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 \( = 1 + \beta \) dose where \( \beta \) is excess relative risk (ERR) per unit of dose
Japanese A-bomb Survivor Solid Cancer Incidence: Excess relative risk

Excess Relative Risk of Solid Cancer

Radiation dose (Gy)
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)
## Pooled breast cancer incidence analyses

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

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/m³ 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
  \[ E(\text{true dose}|\text{estimated dose}) = E(x|z) \]

• 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 uncertainties