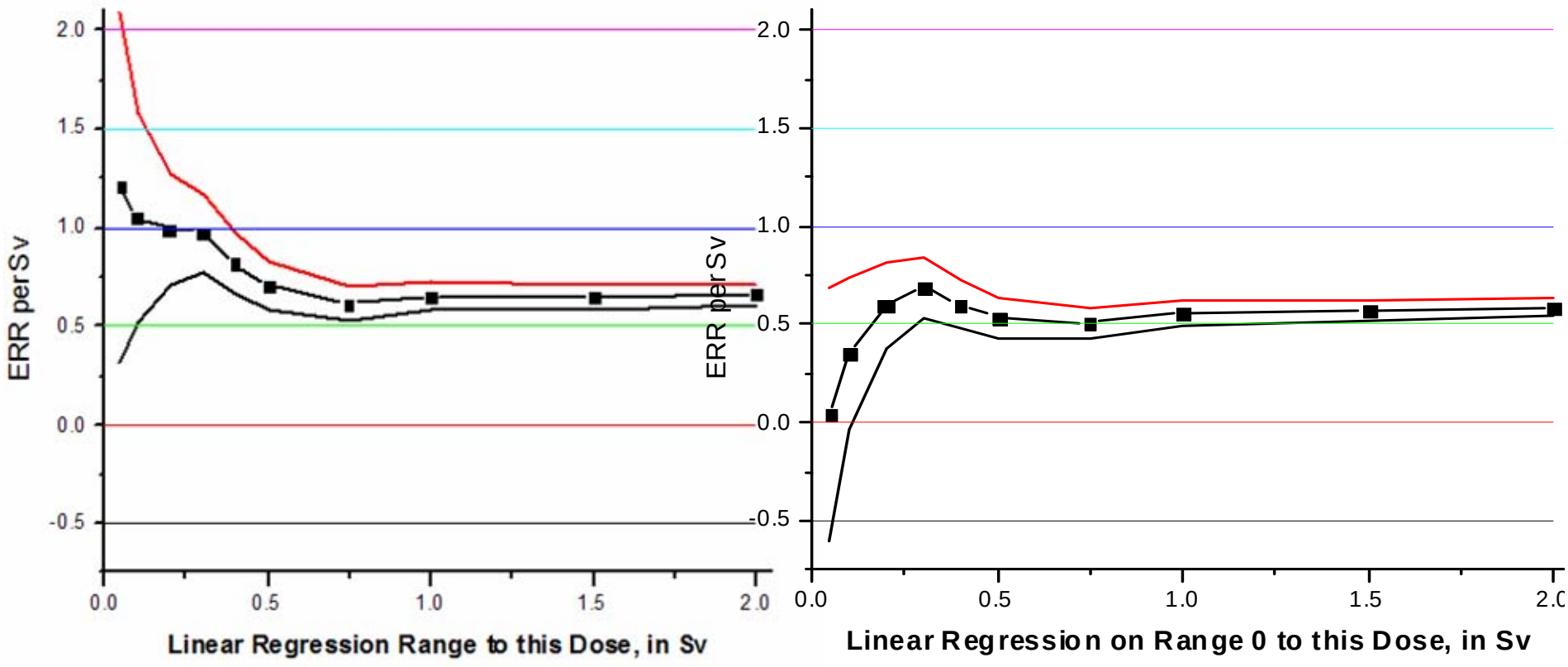

Low-dose detail
(Breast cancer again: note that the NIC rate is 10% less than the 0-dose exposed rate, but not significantly different)
Relative Risk (90% CI)
2.0
1.8
1.6
1.4
1.2
1.0
0.8
NIC
0.00
0.05
0.10
0.15
0.20
0.25
0.30
0.35
Average breast dose, in Sv


Breast cancer example: Effect on linear model estimate of successively trimming high-dose data, ie, 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

Pierce & Preston, Radiation Research, 2000; 154:178:86 (all solid cancers)

Note: error band is " 1 standard deviation





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 higher zero-dose baseline

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

The linear, no-threshold (LNT) model

- Currently, radiation protection philosophy is based on the LNT model
- The model 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 ICRP posits a "dose and dose rate effectiveness factor" (DDREF) of 2 for low-LET radiation at low doses and dose rates for radiation protection
  - Where the DDREF applies, linear-model risk based on high-dose data is divided by it
  - In the example, 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 model

- 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
  - As would that for 1 mGy to 1,000,000 people
  - Or for 0.1 mGy to 10 million people
    - Of course, you'd never be able to prove it
    - It might be expensive to reduce the dose, and the 10 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 model

- If we could agree that there is no radiation-related cancer risk associated with doses below (say) 1 mGy, the 10 million people exposed to 0.1 mGy could relax
- Radiation protection would be cheaper and easier than it is today
- It would be even easier with a threshold at 10 mGy
- Unfortunately, a low-dose threshold at 10 mGy or 1 mGy would be difficult to prove, for the same reasons that make it difficult to demonstrate the opposite

A long-standing issue

- Source: Jennifer Caron, undergraduate thesis
  http://resolver.caltech.edu/CaltechETD:etd-03292004-111416
- Subject was 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 pts, thymic irrad pts, US radiologists
- Fruit fly geneticists found linear dose response for drosophila mutations down to 250 mGy
  - Also, the US radiologists' doses accumulated at rate of ~ 1 mGy per day; i.e., dose, and presumably risk, accumulated daily

Ed 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 mutational factor in radiation leukemogenesis
  - Estimate: 2 excess leukemias per million per cGy per year
  - 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
- 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 mutation
    - i.e., damaged or altered cells can escape cell cycle checkpoint and apoptotic pathways
- 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
- Very different for colon, for which there is clearly a low-dose risk

Epidemiological evidence re: threshold

- For:
  - Shape of dose responses for basal cell skin carcinoma, bone, soft tissue sarcoma, rectum, small intestine
  - Apparent fractionation effect for lung cancer
- Against:
  - 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 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

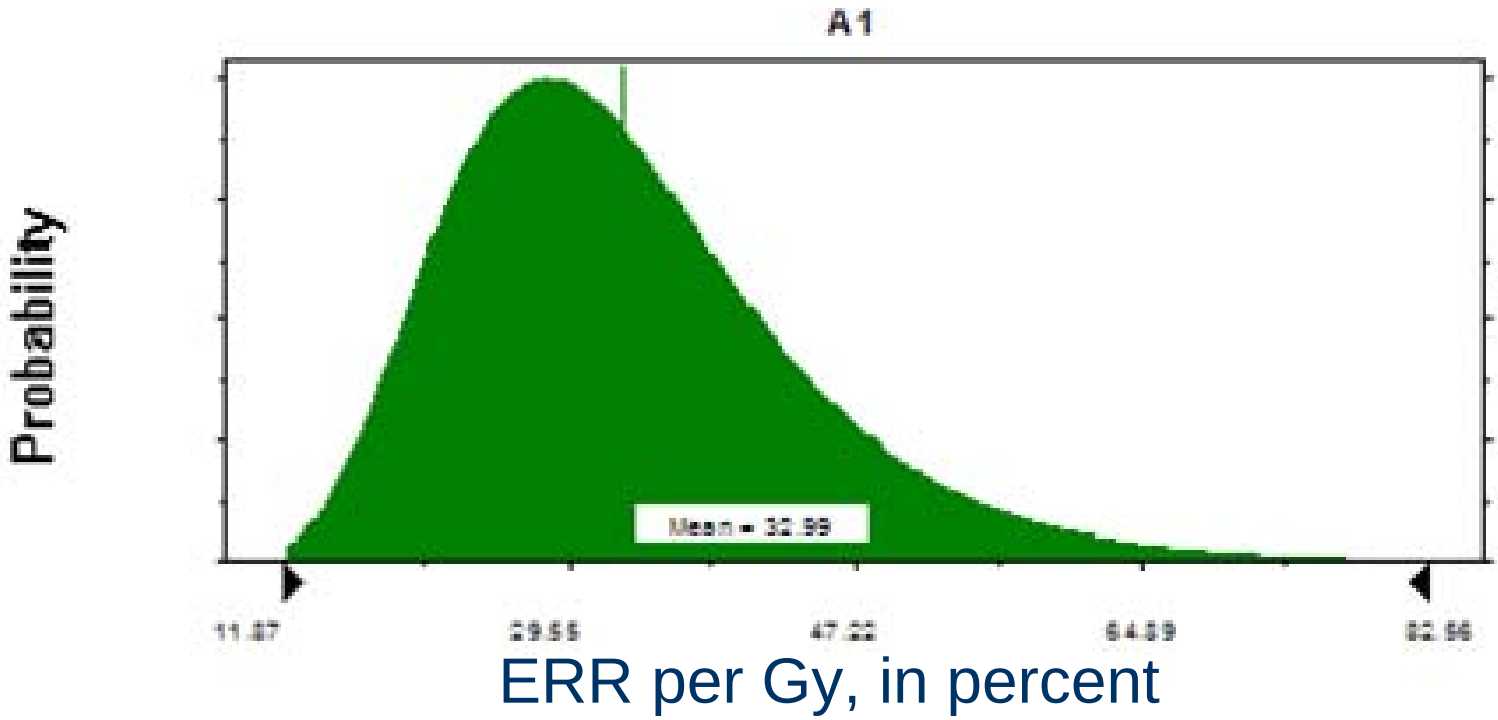
Quantitative Uncertainty Analysis

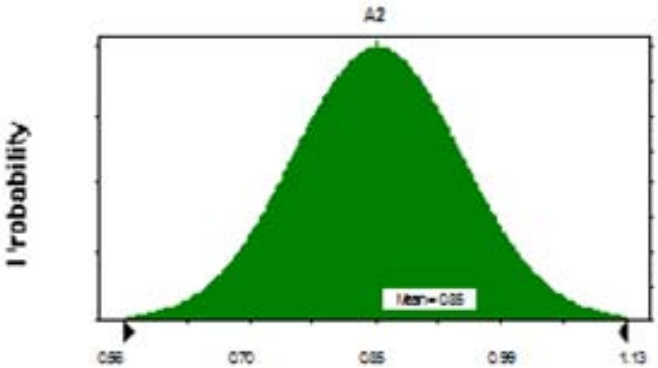
- Method much used in risk analysis
- Has advantage of transparency
- For it to be persuasive, audience has to understand how it works:
  - Identify components of risk estimation process
  - Determine uncertainties of each, and propagate the uncertainties by examining how the components interact
  - Evaluate the uncertainty of the risk estimate

Major uncertain components

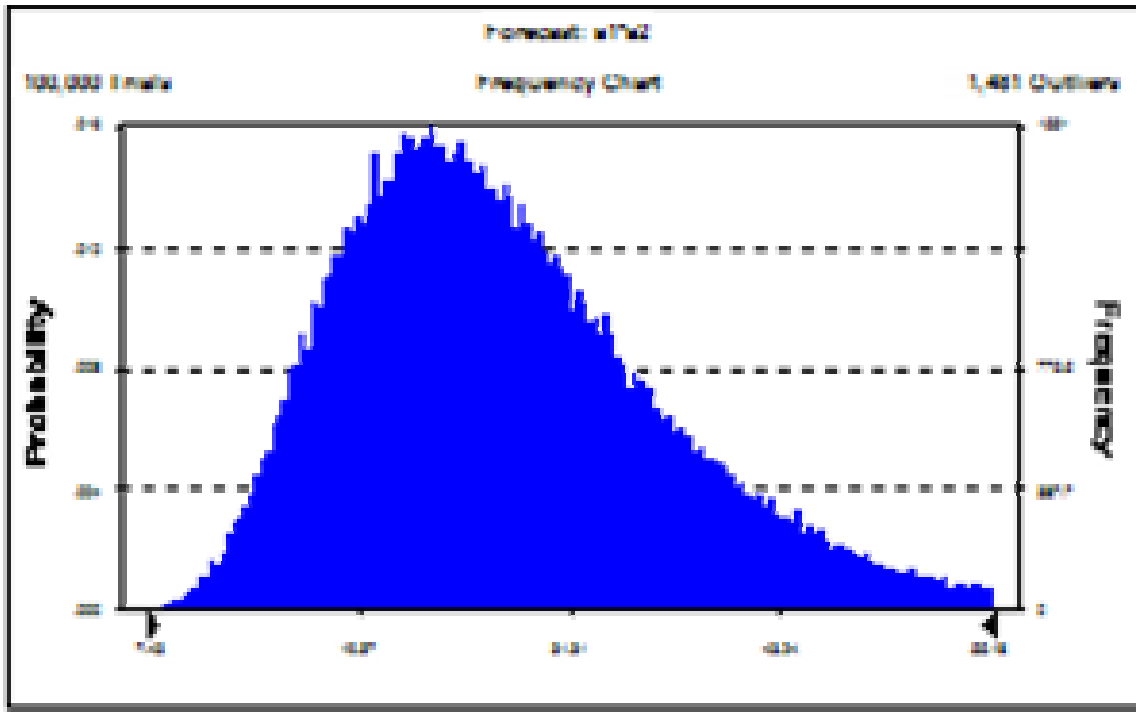
- Linear model estimate of ERR at 1Gy
  - Statistical likelihood contour
- Correction for DS86-related bias
- Correction for transfer from LSS to US population
- DDREF to be applied at low doses and low dose rates
- Possibility of a universal threshold at some dose above that of interest

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% uncertainty limits 0.18 and 0.43. Obtained from likelihood contour.

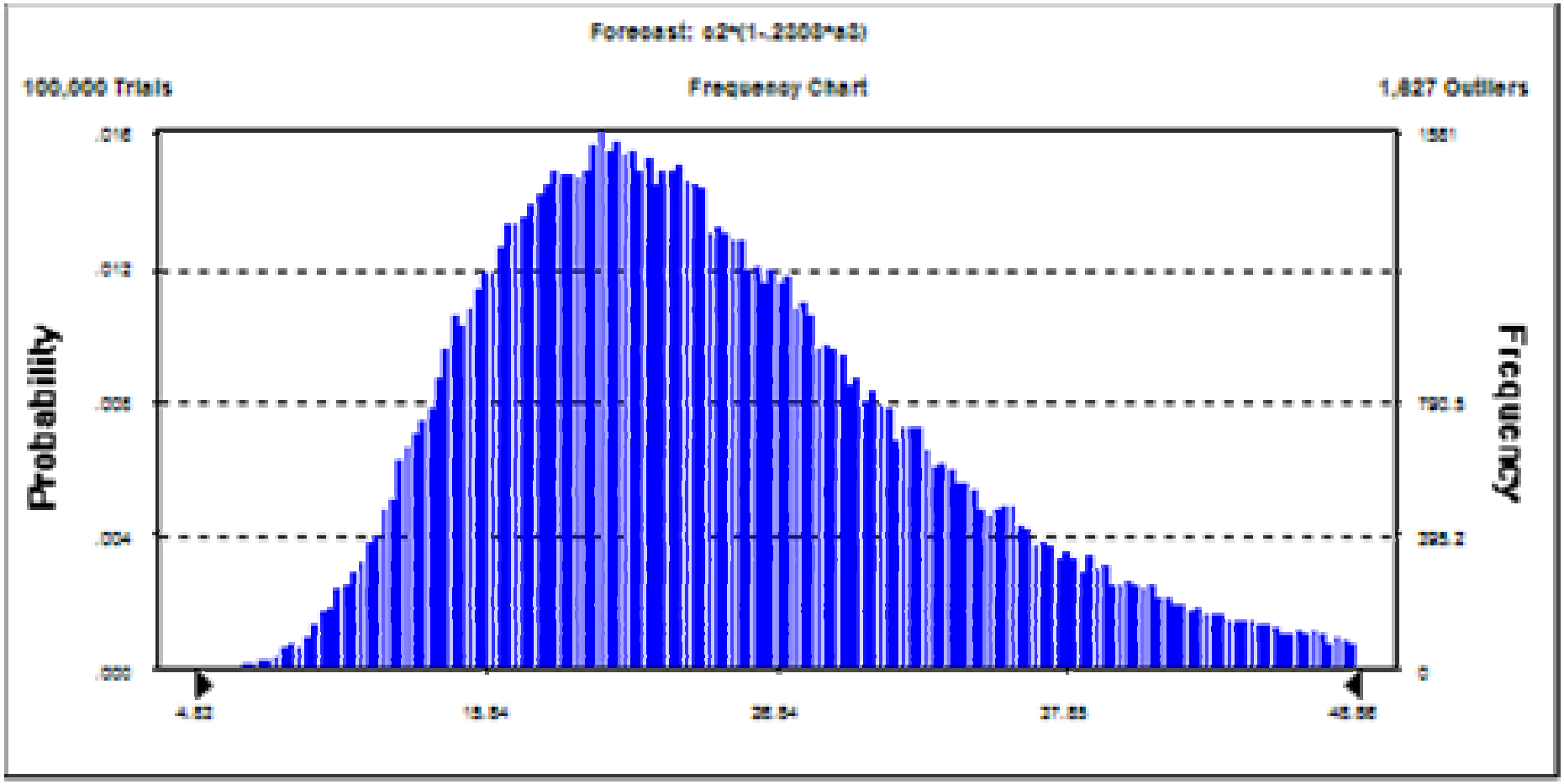




Normal uncertainty distribution for dosimetry bias correction factor, with mean 0.84 and 90% uncertainty limits 0.69-1.0. (From NCRP Rept. 126)

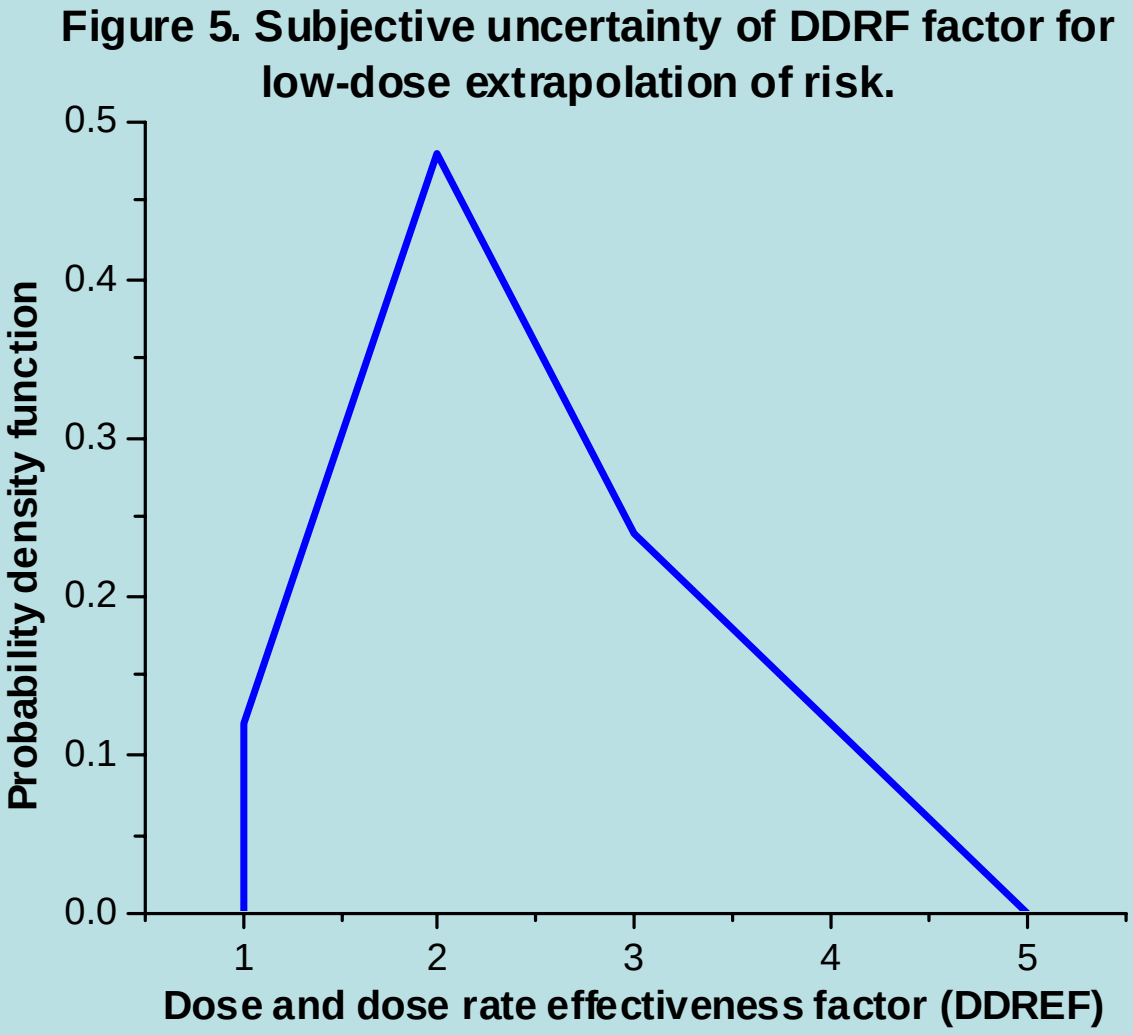


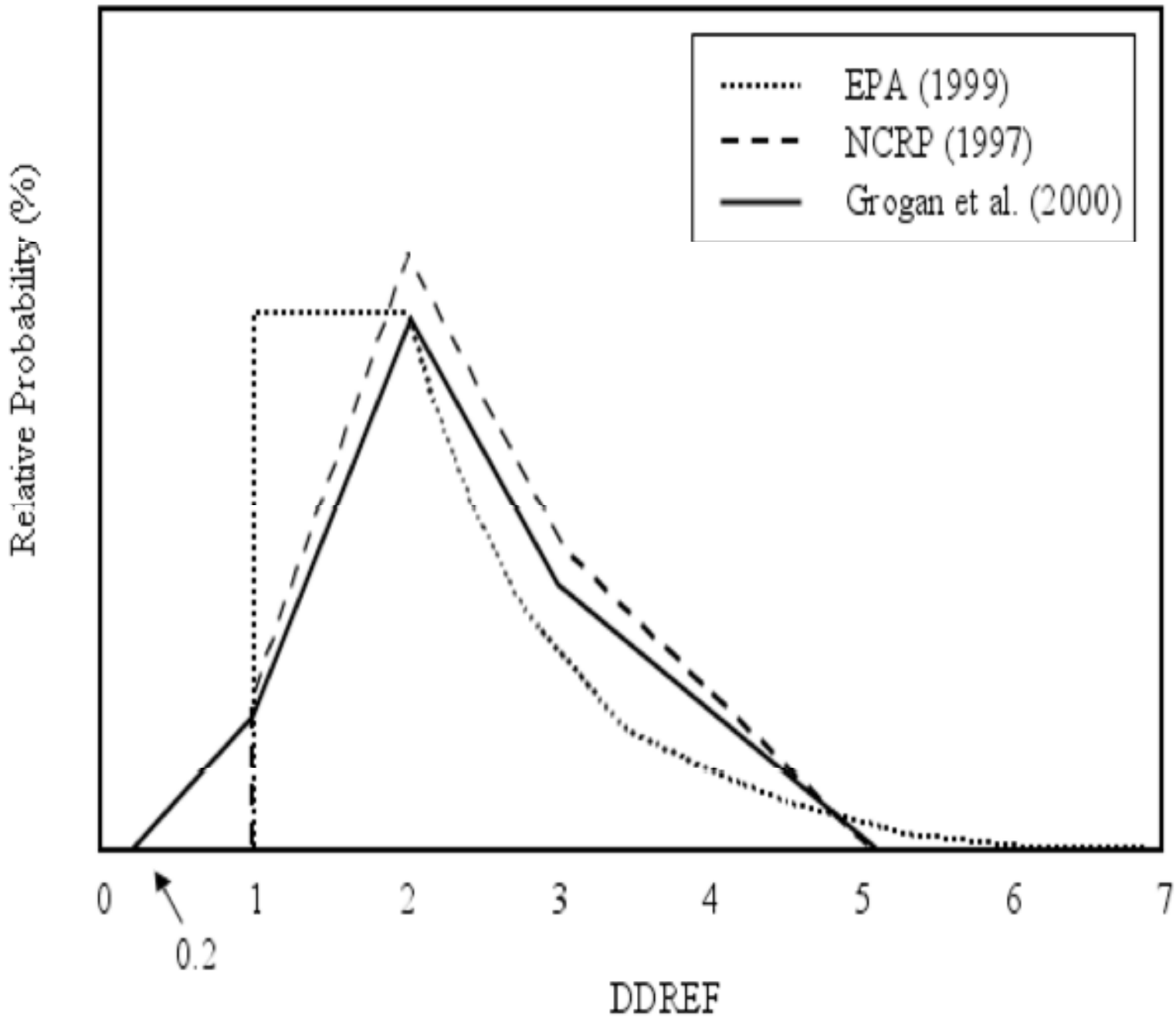
Approximately lognormal, corrected uncertainty distribution for ERR per Gy, with mean 0.26 and 90% uncertainty limits 0.15-0.46.

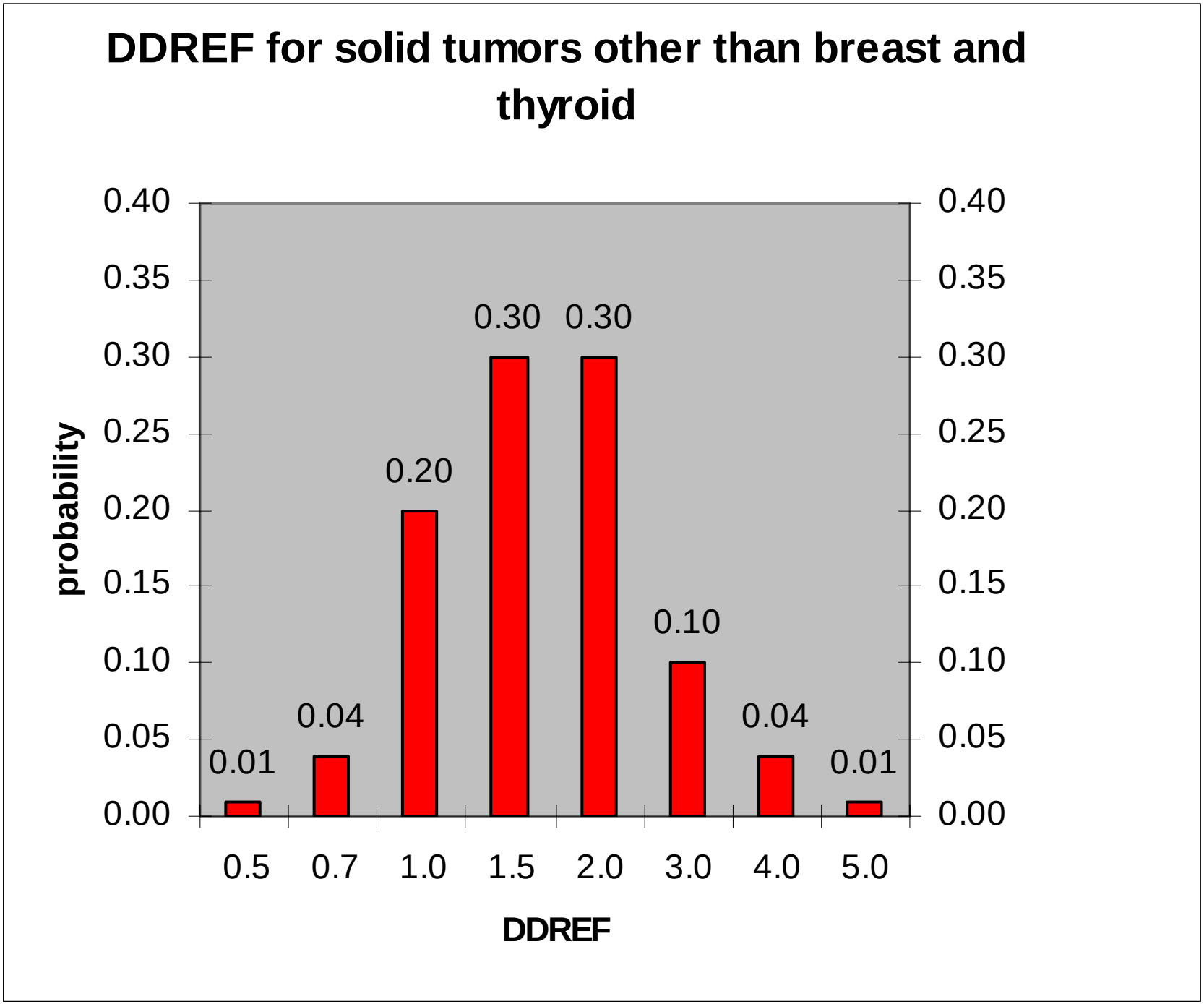


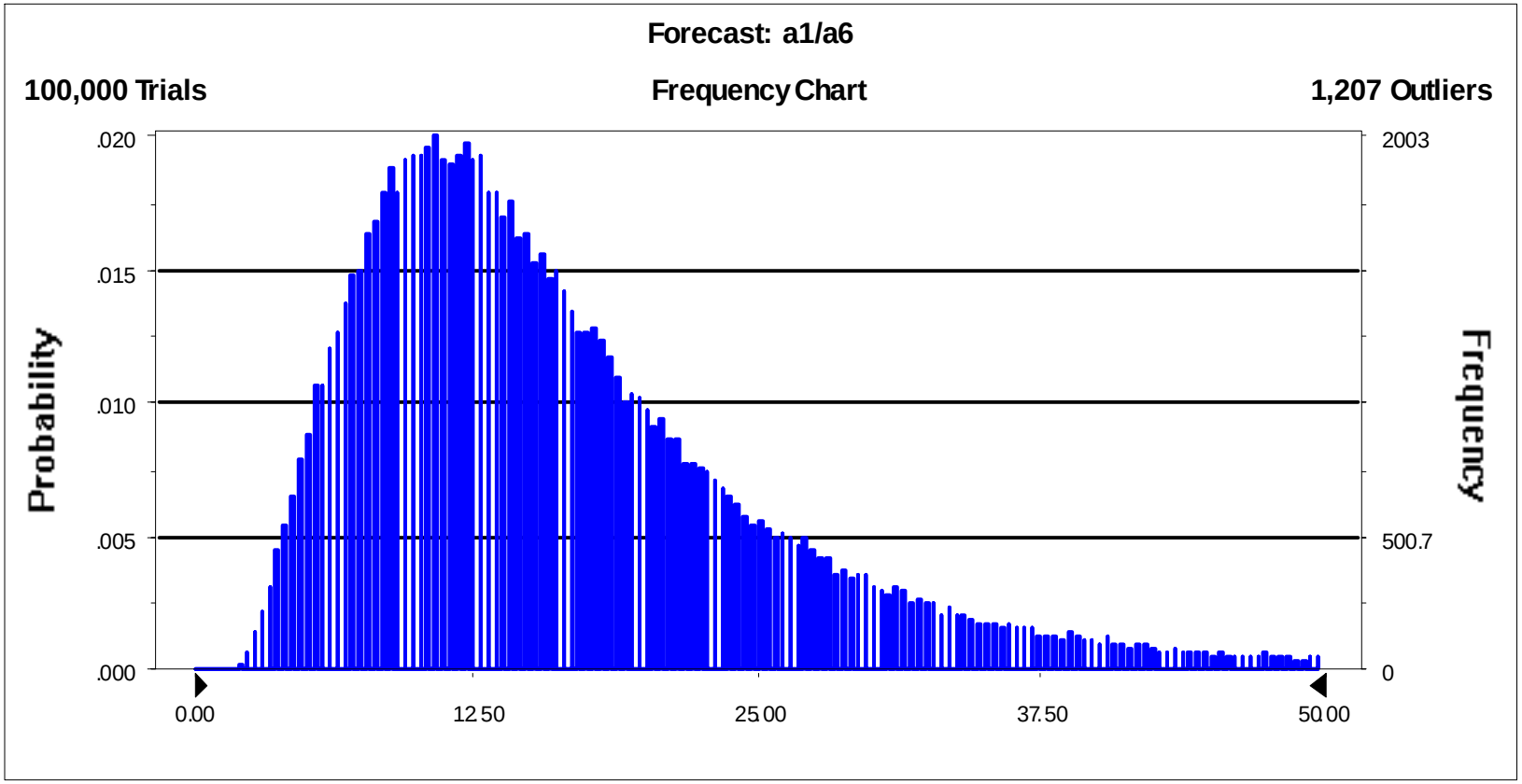
Monte Carlo simulation of the uncertainty distribution for cancer ERR at 1 Sv, after transfer to a U.S. population: the simulated distribution is approximately lognormal with mean 0.25 and 90% probability limits 0.13 – 0.41.

NCRP 126 Uncertainty Model for DDREF:




EPA (1999)
NCRP (1997)
Grogan et al. (2000)
Relative Probability (%)
0
1
2
3
4
5
6
7
0.2
DDREF


DDREF for solid tumors other than breast and thyroid
probability
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
0.01
0.04
0.20
0.30
0.30
0.10
0.04
0.01
0.5
0.7
1.0
1.5
2.0
3.0
4.0
5.0
DDREF



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
- But it is not immune from political considerations

Point of view (cont.)

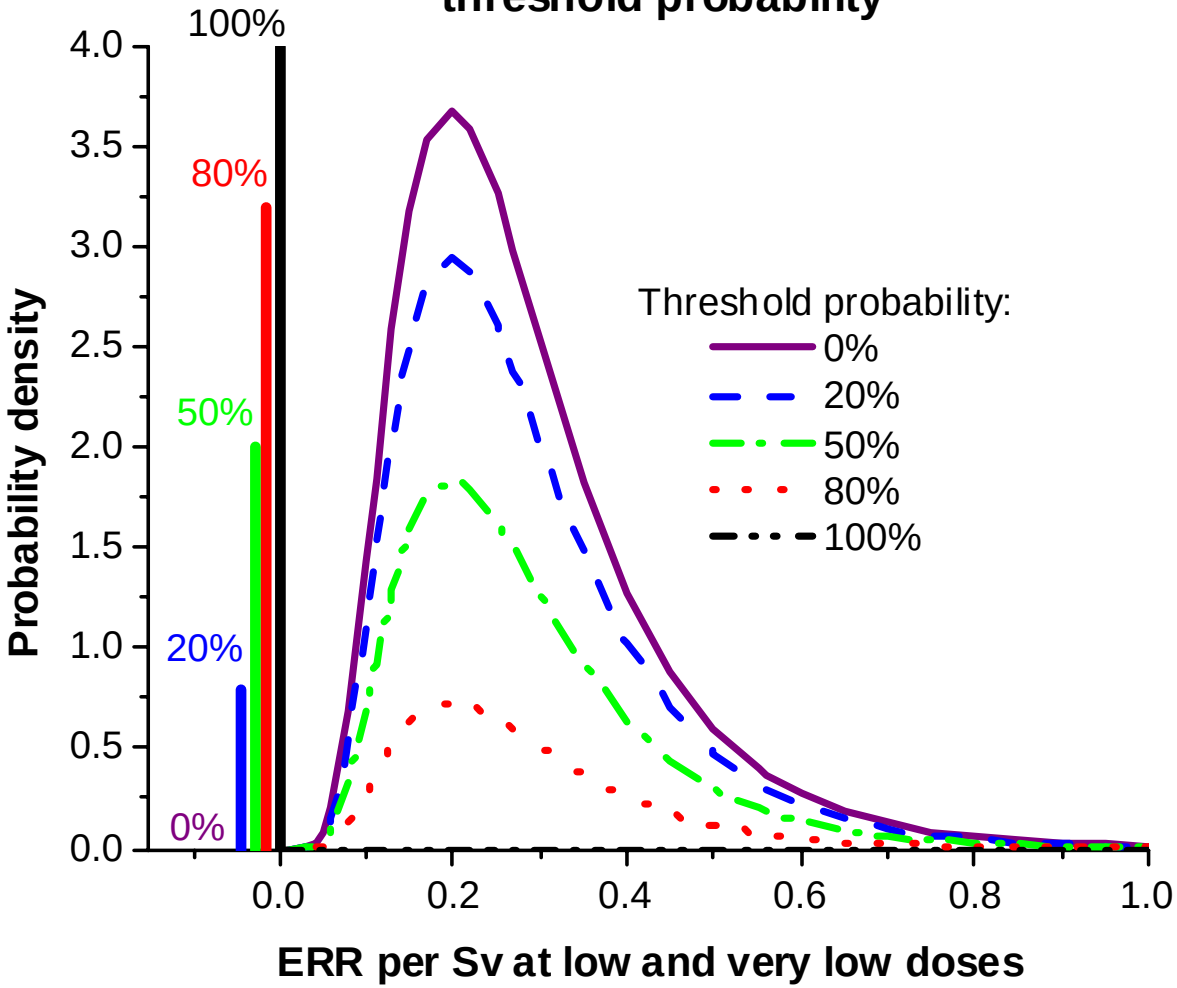
- The uncertainty distribution summarizes all the identified information about risk
  - But we can't think of everything
- The exposed population presumably is concerned with upper limits on risk
  - How bad might it be? Is the benefit really worth the risk?
- Those liable for the expense of dose reduction 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?)
- Sometimes those exposed and those liable for the expense are the same – e.g., radiation workers

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 at 1 mGy would be zero
- And with probability *1-p*, ERR at 1 mGy would be an uncertain quantity, distributed lognormally with mean 0.17 H 0.001 and upper 95% probability limit 0.36 H 0.001

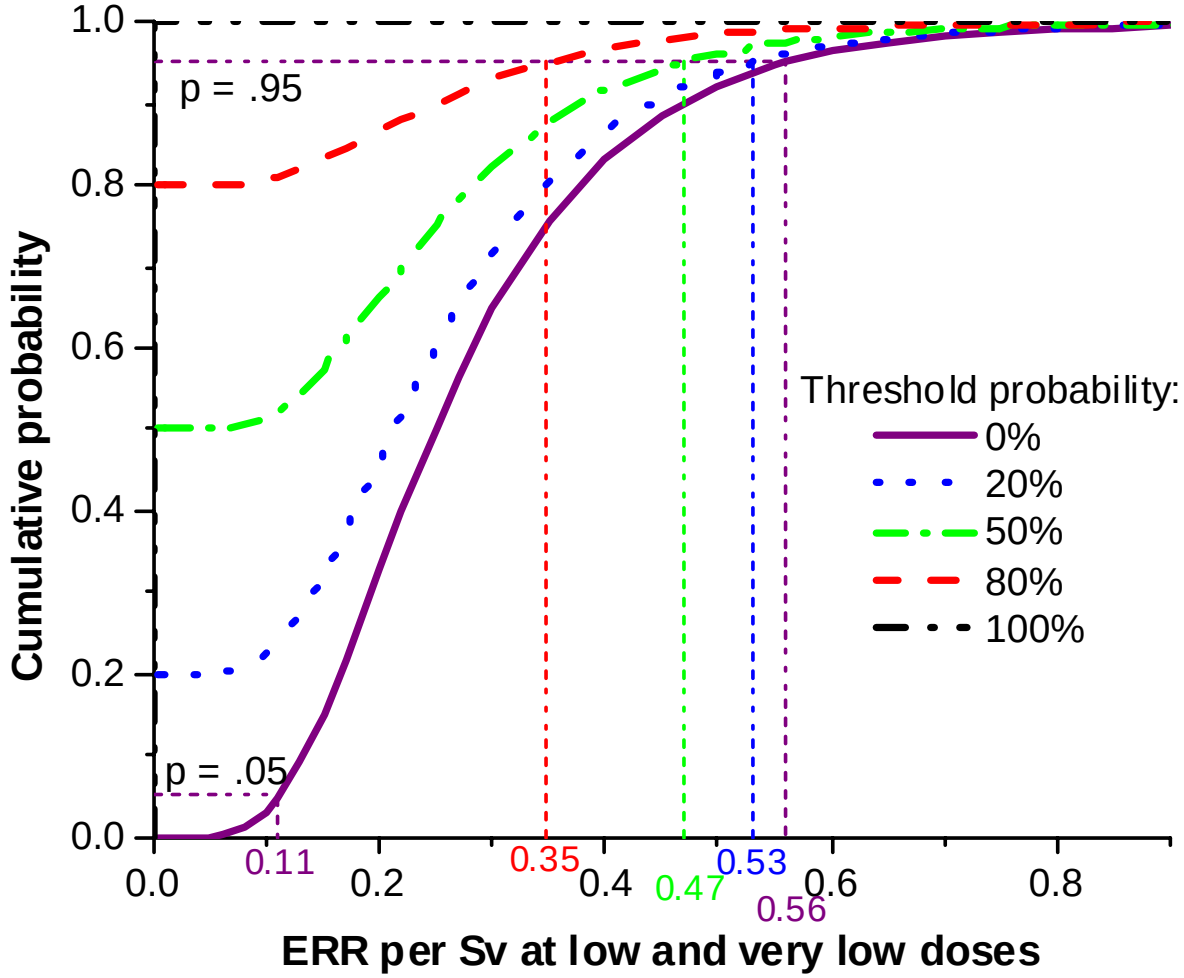
Uncertain possibility of a threshold

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



Uncertain threshold possibility

Figure 9. Influence of assumed threshold probability on upper (and lower) 95% credibility limits for low-dose risk

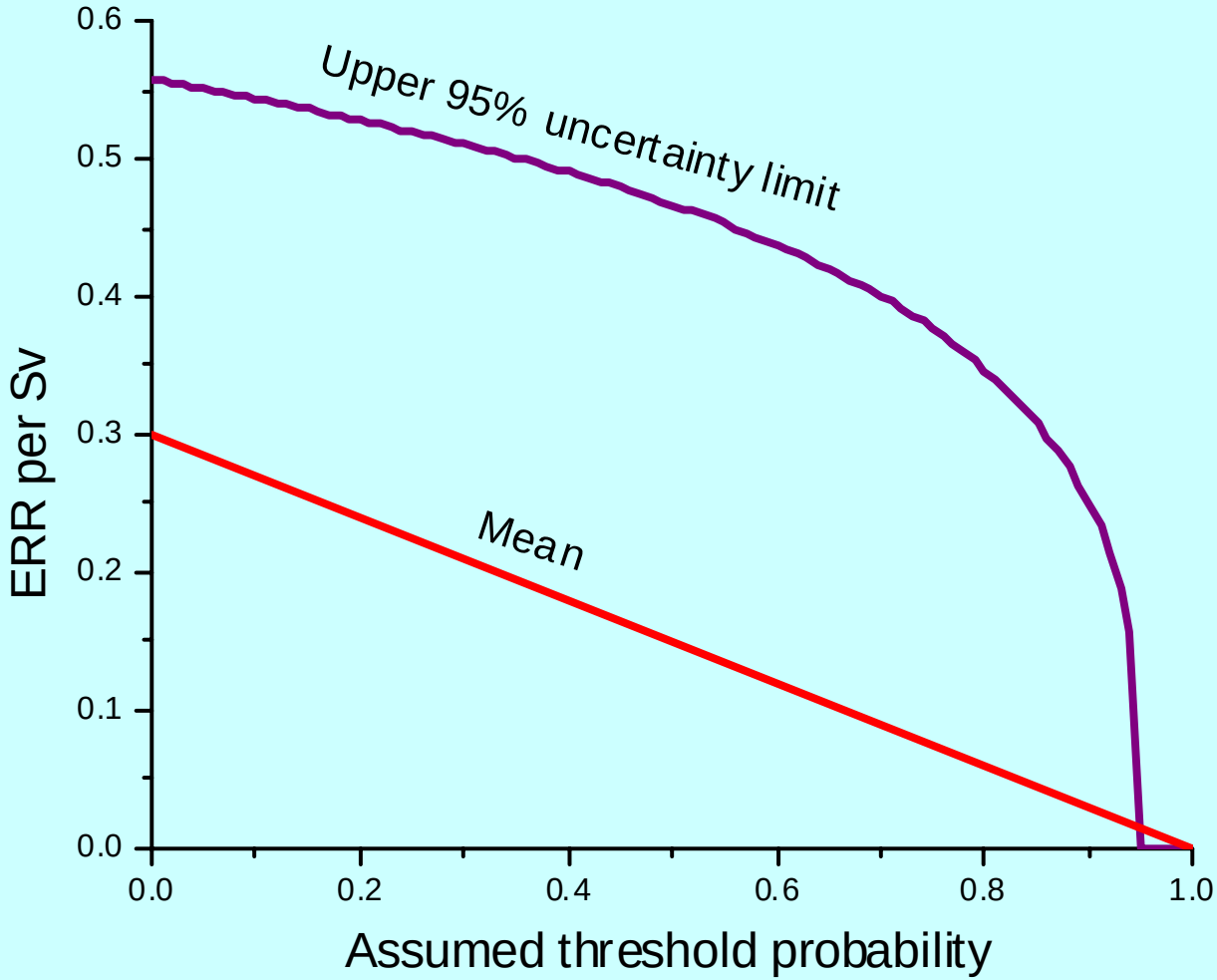


Assume uncertain threshold possibility, with probability *p*

- QUA approach: risk at 1 mSv is
  - zero with probability *p*
  - lognormal (0.025%, 1.64) with probability *1-p*

p	mean	95% upper limit
0	0.03%	0.056%
0.2	0.024%	0.053%
0.5	0.015%	0.047%
0.8	0.006%	0.035%
1	0	0

Effect of uncertain threshold assumption on a lognormal (GM 0.25, GSD 1.64) 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*
  - An upper uncertainty limit also decreases with increasing *p*, but the decrease is rather slow until *p* approaches 1.
- 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