Low-Dose Epidemiology Studies: Summary and Issues to Consider

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Overview of Talk

- Shape of dose-response curve
- Radiation-sensitive organs
- Age and radiation sensitivity
- Genetic risk
- Issues pertaining to low-dose studies
- Considerations regarding Ecological studies
- Alternative study designs and other issues
Shape of dose response for radiation-related cancer?
Potential Dose-Response Shapes

Scenario with a Subpopulation of Highly Sensitive Persons

Life Span Study (LSS) Cohort
(120,321 people)
LSS dose response: Solid-cancer incidence

- No evidence of non-linearity in the dose response
- Significant dose response on 0-150 mGy
- Low dose-range slope consistent with full range

![Graph showing dose response with linear fit and dose-threshold]

\[
\text{ERR/Gy} = 47\% \ (95\% \text{CI: } 40-54\%)
\]

Dose-threshold: 40 mGy

(CI: <0, 85 mGy)

Which organs are at risk of radiation-related cancer?

Note; Estimates standardized to age 70 after exposure at age 30 and averaged, where appropriate, over gender.

(Ozasa, Shimizu et al, Unpublished, 2010)
## Radiation-sensitive Cancers

**A-bomb survivors**
- Total solid cancer
- Oral cavity
- Esophagus
- Stomach *
- Colon
- Liver *
- Gallbladder
- Lung *
- Breast (F) *
- Ovary
- Bladder *
- Brain, CNS *
- Thyroid *
- Leukemia *

**Jablon – Other malignancies studied**
- All malignancies except leukemia
- Hodgkin disease
- Other lymphoma
- Multiple myeloma
- Colon & rectum
- Any digestive organ
- Bone and joint

* Malignancies also considered by Jablon et al, 1991.
Age-related characteristics of radiation-cancer risk?
Excess Rates of Solid Cancer Mortality by Age at Exposure and Attained Age

(Ozasa, Shimizu et al, Unpublished)
Special Groups and Outcomes to Target

- **Most radiosensitive sites:**
  - Leukemia
  - Female breast cancer
  - Thyroid cancer
  - Bladder cancer

- **Most radiosensitive groups:**
  - Exposed in childhood
  - *Childhood leukemia*
How large is the risk to offspring from parental gonadal irradiation?
To date, the frequencies of cancer and other diseases in the offspring are unrelated to parental radiation dose, but 20-30 more years of follow-up are needed to provide definitive evidence.
Considerations Pertaining to Low-Dose Epidemiologic Studies
Sample Size Needed to Study Various Doses, Lifetime Risk

For 10 or 20 independent endpoints and $p = 0.05$:

- Probabilities of at least 1 “statistically significant” result purely by chance are 40% and 64%, respectively.

- Probabilities of at least 2 are 9% and 26%, respectively.
Low-Dose Studies: Bias

- The potential impact of unmeasured confounding variables is often greater in a low-dose study, because the magnitude of confounding may approach or exceed the magnitude of the dose effect.
Lifestyle-related variables may have considerable potential for confounding
- Smoking, alcohol, healthful diet, exercise, etc
- Crude surrogate may be socioeconomic status

Other radiation exposures – e.g., diagnostic medical exposures

Race/ethnicity – distribution may change over time

Effects of the covariates
- These can create bias, i.e., erroneous risk estimates that either exaggerate or nullify the true degree of association
- They also can create statistical “noise” in the dependent variable (health outcome rates) to make the analysis less precise.
Considerations Regarding Ecological Studies
Selection of Unexposed Groups by Jablon, 1991

- Jablon-Boice criteria:
  - % ethnicity distribution
  - % urban/rural
  - % employed in manufacturing
  - % high school graduates
  - Mean family income
  - Net migration rate
  - Infant death rate
  - Population size
  - Same region of country

- Notes:
  - Criteria based on only one time point (1979-1980)
  - Criteria represent averages for an entire county
Issues with “Ecological” Studies

- Can produce erroneous exposure-related differences

  - Due to “ecologic bias” (other related terms: group-level confounding, cross-level bias)
  
  - It may help to use the finest geographic units for which potential confounder information is available, to better adjust for confounding by having more **homogeneity within units**
Ecological Study of Cancer Incidence

- Cancer incidence – issues
  - Length of time incidence data are available
  - Quality of registries

- What level of address detail can be gotten from the tumor registries?
  - This will impact feasibility of using finer geographic units

- Do we aim for county, zipcode, census tract, geographic ring, etc?
  - How do we define “near” to the facility in a way that is relevant to exposure levels?

- We need to use geographic units which have basic sociodemographic data available historically (preferably back to 1950)
Are there feasible alternatives to a simple ecological study design?

- **Before and After ecological study of nuclear facilities**
  - Can help adjust for baseline rates associated with population characteristics, but if siting a nuclear plant in an area changes the population composition, then the comparison may be confounded unless the characteristics can be adjusted for.
  - Issue of new-population mixing – Leo Kinlen

- **Case-control study design?**
  - Difficult to do: over ~120 plant facility sites, and cases go back in time >30 years

- **Spatial clustering study?**
  - Requires very fine-grained historical geographic information on population density
Other Issues

- **Exposures received at the nuclear plant vs. in the residential environment**

- **Medical screening – surveillance bias and disease detection**
  - May be an issue because a fraction of people in the “exposed” geographic areas work at the nuclear plant and receive extra radiographic screening at work or through their health plan
  - Especially a problem for cancers with high surveillance detection – e.g., prostate, thyroid
Thank You