The Needs of a "Customer" of Dose Reconstruction

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Needs of the Epidemiologist

- For this talk, the "customer" is the epidemiologist
  - or statistician analyzing epidemiologic data

- Other users of these doses may have different needs

Epidemiologic Studies of Persons Exposed to Radiation

- Japanese A-Bomb Survivor Studies
- Medical Radiation Studies
- Occupational Radiation Studies
- Environmental Studies

Why are We Doing These Studies?

- Develop the quantitative information needed to estimate risks from radiation exposure in other populations

- Increase our understanding of radiation carcinogenesis
  - How do dose-rate, dose protraction, LET, age, gender, and other risk factors affect risk?

Today's Studies

- Japanese A-bomb survivors
  - Premier study for quantifying risks from acute low-LET radiation
- Other studies address:
  - Dose-rate and protraction of dose
  - Risks from alpha emitters and I-131

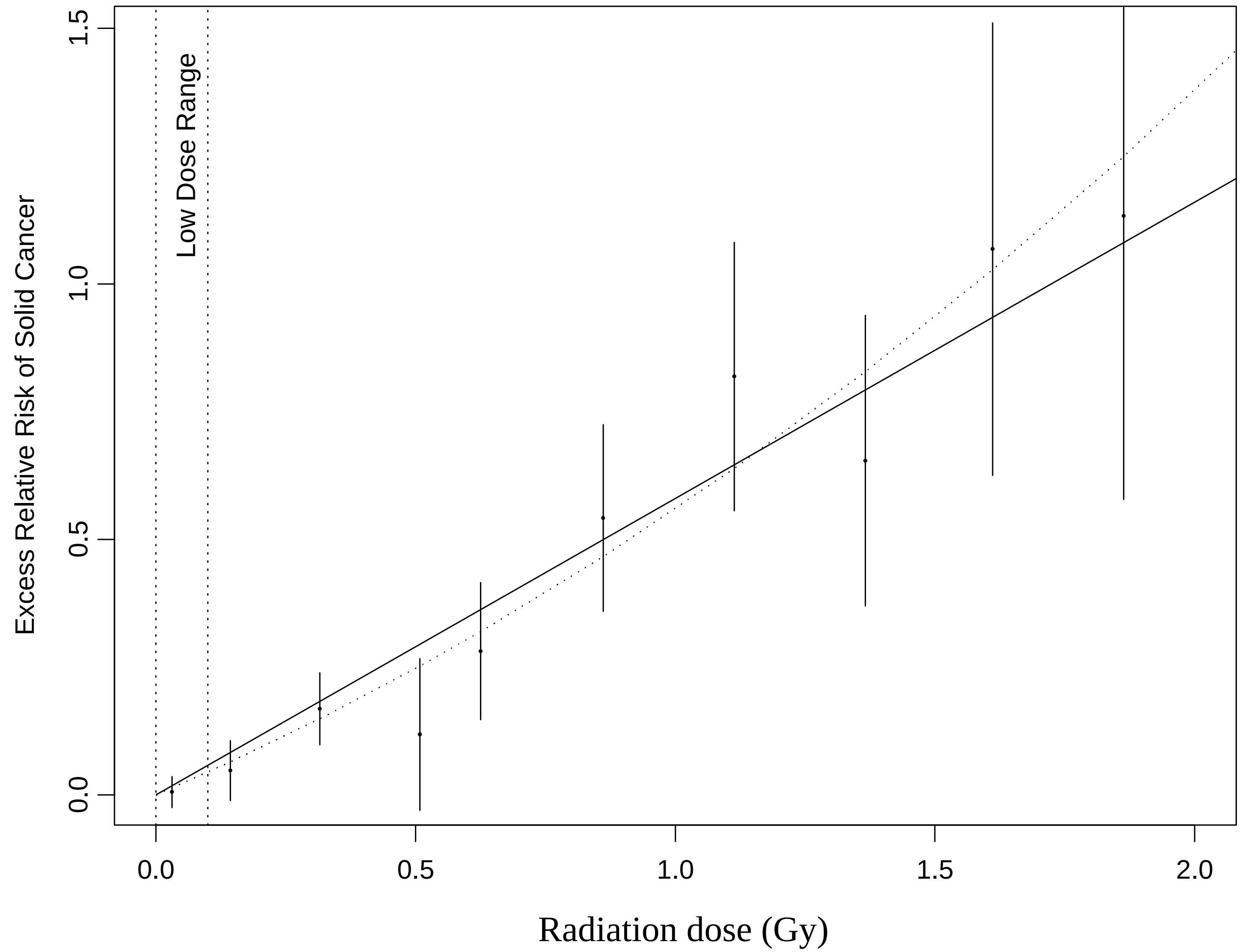
Role of Doses in Epidemiology

- Allow us to explore the dose-response relationship
  - Shape of dose-response
  - Quantify risk as a function of dose

- Linear (and linear-quadratic) dose-response plays important role in radiation epidemiology

- Relative risk = 1 + β dose where β is excess relative risk (ERR) per unit of dose

Japanese A-bomb Survivor Solid Cancer Incidence: Excess relative risk



Role of Doses in Epidemiology

- Allow us to investigate the modifying effects
  - Gender
  - Age at exposure
  - Dose-rate
  - LET

- Compare risks (ERR/Gy) across
  - Subgroups (male versus female etc.)
  - Studies (e.g., acute versus protracted exposure)

Excess Relative Risk (ERR) per Gy for Leukemia excluding CLL

15-country study nuclear worker study:
1.9 (< 0, 8.5)

A-bomb survivors*:

Linear	**3.2 (1.6, 5.7)**
Linear-quadratic	**1.5 (<0, 5.3)**

*Estimates for males exposed at ages 20-60

Cardis et al. 2005

Role of Doses in Epidemiology

- Allow analyses that combine data from several studies that address a common issue
- Examples:
  - Breast cancer in A-bomb and medical studies (Preston et al. 2002)
  - Thyroid cancer in A-bomb and medical studies (Ron et al. 1995)
  - Lung cancer in 11 cohorts of underground miners (BEIR VI 1999)
  - Nuclear workers in 15 countries

    (Cardis et al. 2005, 2007)

Pooled breast cancer incidence analyses

Cohort	Exposed cases	Mean dose (Gy)
Massachusetts fluoroscopy		
Original	71	1.0 (0.02 – 6)
Extension	49	0.7 (0.02 – 5)
New York mastitis	52	3.8 (0.6 – 14)
Rochester thymus	22	0.7 (0.02 – 7.5)
Benign breast disease	115	5.8 (0.02 – 50)
Gothenburg hemangioma	59	0.2 (0.02 – 22)
Stockholm hemangioma	97	0.5 (0.02 – 35)
A-bomb survivors	360	0.3 (0.02 – 5)
Total	**1502**	

Preston et al. 2002

Which dose or measure of exposure?

- Organ dose is usually best choice for epidemiology.
  - Most biologically relevant
  - Allows comparison of risks across studies, and types of exposure (e.g. alpha versus gamma)
  - Allows use of study results to predict risks in other populations

- Some exceptions
  - For example, use of Bq/m^3 in residential radon studies

Dosimetry Needs for Epidemiology

- Ideal: Unbiased estimates of organ dose
  - Rarely possible to be certain there is no bias

- Minimize differential bias
  - By disease status
  - By magnitude of dose
  - By subgroups (e.g. age, sex)
  - Across studies

Dose Measurement Uncertainties

- Dose estimates subject to uncertainties
- In most studies, dose estimation is retrospective
- Complex systems often needed to estimate dose

Possible Effects of Errors in Dose Estimates

- Reduction in statistical power for detecting dose-response relationships

- If errors not accounted for –
  - Bias in estimates of linear risk coefficients
  - Distortion of the shape of the dose-response function
  - Underestimation of uncertainty

Types of error

- Impact on dose-response analyses depends on distinctions between --
- Classical errors and Berkson errors
- Shared errors and Errors that are independent for different subjects

Classical Error (Measurement Error)

- Error that arises from an imprecise measuring device
- Error is independent of true dose
  (Estimated dose varies about true dose)
- Adjustment needed to avoid distortion of dose-response
- Variance of estimated doses larger than variance of true doses

Examples of Classical Errors

- Errors in readings of film badge dosimeters

- Errors in bioassay measurements used in estimating internal doses

- Errors in questionnaire data used in estimating doses

Berkson Error
(Grouping Error)

- Error that results when
  - Single mean dose used to represent group
  - Same model is used to estimate doses for a group

- Error is independent of estimated dose
  (True dose varies about estimated dose)

- Little distortion in linear dose-response
- Variance of true doses larger than variance of estimated doses

Shared Errors

- Also known as systematic errors

- Examples
  - Errors in the source term for an environmental exposure
  - Errors in doses assigned to groups of subjects
  - Errors in parameters of models used to convert measurements to doses

Statistical approaches for accounting for dosimetry uncertainties

What they can't do

- Improve power and precision of estimated risk coefficients

What they can do

- Avoid misleading results
- Correct biases in risk coefficients
- Widen confidence intervals to reflect dosimetry uncertainties

Statistical approaches for accounting for dosimetry uncertainties

- Maximum likelihood
- Regression calibration
- Multiple realizations

Full maximum likelihood

- **Regression model** : Relates disease to true dose
  - Linear relative risk model a common choice

- **Measurement model**: Relates estimated doses (z) to true doses (x)

- **Exposure model**: Specifies distribution of true doses (x)

Clayton 1990

Conditional maximum likelihood

- Start with full likelihood and integrate out true doses to form likelihood based on disease outcome and estimated doses

- Markov Chain Monte Carlo (MCMC) useful in performing computations

- Has been applied to data from European residential radon study (Fearn et al. 2008)

Regression Calibration

- Replace the estimated doses with
  E (true dose|estimated dose) = E(x|z)

- Easy to apply once have the E(x|z)

- Leads to unbiased estimates of linear risk coefficients.

- Limitations
  - An approximation for non-linear models
  - Uncertainty in risk estimates may be underestimated

Regression Calibration Examples

- A-bomb survivors (Pierce et al. 1990; 2009)
  - Increased slope by 10%
- European residential radon case-control studies
  (Reeves et al. 1998; Darby et al. 1998; Fearn et al. 2008)
  - Increased slope by 100%
- Colorado uranium miners (Stram et al. 1999)
  - Decreased magnitude of inverse exposure-rate effect

Multiple Realizations

- Use Monte Carlo methods to generate N realizations of the true doses based on observed data and assumptions about uncertainties

- Take account of correlations (shared errors)

- Berkson process

  "We take as our starting point a Berkson model …"
  (Stayner et al. 2007; Stram and Kopecky 2003)

  - Preliminary work needed to address classical error (regression calibration)

Multiple Realizations

- What do epidemiologists and statisticians do with the results?
- Maximum likelihood: Estimating likelihood function for each realization and then average
- Extremely computer intensive

Error Structure

- Identify sources of error
- Nature of the error from each source
  - Classical or Berkson?
  - Shared or unshared?
- Describe the magnitude and distribution of error from each source
  - Subjective judgments often required
- An uncertainty interval for the dose of each subject is not enough!

Dosimetry Uncertainties

- Increasingly, efforts are being made to take account of dosimetry uncertainties in epidemiologic studies
- Requires understanding of error structure
  - Lots of communication between dosimetrists and statisticians
- Accounting for dosimetry uncertainties in complex situations remains challenging

Examples where dose estimation errors have been taken into account

- **A-bomb survivors** (Pierce et al. 1996; 2008)
- **Residential radon exposure** (Reeves et al. 1998; Fearn et al. 2008)
- **Utah fallout study** (Thomas et al. 1999; Mallick et al. 2002; Li et al. 2007)
- **Underground miners** (Stram et al. 1999)
- **ORNL nuclear workers** (Stayner et al. 2007)
- **Hanford fallout study** (Stram and Kopecky 2003; Hoffman et al. 2007)
- **Tinea capitis patients** (Schafer et al. 2001; Lubin et al. 2004)
- **Chornobyl thyroid study** (Kopecky et al. 2006)

Summary:
Needs of the Epidemiologist

- **Unbiased estimates of organ dose**
- **Minimize differential bias by disease status, dose magnitude, subsets, or studies**
- **Collaboration of dosimetrists and statisticians needed**
  - **Particularly to address dose uncerta**inties