Exposure Assessment – Implications for Epidemiological Studies of Ionising Radiation

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Introduction

- Epidemiological studies of the health effects of ionising radiation exposure have often benefited from the availability of quantitative estimates of exposure

- However, for various reasons, the quality of these exposure estimates can vary

Some issues regarding exposure estimates

- Specific to individuals or generic values for groups?
- Missing for some individuals?
- Based on contemporary measurements or retrospective assessments?
- Represent surrogates of exposure?
- Based on exposure assessment models?
- Impact of uncertainties in exposure estimates?
- Impact of not considering all radiation sources?

Aims of presentation

- To illustrate ways in which ionising radiation exposures have been assessed, through reference to some epidemiological studies of childhood leukaemia

- To discuss the implications for the interpretation of radiation epidemiological studies

Examples of studies of ionising radiation & childhood leukaemia

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Environmental exposures

- Vicinity to nuclear installations
- Chernobyl – geographical & case-control studies

Medical exposures

- Prenatal obstetric x-rays – Oxford Survey of Childhood Cancers

Natural exposures

- Gamma radiation & radon – UK Childhood Cancer Study

Parental occupational exposures

- UK Record Linkage Study

Are exposure estimates specific to the individuals concerned?

- Some studies have compared leukaemia rates on the basis of generic measures of exposure, eg.
  - *proximity of communities or geographical areas to a nuclear installation*
  - *average doses in different parts of Europe due to the Chernobyl accident*

- However, within these areas, doses can vary
  - *potential for "ecological bias" associated with analysis of grouped data?*

Deriving individual-specific exposure estimates

- Often addressed via case-control studies, in which exposure estimates are derived specific to childhood leukaemia cases and matched controls, eg. by
  - *calculating proximity to a nuclear installation more precisely (Kaatsch et al, Int J Cancer, 2008)*
  - *calculating doses to children in Belarus, Russia & Ukraine due to the Chernobyl accident using information on their residence, diet, etc (Davis et al, Int J Epidemiol, 2006)*

Lack (or variability in form) of exposure estimates for some individuals?

- In questionnaire-based case-control studies, the parents of some children may decline to take part
  - *response bias would arise if the decision is related to both disease status & the child's level of exposure*
- May be possible sometimes to include such children with a surrogate measure of exposure
  - *but need to consider impact of differences between children in the form of exposure estimates*
- These issues should not arise in geographical studies based on generic measures of exposure

Potential impact of lack of exposure estimates for some individuals

- In the UK Childhood Cancer Study (*Br J Cancer, 2002*), radon measurements were made in the homes of 58% of interviewed cases and 49% of interviewed controls
  - *might the low response rates explain the decreasing trend in childhood cancer risk seen with increasing concentrations of indoor radon?*
- Factors associated with high radon levels, such as double glazing and central heating, were more prevalent in the controls' than in the cases' homes
  - *but adjusting for these factors did not change the main findings*

Use contemporary exposure measurements or assess exposures retrospectively?

- Since case-control studies are conducted after diseased cases have been identified, exposure estimates are usually assessed retrospectively

- However, possible problems with response bias and difficulties in reconstructing past exposures may be avoided if contemporary measurements are available for those in the study

Example of use of contemporary measurements

UK Record Linkage Study (*Draper et al, BMJ, 1997*)

- The UK National Registry for Radiation Workers was linked to national databases of childhood cancer cases and controls
- Aim: to look for any association between parental occupational radiation exposures (particularly those prior to conception) and the risk of childhood cancer in offspring
- Study made use of contemporary records of parental occupational exposures
- *Similar approaches could be valuable elsewhere*

Use of surrogate measures of exposure

- Sometimes, even when contemporary data are available, they may not provide a direct measure of exposure

- Example: In the Oxford Study of Childhood Cancers (*eg. Stewart & Kneale, Lancet, 1970*), the number of obstetric x-ray examinations and the number of x-ray films used in each examination may be insufficient to assess doses to the fetus, owing to wide variations in the dose per film

  – *need at least to take account of temporal variation in doses*

Use measurements to assess exposures retrospectively?

- Even when exposures are assessed retrospectively, this task can sometimes be achieved by making measurements
- Example: in the UK Childhood Cancer Study (*Br J Cancer, 2002*), measurements were made of gamma radiation and radon levels in homes occupied by childhood cancer cases and controls
- In such studies, need to consider whether these measurements are representative of past exposures – *should be of less concern for studies of diseases in childhood than in adulthood*

Use of exposure assessment models

- If measurement data are unavailable or insufficient by themselves to assess exposures, a modelling approach that incorporates measurement data, information from questionnaires, etc may be used

- Example: in studying Chernobyl fallout in Belarus, Russia & Ukraine, Davis et al (*Int J Epidemiol, 2006*) used, amongst other things,
  - *environmental measurements of external doses and caesium deposition*
  - *information from mothers on residential and dietary history (eg. consumption of milk)*

Use of exposure assessment models (continued)

- This approach is becoming more popular in radiation epidemiology
- However, here – as in other studies – it is important to assess the impact of errors in dose estimates
  - *eg. by placing probability distributions on the input parameters for the dose calculations and running multiple simulations*
- Since doses calculated using a model depend on common quantities, mis-specification of such quantities would lead to errors in doses that are shared across individuals – *not possible to draw generic conclusions about their impact*

"Berkson" measurement errors

- The true exposures are independently distributed around the assigned values
  - *eg. true doses from prenatal x-rays should be distributed around values assigned on the basis of numbers of x-ray films used, etc.*
- If they have zero mean and are independent of disease status, these errors would **generally** not bias the estimated trend in risk with exposure
  - *but they would increase the width of the confidence interval for the estimated trend (over and above the nominal value)*

"Classical" measurement errors

- Measured exposures are independently distributed around the "true" values
  - *eg. repeat radon measurements in the same house show considerable variability, reflecting both temporal and sampling variation*
- If they are independent of disease status, these errors tend to – **but do not always** - yield under-estimates (in absolute terms) of the trend in risk with exposure
  - *in addition, the uncertainty in the estimated trend would be under-stated*

References on dosimetric uncertainties in radiation epidemiology

- "Uncertainties in Radiation Dosimetry and Their Impact on Dose-Response Analyses" (eds. E Ron & FO Hoffman) – *NIH Publication 99-4541* (1999)
- Special issue of "*Radiation Research*" (July 2006) on dosimetry in radiation epidemiology
- More advanced: uncertainty analysis for epidemiological studies using a complex dosimetry system –*Stram & Kopecky* (*Radiat Res, 2003)*

Excluding other sources of radiation exposure

- Normally studies consider only one source of radiation
- However, this approach could be problematic if doses from natural or medical sources dominate those from the source under investigation
  - *eg. Simmonds et al (NRPB-R276, 1995) estimated that about 80% of the total dose to children and young people living in the village of Seascale, near the Sellafield nuclear plant in the UK, arose from natural radiation*

Excluding other sources of radiation exposure (continued)

- Need to be aware that different forms of ionising radiation may have different effects on health
  - *in particular, low and high Linear Energy Transfer (LET) radiations*

- However, even when considering low and high-LET radiations separately, assessed doses to children and young people in Seascale from natural sources still dominate those from operations at the Sellafield plant *(Simmonds et al, NRPB-R276, 1995)*

Concluding comments

- Many of the issues that affect exposure assessment in epidemiological studies of ionising radiation also affect studies of other agents
- There is no single "correct" way to undertake exposure assessment in ionising radiation epidemiology
  - *comparison of findings based on differing approaches may sometimes be useful*
- However, some approaches are preferable to others
  - *need to consider on a case-by-case basis*
  - *important to consider potential impact of exposure uncertainties*