

Lauriston S. Taylor Lecture

Radiation Protection and Public Policy in an Uncertain World

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March 8, 2010

A personal note

- My interest in radiation science began in 1966 when I was recruited from graduate school by Gilbert Beebe and Seymour Jablon for a 2-year tour as a junior statistician at the Atomic Bomb Casualty Commission.
- Since then, I have continued to be involved to varying degrees with the A-bomb survivor studies at the ABCC and (since 1975) the RERF. This includes my tenure at the NCI from 1975 until my retirement last year.
- Accordingly, much of this presentation is centered around the A-bomb survivor studies as the most important single source of information about radiation-related risk.

Some background

- Aug 1945: Hiroshima-Nagasaki A-bombs
- March 1947: establishment of Atomic Bomb Casualty Commission (ABCC)
 - Nov 1947: hematol. study (Lt. James V. Neel)
 - 1948-1956 studies:
 - radiation cataracts early leukemia excess
 - aging & mortality sex ratios of newborns
 - genetics miscarriages
 - teratogenesis (microcephaly)

1956-58 Reorganization

Unified Epidemiological Study

- Life Span Study cohort
 - Identified from supplement to 1950 census
 - 54,000 survivors exposed within 2.5 km
 - 40,000 sampled from 2.5-10 km
 - 26,580 non-exposed residents circa 1950
- Mortality notification and death certificate diagnosis obtained through Japanese registries

Unified Epidemiological Study

- ABCC departments of clinical medicine, genetics, pathology, radiology, & statistics
- Clinical (Adult Health Study) subsample of 20,000 LSS members
 - Biennial clinical examinations at ABCC
- Active autopsy program
- H & N tumor registries in 1957 & 1958
 - 1st population-based registries in Japan
- Pathology-based tissue registries in 1973

Dose reconstruction

- Early analyses based on distance:
 - Proximal vs. distal, distance in meters
- T57 (York) : bomb yield, distance & shielding
- T65D: epicenter changes, drastically modified air-dose curves, esp. for Hiroshima; regression approach to attenuation by shielding
- DS86: Hiroshima yield and γ dose increased, neutron dose reduced 10-fold (H) & 3-fold (N)
- DS02: current dose system

The LSS Tumor Registry

- Leukemia registries founded in late 1940s, before the 1950 census that defines the LSS
- H&N tumor registries rehabilitated (Mabuchi et al, Thompson et al, Ron et al, Preston et al, 1994)
 - 1950-87 for leukemia, 1958-87 for solid cancers
 - Primary basis for site-specific estimates used in 2003 NCI-CDC report to revise the 1985 radio-epi tables
- Most recent report (Preston et al, 2007)
 - Covered solid cancers 1958-1998
 - Used by BEIR VII and the NCI RadRisk program, which estimates lifetime risk

LSS mortality vs. LSS incidence

- Cause-specific death certificates from 1950
- Site-specific ca incidence from H&N tumor registries (1958+) & leukemia registries (1950+)
- Death certificate data virtually complete; incidence largely restricted to cases diagnosed locally
- Person-year denominators for TR cases must be adjusted (i.e., estimated) to reflect this fact
- Death certificates miss non-fatal cancers, TR diagnoses are more detailed and more accurate

Dosimetric and statistical uncertainty

- Dose-response relationships quantified by fitting incidence and mortality data from exposed populations to dose and other possible risk-modifying factors
- Uncertainty in estimated radiation doses leads to loss of statistical power, and bias or distortion of fitted dose response.
- For LSS, problem recognized & discussed by Jablon (1971), Gilbert (1984), and in several papers by Pierce et al. between 1989 and 2008

Pierce et al (2008) uncertainty correction for DS02

- Uncertainties involve “measurement error” ϵ_M (also called “classical error”)
 - Example: if related to estimated distance and shielding based on detailed interview
- And “averaging error” ϵ_A (also called “Berkson error”, “error due to individual peculiarities”)
 - Example: if related to using local defaults for location & shielding for persons known only to have been exposed in a given neighborhood

- In log scale, for *uncertain estimate* (\hat{D}) of kerma in air and *unknown, uncertain true value* (D),
 - $\ln \hat{D} = \ln D + \varepsilon_M + \varepsilon_A$
 - **The estimate, true value, and errors are all random variables**
 - ε_M and ε_A are uncorrelated $N(0, \sigma_M)$, $N(0, \sigma_A)$
 - ε_M and $\ln D$ are uncorrelated, as are ε_A and $\ln \hat{D}$
- Recommended solution (Pierce et al, 2008)
 - replace the estimate $\ln \hat{D}$ by the conditional expected value of $\ln D$, given $\ln \hat{D}$: $E(\ln D | \ln \hat{D})$
 - assume $\sigma_M = 0.40$ and $\sigma_A = 0.20$
 - truncate resulting assigned kerma at 4 Gy

Application of LSS ERR/Gy to a second population

- Dose uncertainty in 2nd population is uncorrelated with dose-response information from the LSS
- Thus, calculating uncertainty of the product,
dose × estimated risk per Gy,
is straightforward

Quantitative uncertainty analysis

- **A Guide for Uncertainty Analysis in Dose and Risk Assessments Related to Environmental Contamination (NCRP Commentary No. 14 (1996))**
 - Evaluations based on combination of statistical and subjective sources of uncertainty
- **Uncertainties in Fatal Cancer Risk Estimates Used in Radiation Protection (NCRP Report 126 (1997))**
 - “New paradigm” to express radiation-related risk
 - And to deal with what we don’t know well but can’t ignore

Some Examples

- Report of the NCI-CDC Working Group to Revise the 1985 NIH Radio-epidemiological Tables
 - NIH pub. 03-5387 (2003)
- Low-dose Extrapolation of Radiation-related Cancer Risk
 - ICRP Report 99 (2005)
- Health Risks from Exposure to Low Levels of Ionizing Radiation (BEIR VII)
 - NAS/NRC (2006)

The process

- Statistical analysis of epidemiological data (e.g., from LSS), after correction for dosimetric uncertainty
- Yields estimated excess risk per Gy (in linear case), with a statistical uncertainty distribution (e.g., for defining confidence limits)
- Quantitative Uncertainty Analysis (QUA) uses necessary, but uncertain, assumptions required for risk analysis based on statistical information

Technical notes

- “***Risk***” is an actuarial concept
 - can be estimated and verified only on basis of population rates
 - applied to individual as property of population
- ***Excess risk*** can be expressed in relative (ERR) or absolute (EAR) terms as a multiple of baseline, or an addition to baseline
 - Thus, $EAR = \text{baseline} \times ERR$
 - $ERR = EAR / \text{baseline}$

Standard parameterizations

- Additive (excess absolute risk) model:

$$R = \text{baseline} + \text{EAR}$$
$$= \exp\{\alpha_0 + \sum \alpha_i X_i\} + \beta D \times \exp\{\sum \gamma_j Y_j\}$$

- Where the X 's and Y 's are modifiers of baseline and excess absolute risk, resp.
- Multiplicative (excess relative risk) model:

$$R = \text{baseline} \times [1 + \text{ERR}]$$
$$= \exp\{\alpha_0 + \sum \alpha_i X_i\} \times [1 + \beta^* D \times \exp\{\sum \delta_j Z_j\}]$$

- Consider that factors affecting baseline risk (e.g., age, sex, smoking) may also affect dose-related excess risk, and vice-versa
- If we then parameterize risk accordingly,

$$R = \exp\{\alpha_0 + \sum \alpha_i X_i\} + \beta D \times \exp\{\sum \gamma_i X_i\}$$

$$= \exp\{\alpha_0 + \sum \alpha_i X_i\} \times [1 + \beta' D \times \exp\{\sum \delta_i X_i\}],$$

So that the same modifiers are used for baseline and excess risk,

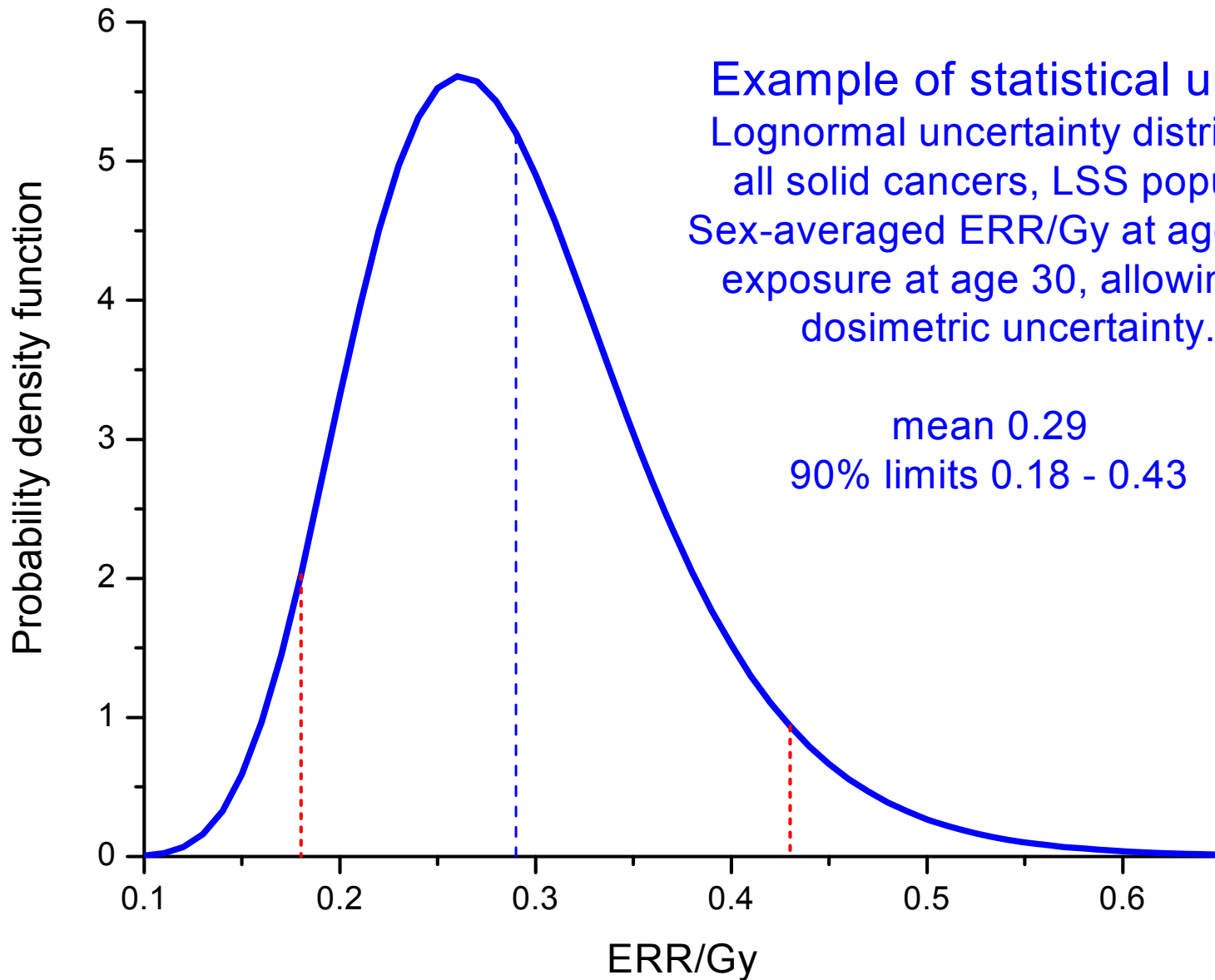
In this special (but common) case, absolute and relative risk model predictions are identical

Uncertainty distributions

- Example using a simple model for EAR, where modifiers are age at exposure and at cancer dx:

$$EAR = \exp\{\alpha_0 + \alpha_1 a + \alpha_2 e\} + \beta D \times \exp\{\gamma_1 a + \gamma_2 e\}$$

- Statistical uncertainty distribution for EAR per Gy
 - at attained age $a = 50$
 - following exposure at age $e = 30$
- Is obtained from fitted statistical likelihood function for parameter β when ages a and e are replaced by $a-50$ and $e-30$, respectively



Example of statistical uncertainty:
Lognormal uncertainty distribution for
all solid cancers, LSS population.
Sex-averaged ERR/Gy at age 50 after
exposure at age 30, allowing for
dosimetric uncertainty.

mean 0.29
90% limits 0.18 - 0.43

* Based on 1958-1987 LSS Tumor Registry Data, Thompson et al, Rad Res 1994

Other sources of uncertainty

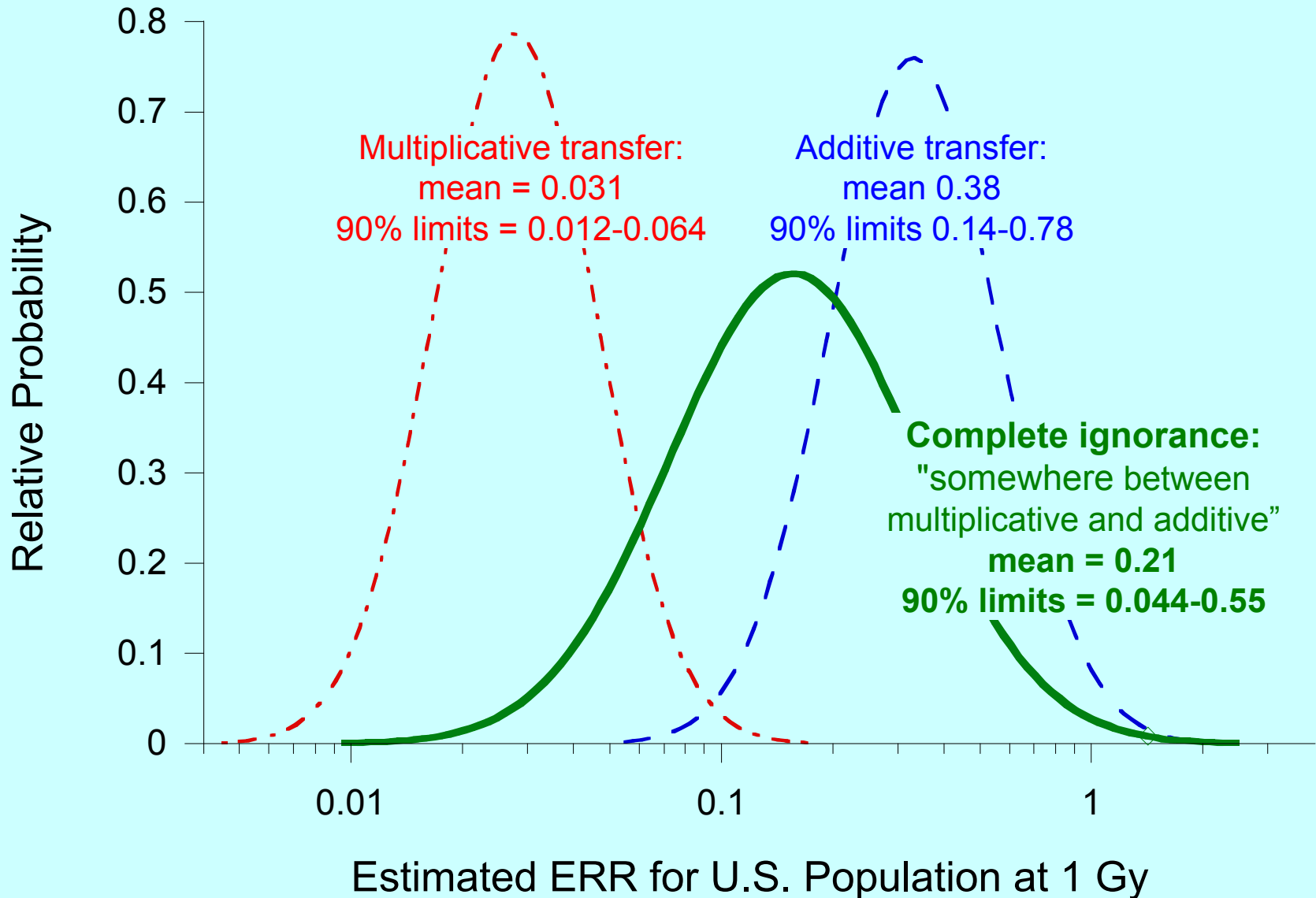
- 1. Transfer of risk estimates between populations
 - If baseline cancer rates differ greatly between populations, it can make a big difference whether we transfer ERR or EAR
 - Extreme example: stomach cancer rates in Japan are about 12-fold higher than in US
 - Multiplicative transfer: $ERR(US) = ERR(Japan)$
Implies $EAR(US) = EAR(Japan) / 12$
 - Additive transfer: $EAR(US) = EAR(Japan)$
Implies $ERR(US) = ERR(Japan) \times 12$

Population transfer (cont.)

- **Very few data on how to do it: we don't know enough to resolve this problem, but we can't ignore it**
- **One approach: treat multiplicative and additive transfer as the extremes**
- **And incorporate uncertainty into the estimation process**
 - **E.g., $ERR = p \times \text{multiplicative} + (1 - p) \times \text{additive}$,**
 - **Where p is a random variable uniformly distributed between 0 and 1 (for example)**

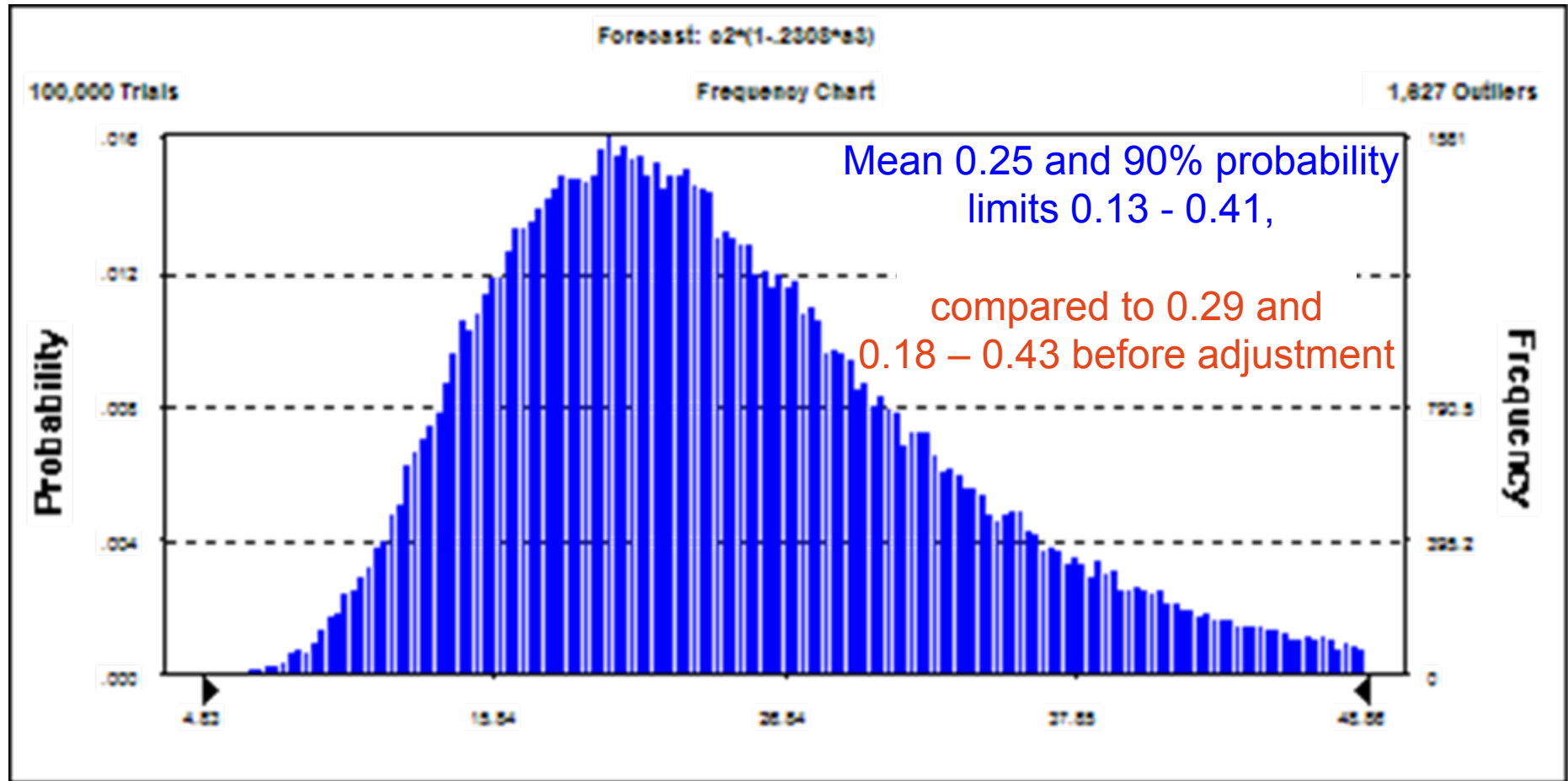
- In this example, we identify a crucial problem (transfer between populations)
- We don't know which, if either, of the two (additive and multiplicative) approaches is correct
- But it seems reasonable to suppose that the truth is somewhere between them
- We formalize that assumption as subjective information about uncertainty
- And proceed from there

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



For all solid cancers combined

- Japanese baseline rates are a little lower than US rates
- Difference far less than for stomach cancer, but still requires adjustment
- Result is a widening of the uncertainty distribution and a small shift to the left

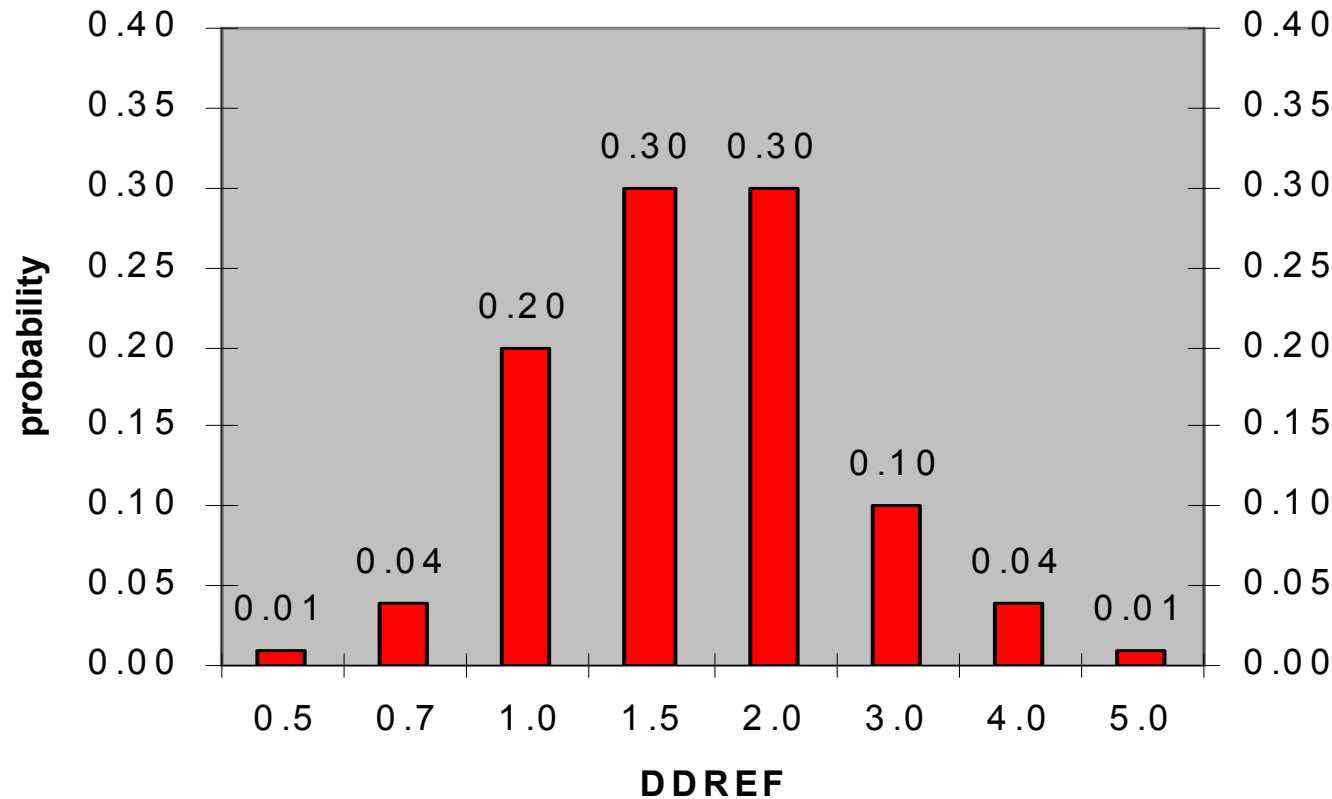


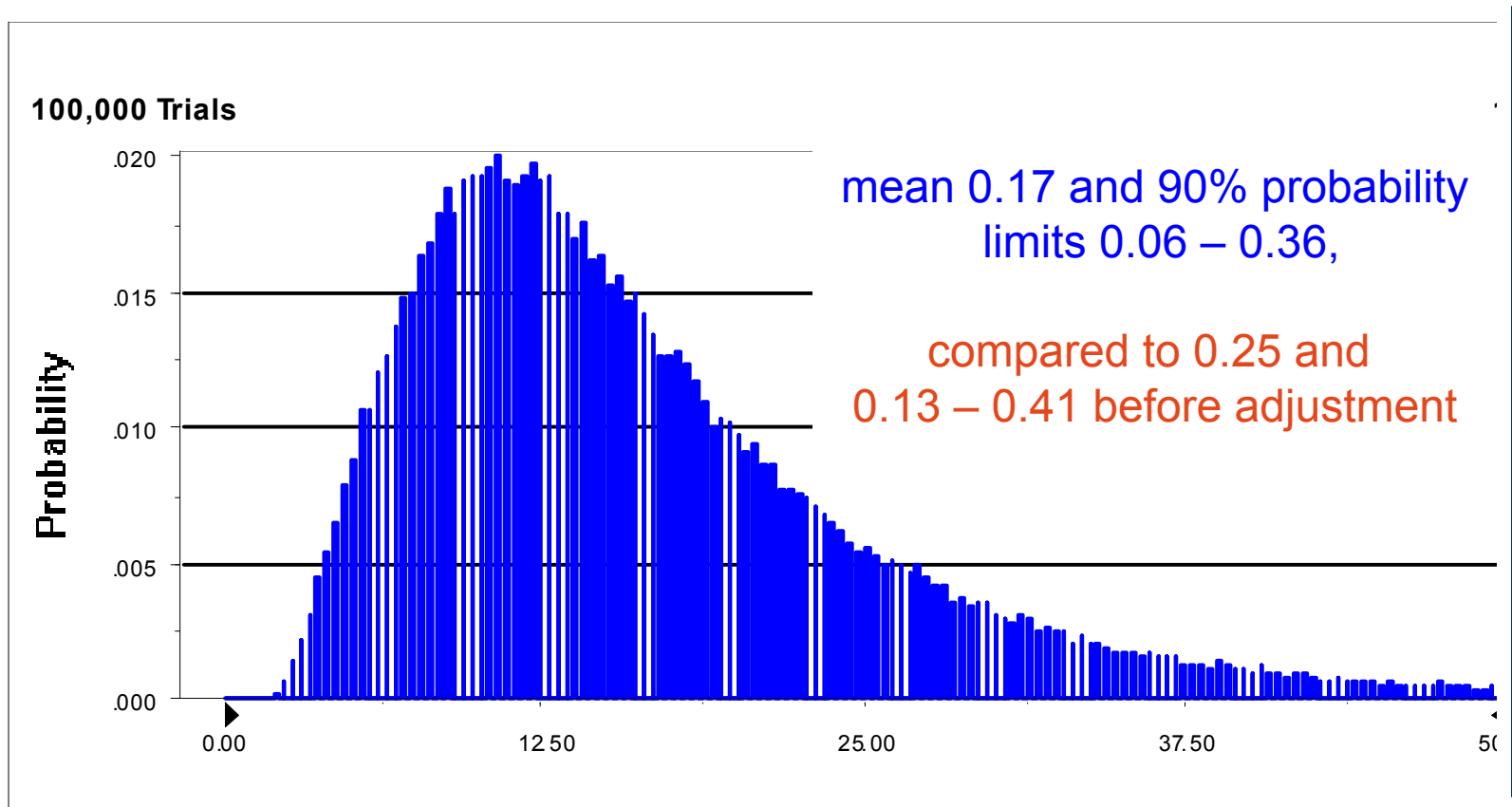
Monte Carlo simulation of the uncertainty distribution for all solid cancer: ERR at 1 Gy, after transfer to a U.S. population: the simulated distribution is approximately lognormal

Uncertain DDREF for low-dose extrapolation

(for example) this subjective uncertainty distribution:

DDREF for solid tumors other than breast and thyroid





Monte Carlo simulation of the uncertainty distribution for low-dose cancer ERR per Gy. After division by an uncertain DDREF the simulated distribution is roughly lognormal;

Recap

- **“New paradigm” approach uses objective and subjective information about radiation-related cancer risk**
- **Approach is transparent**
 - **Highlights crucial uncertain factors**
 - **& requirements for more information, i.e., more research**
- **Also provides an interim basis for making decisions**

Radiation Protection

- **Political process, with stakeholders**
 - Who may feel threatened by radiation exposure
 - Or who may value certain benefits that involve radiation exposure to themselves and/or others
 - Most of us belong to some extent to both groups
- **Useful to address stakeholders' concerns from their particular viewpoints**
 - What actual or potential benefit to you or others is associated with the exposure?
- **What is highest acceptable risk level?**
 - With a benefit?
 - Without a benefit?

- **Methodology can provide information on:**
 - **Average value of risk**
 - **Plausibility of high and low risk values**
- **Allows comparison of these risks with other risks**
 - **That a stakeholder might tend to disregard**
 - **Or to strenuously avoid**
- **And comparisons of risk with known or uncertain benefits**

Probability of Causation

- For ERR and EAR pertaining to a particular cancer type diagnosed at a given age, following a given history of radiation doses at different exposure ages,

$$\text{ERR}/(1+\text{ERR}) = \text{EAR}/(\text{baseline} + \text{EAR})$$

is called the “attributable risk” or the proportion of total risk assigned to that history of exposure

Also called “assigned share” or “probability of causation” (PC) when applied to an individual

PC-based adjudication of compensation claims

- UK Nuclear workers (Wakeford, 1998)
 - Negotiated agreement between representatives of employers & employees
 - Sliding scale from full compensation at 50% PC to zero compensation for PC < 20%
 - Quant Uncertainty Analysis not used

NIH radio-epidemiological tables (NIH 1985, 2003)

- First use of QUA approach to evaluate significance of radiation exposure in risk estimation
- Used by DVA for claims by military veterans
- And for claims by employees of DOE & its contractors (EEOICPA)
- By law, key decision factor is value of 99th percentile of uncertainty distribution for PC:
is it greater than or equal to 50%?

Some dividends

- The 2003 NIH report replaced the 1985 Radio-Epidemiological Tables by an Interactive Radio-Epidemiological Program (IREP)
 - IREP uses site-specific RERF tumor registry data to calculate PC for arbitrary doses, radiation quality, exposure ages, age at cancer dx, etc.
 - Note: we can calculate age-specific EAR from PC:
 - $EAR = PC / (1 - PC) \times \text{baseline}$

The NCI RadRisk Program

- Interactive program based on IREP logic
- Estimates lifetime excess cancer risk as the life table-weighted sum of age-specific EAR values associated with a given exposure history
- Used by Berrington de Gonzales et al (2009) to estimate lifetime risk associated with CT screening
- Easily adapted to other uses

For example:

- Given detriment $\text{det}(c,a)$ (e.g., expected years of life lost) associated with dx of site-specific cancer \underline{c} at age \underline{a}
 - Life table probability $L(a)$ of living until age \underline{a} ,
 - and uncertain risk $R_e(c,a)$ of cancer \underline{c} at age \underline{a} associated with exposure history \underline{e}

- The sum over ages \underline{a} and cancers \underline{c} ,

$$\sum \sum \{L(a) \times R_e(c,a) \times \text{det}(c,a)\},$$

expresses the lifetime detriment from exposure history \underline{e}

A modest proposal

- Currently, radiation protection is based on risk, as mediated by effective dose.
- Programs like RadRisk can quickly and directly calculate lifetime detriment for arbitrary exposure histories
- Such programs can be expected to become much faster in the very near future
- Why not base radiation protection more directly on risk as calculated by modern computing practices?

- It would be a useful exercise for NCRP to explore how a more direct risk-based system would compare with the present one based on effective dose
- And to consider how uncertainty might be usefully incorporated into the process

- In radiation protection, the underlying uncertainty distribution for risk, or for detriment, will be interpreted in the context of other considerations, e.g., the likelihood of an immediate benefit from a radiation procedure vs. the likelihood of a later detriment

The goal is to provide improved, tested, timely, and more nuanced guidance for radiation protection, based on the best information available to us

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