Introduction to Principles of Epidemiology Applicable to Radiation Epidemiology

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DCEG Radiation Epidemiology and Dosimetry Course 2019
Objective

Provide a brief overview of epidemiologic concepts, study design, and study components pertinent to radiation epidemiology
Outline

- Epidemiology: history & definitions
- Descriptive patterns
- Disease models and causation
- Exposures & outcomes: sources and assessment methods
- Study designs
- Confounding, effect modification, bias
Epidemiology

A scientific discipline that provides quantitative information about human health risks associated with specific exposures
History and Definitions
# History of epidemiology

<table>
<thead>
<tr>
<th>Pre-formal Epidemiology</th>
<th>Formal epidemiology: infectious diseases</th>
<th>Formal epidemiology: chronic diseases</th>
<th>Post-modern epidemiology (Rothman)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippocrates</td>
<td>Frost</td>
<td>Lane-Claypon</td>
<td>Sophisticated exposure &amp; outcome</td>
</tr>
<tr>
<td>Graunt</td>
<td>Langmuir</td>
<td>Hill</td>
<td>assessment, statistical modeling</td>
</tr>
<tr>
<td>Louis</td>
<td>Francis</td>
<td>Doll</td>
<td>Electronic linkages</td>
</tr>
<tr>
<td>Farr</td>
<td>Henderson</td>
<td>MacMahon</td>
<td>Genomics, other ‘omics’</td>
</tr>
<tr>
<td>Snow</td>
<td></td>
<td>Lilienfeld</td>
<td>Pathology &amp; clinical</td>
</tr>
<tr>
<td>Koch</td>
<td></td>
<td>Fraumeni</td>
<td>&gt; deep learning</td>
</tr>
<tr>
<td>Lind</td>
<td></td>
<td>Susser</td>
<td>&gt; artificial intelligence</td>
</tr>
</tbody>
</table>
<pre><code>                                       |                                          | Willett                              | Consortia                        |
                                       |                                          |                                      | Prevention                        |
                                       |                                          |                                      | Clinical translation              |
</code></pre>
What is epidemiology?

- The study of the distribution of a disease or conditions in human populations and the factors that influence the distribution

- **Who**: Populations
- **What**: Risk factors for disease
- **When**: Temporal aspects
- **Where**: Geographical distribution
- **How**: Methods, mechanisms, biology
What is epidemiology?

- The study of the distribution of a disease or conditions in human populations and the factors that influence the distribution

Who: Populations

What: Risk factors for disease

When: Temporal aspects

Where: Geographical distribution

How: Methods, mechanisms, biology
Populations

- Groups of persons that may be at higher or lower risk of developing a disease(s) or condition(s) due to an agent or substance presumed to be causal
  - Cohorts: exposed vs unexposed/low-level exposure
  - Cases vs. controls

Examples of radiation-exposed populations
**What is epidemiology?**

- The study of the distribution of a disease or conditions in human populations and the factors that influence the distribution

**Who:** Populations

**What:** Risk factors for disease
  - Exposures
  - Outcomes

**When:** Temporal aspects

**Where:** Geographical distribution

**How:** Methods, mechanisms, biology
Exposures

- Agents or substances presumed to be causal of a disease or event (exposure surrogate is a factor indicating exposure potential, *e.g.*, job title)

‘Exposures’ include radiation, pesticides, obesity, cigarettes
Outcomes

- Diseases, conditions, precursors to diseases or conditions

Radiation-related adverse outcomes include most cancers, cataracts, heart disease, and probably leukemia precursors such as myelodysplastic syndromes.
What is epidemiology?

- The study of the distribution of a disease or conditions in human populations and the factors that influence the distribution

Who: Populations

What: Risk factors for disease
  > Risk factor relationships
  > Risk measures

When: Temporal aspects

Where: Geographical distribution

How: Methods, mechanisms, biology
Correlation, Association, Causation

- **Correlation**: the degree to which variables change together (no direction assumed)

- **Association**: a disease occurs more (or less) frequently in the presence of an exposure than in its absence & varies by exposure level

- **Causation**: in an individual, an exposure caused a given disease; within a population, at least some cases of the disease would not have occurred in the absence of the exposure
Measures of risk

Definitions

- **Risk**: the probability of disease developing in a population in a specified time interval

- **Relative risk or risk ratio (RR)**: a measure of the risk of a certain event happening in one group compared to the risk of the same event happening in another group; the incidence/mortality of disease in an exposed group divided by the incidence/mortality of disease in a non-exposed group

Examples

- If RR = 1.0, then no difference between the two groups

- If RR >1.0, then being exposed to a certain substance or factor increases the risk of cancer

- If RR <1.0, then being exposed to a substance/factor decreases the risk of cancer
Other measures of risk

- **Attributable risk:** the maximum proportion of a disease attributable to a given exposures

- **Absolute risk:** the observed or calculated probability of occurrence of an event in a population related to a specific exposure

  Example: Among patients treated with a specific agent at ages 5-10 and followed up through age 75, four percent will develop cardiac insufficiency
Descriptive Patterns & Trends and Disease Classification
Descriptive epidemiology: Rationale for study

Why study disease patterns and trends?

- Explain occurrence (temporal, geographic) and natural history
- Provide guidance for health services: identify susceptible populations
- Suggest hypotheses to elucidate causal inferences and mechanisms
What is epidemiology?

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* Descriptive epidemiology frequently involves factors in addition to temporal aspects
Rates

**Rate**: a measure of change in a quantity per unit time

- **Incidence**: the total number of new-onset disease events divided by the total person-time at risk during a given period of time

- **Mortality**: the total number of deaths from a disease divided by the total person-time at risk during a given period of time
Disease classification: purpose

What is the purpose of disease classification?

- Group ill persons into categories to distinguish one category from another
- Arrange diseases into groups with common characteristics
Disease classifications internationally used

International Classification of Diseases (ICD)
- Anatomic site
- Periodically modified to reflect ↑knowledge (currently ICD-10)

International Classification of Diseases for Oncology (ICD-O)
- Two major categories: morphology and topography (anatomic site)
- Latest revision includes clinical, immunological, treatment-related and molecular characteristics of some neoplasms (ICD-O-3)

Specialty classifications
- Example: International Classification of Childhood Cancer
<table>
<thead>
<tr>
<th></th>
<th>International Classification of Childhood Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.</td>
<td>Leukemia</td>
</tr>
<tr>
<td>II.</td>
<td>Lymphomas and reticuloendothelial neoplasms</td>
</tr>
<tr>
<td>III.</td>
<td>CNS and other intracranial and intraspinal neoplasms</td>
</tr>
<tr>
<td>IV.</td>
<td>Sympathetic nervous system tumors</td>
</tr>
<tr>
<td>V.</td>
<td>Retinoblastoma</td>
</tr>
<tr>
<td>VI.</td>
<td>Renal tumors</td>
</tr>
<tr>
<td>VII.</td>
<td>Hepatic tumors</td>
</tr>
<tr>
<td>VIII.</td>
<td>Malignant bone tumors</td>
</tr>
<tr>
<td>IX.</td>
<td>Soft tissue sarcomas</td>
</tr>
<tr>
<td>X.</td>
<td>Germ cell, trophoblastic, &amp; other gonadal neoplasms</td>
</tr>
<tr>
<td>XI.</td>
<td>Carcinomas &amp; other malignant epithelial neoplasms</td>
</tr>
<tr>
<td>XII.</td>
<td>Other and unspecified malignant neoplasms</td>
</tr>
</tbody>
</table>
Childhood Cancer Statistics - USA

Total childhood cancers ages 0-19

- 15,590 estimated annual incident cases
- 1,780 estimated annual deaths
- 5-yr survival 78%

Data shown in figure from NCI SEER program:
Howlader N, Noone AM, Crapcho M et al. SEER Cancer Statistics Review, 1975-2016, National Cancer Institute, Bethesda, MD
https://seer.cancer.gov/csr/1975_2016 based on November 2018 SEER data submission,
Posted to the SEER web site, April 2019
## Childhood cancer risks vary by type and subgroup

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Subgroup</th>
<th>↑ Risks by subgroup &amp; cancer type</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Age</td>
<td>infancy</td>
<td>neuroblastoma, CNS, leukemia, retinoblastoma</td>
</tr>
<tr>
<td></td>
<td>adolescence</td>
<td>Hodgkin lymphoma, germ cell cancers, CNS, leukemia</td>
</tr>
<tr>
<td>- Gender</td>
<td>male</td>
<td>lymphoma</td>
</tr>
<tr>
<td>- Race</td>
<td>Caucasian</td>
<td>Ewing’s sarcoma, acute lymphoblastic leukemia</td>
</tr>
<tr>
<td></td>
<td>African-American</td>
<td>Wilms’ tumor, retinoblastoma</td>
</tr>
<tr>
<td></td>
<td>African</td>
<td>endemic Burkitt’s lymphoma</td>
</tr>
</tbody>
</table>
Trends in U.S. Childhood Cancer Incidence

- Incidence rose about 0.7% per year for all childhood cancers, 1975-2016
- Rate of increase was lower (e.g., 0.2% per year) during 1990-2006, but rose more rapidly after 2006
- Mortality steadily declined since chemotherapy introduced in 1960s, but decrease has leveled off

Data shown in figure from NCI SEER program:
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When: Temporal aspects

Where: Geographical distribution

How: Methods, mechanisms, biology
Geographic (and Population) variation in incidence

- **Background disease rates** in a geographic area and population are important for interpretation and extrapolation
  - Japanese atomic bomb survivors: low background rates of female breast cancer and chronic lymphocytic leukemia
  - African-Americans: low background rate of childhood leukemia

Endemic (background) vs epidemic

- **Endemic or background rates:** usual incidence of a given disease within a defined geographic area
- **“Epidemic:”** excess occurrence of a group of illnesses of a similar nature in a defined area
  - Thyroid cancers in young persons in Belarus after the Chernobyl accident
  - Breast cancer in Hodgkin lymphoma survivors following radiotherapy
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Why: Rationale for methods used
- Disease models
- Natural history
- Association vs. causation

How: Methods, mechanisms, biology
Disease Models
Dynamics of infection and disease

Dynamics of Infectiousness
- Time of infection
  - susceptible
  - latent period
  - infectious period

Infection status
- no organism
  - no sequelae
- sequelae
  - chronic infection

Dynamics of Disease
- susceptible
- incubation period
- symptomatic period

Outcome
- recovered
- chronic disease
- deceased

Dynamics of exposure and chronic disease

Lung cancer as an example

- Smoking
- Radiation
- Specific genes

Incompletely understood carcinogenic mechanisms

Effect modifiers: Sex, SES, Asbestos

Lung Cancer
Natural history
Steps in Malignant Transformation

Figure showing steps in initiation, promotion, and progression for DNA-damaging agents such as radiation
Natural History of Chronic Disease

- Time periods vary among different steps in process
- Time periods may vary for different exposures and different outcomes

Figure showing steps from pre-disease state through pre-clinical then clinical manifestations to resolution, chronicity or death
Dynamics of exposure and chronic disease

Lung cancer as an example

- Smoking
- Radiation
- Specific genes

Incompletely understood carcinogenic mechanisms

Effect modifiers: Sex, SES, Asbestos

Lung Cancer
Diseases with Familial Occurrence

- **Familial occurrence**
  - Rare diseases that are common within affected families (X-linked lymphoproliferative syndrome)
  - Rare genetic syndrome with multiple cases of different phenotypes within affected families (Li-Fraumeni)
  - Small increase in risk within families (sibs with childhood leukemia)

- **Age at onset sometimes notably younger than for sporadic cases**
Genetic vs environmental components of disease

<table>
<thead>
<tr>
<th>Study goal: to identify</th>
<th>Study type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial clustering</td>
<td>Family aggregation</td>
</tr>
<tr>
<td>Genetic vs environmental</td>
<td>Twin/adoption/half-sibling/migrant studies</td>
</tr>
<tr>
<td>Mode of inheritance</td>
<td>Segregation analysis</td>
</tr>
<tr>
<td></td>
<td>- single gene</td>
</tr>
<tr>
<td></td>
<td>- multiple genes</td>
</tr>
<tr>
<td>Disease susceptibility loci</td>
<td>Linkage analysis</td>
</tr>
<tr>
<td>Disease susceptibility markers</td>
<td>Association studies</td>
</tr>
<tr>
<td></td>
<td>- population-based</td>
</tr>
<tr>
<td></td>
<td>- family-based (trios)</td>
</tr>
</tbody>
</table>

Pictures of pedigree (top left), twins (mid-left), comparative migration (bottom left), and heat map of genes & other (top right)
Genetic and other molecular population association studies

- Genetic population-based association studies
  - Genotypes: genome-wide association studies (Next Generation Sequencing studies)
    - Germline
    - Somatic
  - Other gene-related
    - RNA
    - Gene expression → metabolic pathways
- Epigenetics: DNA, RNA methylation
- Other molecular studies: O’mics
  - Proteomics
  - Metabolomics

Pictures of single nucleotide polymorphisms (SNPs) (top left), epigenetics (lower left), and global gene expression regulatory network (lower right)
Biology and mechanisms: Radiation carcinogenesis

- **Hallmark of radiation damage**
  - DNA double strand breaks (DSB)
  - Clustered complex lesions
  - DNA repair processes
    - non-homologous end-joining (NHEJ): error prone, can lead to chromosome aberrations
    - homologous recombination (HR): error free

- **Non-targeted effects**
  - Effects in tissues far from ‘in-field radiation’
  - Genomic instability: manifests after several generations of cell division

Pictures showing direct (targeted) and bystander (non-targeted) effect (top) and DNA double-strand break (bottom)
Statistical Association versus Disease Causation
**Statistical Association**

**Definition:*** Statistical dependence between two or more events, characteristics or other variables. An association is present if the probability of occurrence of an outcome, depends upon the occurrence of one or more exposures or characteristics.

*A statistical association does not imply causation*

## Criteria for causation

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength</td>
<td>Level of risk</td>
</tr>
<tr>
<td>Consistency</td>
<td>Repeatedly observed in different populations</td>
</tr>
<tr>
<td>Specificity</td>
<td>“If...limited to specific workers and to specific types of disease...then clearly that is a strong argument in favor of causation”</td>
</tr>
<tr>
<td>Plausibility</td>
<td>“What is biologically plausible depends on the biological knowledge of the day”</td>
</tr>
<tr>
<td>Coherence</td>
<td>“…the cause and effect interpretation... should not...conflict with the...known... natural history and biology of the disease”</td>
</tr>
<tr>
<td>Experiment</td>
<td>“Occasionally is it possible to appeal to experimental or semi-experimental evidence?”</td>
</tr>
<tr>
<td>Analogy</td>
<td>“With the effects of thalidomide and rubella before us we would surely be ready to accept slighter but similar evidence with another drug or another viral disease in pregnancy”</td>
</tr>
</tbody>
</table>

Types of causal associations

Common Cause:
- Radiation

Different outcomes
- Leukemia
- Cataracts

Different Causes
- Ultraviolet radiation
- Ionizing radiation

Common outcome
- Cataracts
Causal model - necessary vs sufficient

- **Necessary:** must be present to cause disease  
  (more common with infections: HIV → AIDS)
- **Sufficient:** can independently cause disease  
  (acute administration of 20 Gray whole body radiation)

<table>
<thead>
<tr>
<th>Necessary (+ or -)</th>
<th>Sufficient (S+)</th>
<th>Not sufficient (S-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Necessary (N+)</td>
<td>N+S+ (necessary &amp; sufficient)</td>
<td>N+S- (necessary but not sufficient)</td>
</tr>
<tr>
<td>Not necessary (N-)</td>
<td>N-S+ (sufficient but not necessary)</td>
<td>N-S- (neither necessary nor sufficient)</td>
</tr>
</tbody>
</table>

Example: smoking is neither a necessary or sufficient cause of lung cancer
Causal model: Types of non-causal associations

- **Chance association**

- **Bias may result in spurious associations**
  - **Selection bias** (differential selection or participation of exposed vs. unexposed or controls vs. cases)
  - **Recall bias** (differential recall by exposed vs. unexposed or controls vs. cases)
  - **Confounding** (association of disease and an exposure with a third variable may introduce spurious associations)
Multi-factorial disease causation

<table>
<thead>
<tr>
<th>Individual-level factors</th>
<th>Societal factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Sex</td>
<td>▪ Neighborhood</td>
</tr>
<tr>
<td>▪ Race/ethnic group</td>
<td>▪ Cultural</td>
</tr>
<tr>
<td>▪ Lifestyle, behavioral</td>
<td>▪ Economic</td>
</tr>
<tr>
<td>▪ Environmental</td>
<td>▪ Social</td>
</tr>
<tr>
<td>▪ Occupational</td>
<td>▪ Environmental</td>
</tr>
<tr>
<td>▪ Medical</td>
<td></td>
</tr>
<tr>
<td>▪ Genetic predisposition</td>
<td></td>
</tr>
</tbody>
</table>
What is epidemiology?

- The study of the distribution of a disease or conditions in human populations and the factors that influence the distribution.

  Who: Populations
  What: Risk factors for disease
  When: Temporal aspects
  Where: Geographical distribution

Why: Rationale for methods used
- Disease models
- Natural history
- Association vs. causation

How: Methods, mechanisms, biology
METHODS
Epidemiologic Study Designs
Cohort studies

- **Distinguishing features**
  - population defined by exposures prior to onset of disease
  - population followed over time to estimate disease/death rate
  - compare rates in exposed vs unexposed groups
    or internal comparison (zero or low-level exposure)

- **Retrospective vs prospective follow-up***

  * Retrospective follow-up is by far the most common method used in cohort studies; if high quality methods are used and care is taken, this approach can be just as methodologically sound as a prospective approach
Follow-up: Multiple axes of time

- 1900 born
- 1915 starts smoking
- 1920 start follow-up
- 1940 stops smoking
- 1950 dies from lung cancer

Follow-up time (years)

Age (years)
Case-Control Studies

- **Definition:** compare proportion with exposures in diseased cases vs controls

- **Study base:** composed of population at risk of exposure during period of risk of exposure; cases and controls should emerge from same study base & have same exposure opportunity

- **Associations identified from case-control studies:** smoking and lung cancer; DES and vaginal adenocarcinoma; post-menopausal estrogen and endometrial cancer

- **Nested case-control studies:** composed of cases identified from a cohort compared to a random sample or matched controls from the same cohort: Chronic lymphocytic leukemia compared with leukemia excluding chronic lymphocytic leukemia in Chernobyl clean-up workers
Case-Control Studies

- **Distinguishing features**
  - determine exposures prior to diagnosis/referent date using interviews, medical records or other records
  - compare proportion of cases with exposure to proportion of controls with exposure
  - estimate risk using odds ratio $= \frac{a \times d}{b \times c}$

- **Framework**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>With disease</th>
<th>Without disease</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>With exposure</td>
<td>$a$</td>
<td>$b$</td>
<td>$a + b$</td>
</tr>
<tr>
<td>Without exposure</td>
<td>$c$</td>
<td>$d$</td>
<td>$c + d$</td>
</tr>
<tr>
<td>Total</td>
<td>$a + c$</td>
<td>$b + d$</td>
<td>$a + b + c + d$</td>
</tr>
</tbody>
</table>
Cross-Sectional Studies

- Not used much in radiation epidemiology except dosimetry studies

- Study types
  - compare exposures of radiation-exposed groups at a given point in time: problematic without considering earlier exposures, age first exposed, sex, age last exposed, and many other factors
  - compare proportion of cases with exposure to proportion of controls with exposure at the time of the study: problematic without considering earlier exposures, age first exposed, sex, age last exposed, and many other factors
METHODS
Sources of exposure data, strategies for exposure assessment, and types/sources of associated error
 Sources of exposure information

- **Measurements**
  - Group: air levels
  - Individual
    - External: badge
    - Internal: blood

- **Questionnaires**
  - Medical history
  - Work history

- **Medical records**

- **Administrative records**
  - birth certificates
  - job records

Pictures of ground radiation monitor (upper left), CT scanner (lower left), radiation badge (upper right) and questionnaire (immediately above)
## Strategies for exposure assessment

<table>
<thead>
<tr>
<th>Strategies for exposure assessment</th>
<th>Component</th>
</tr>
</thead>
</table>
| **Definition**: Process of estimating magnitude, frequency, and duration of exposure to an agent | - Who is exposed?  
- Agent location: air, water, skin, other  
- Intensity, frequency, duration |
| **Exposure pathway** | Source to receptor |
| **Exposure route** | - Inhalation  
- Ingestion  
- Skin |
| ‘Direct’ measurements | - Personal sampling  
- Biological sampling |
| Surrogate measurements | Job title, residence general location |
## Types and sources of exposure measurement error

<table>
<thead>
<tr>
<th>Types/sources of error</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical measurement error</td>
<td>Random error in dose measurement</td>
</tr>
<tr>
<td>Berkson measurement error</td>
<td>Error when the mean for a group is substituted for the individual dose</td>
</tr>
<tr>
<td>Shared error</td>
<td>Error when incorrect group mean is assigned to all individuals in group</td>
</tr>
<tr>
<td>Differential error</td>
<td>Dose estimation error that is not independent of case status</td>
</tr>
<tr>
<td>Non-differential error</td>
<td>Dose estimation error independent of case status</td>
</tr>
<tr>
<td>Missing dose</td>
<td>Doses of subjects not accounted for in dose-response analyses</td>
</tr>
</tbody>
</table>
METHODS
Sources of outcome data, strategies for ascertaining outcomes, and types/sources of associated error
Sources of Outcome Information

- **Vital records**
  - death certificates
  - birth certificates

- **Morbidity surveys**
  - Health Interview Survey
  - Health Examination Survey

- **Disease notification & registration**
  - Cancer registries
  - Infection notification
  - Electronic medical records

Pictures of death certificate template (left) and medical Record release form (right)
## Strategies for outcome assessment

<table>
<thead>
<tr>
<th>Strategies for outcome assessment</th>
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</tr>
</thead>
</table>
| **Definition**: Process of ascertaining disease outcomes in study populations (e.g., in exposed and comparison cohorts and target population(s) for case-control studies) | - Cohort studies: comprehensive follow-up; linkage with outcome sources, questionnaires, surveys, and other databases to achieve complete ascertainment  
- Case-control studies: multiple sources of outcomes (hospitals, clinics, national/regional healthcare organizations, health maintenance organizations) |
| **Specific outcome(s) to be evaluated** | - Mortality vs. incidence or both  
- Specific diseases |
| **Disease classification** | - International classification of diseases (ICD) revision(s)  
- International classification of diseases for oncology (ICD-O) revision(s)  
- Special classifications |
## Types and sources of outcome assessment error

<table>
<thead>
<tr>
<th>Types/sources of error</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss to follow-up (LTF)</td>
<td>Usually due to re-location and loss of contact, discontinued participation; date of LTF can be known or unknown</td>
</tr>
<tr>
<td>Under-ascertainment</td>
<td>Outcomes not identified or misclassified as another condition</td>
</tr>
<tr>
<td>Over-ascertainment</td>
<td>May occur due to screening, or a precursor is identified as the outcome</td>
</tr>
<tr>
<td>Misclassification</td>
<td>Incorrect classification</td>
</tr>
<tr>
<td>Changes in classification over time</td>
<td>Generally increased specificity of histologic/molecular subtypes</td>
</tr>
</tbody>
</table>
METHODS

Confounding
Selection bias
Recall bias
Confounding, selection bias, recall bias

<table>
<thead>
<tr>
<th>Sources of potential bias: definitions</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Confounding</strong>: comparison groups may differ from exposed groups (cohort studies) or from the cases (case-control studies) by factors related to the disease of interest</td>
<td>A population exposed to occupational radiation may undergo more diagnostic imaging exams than the comparison group; smoking</td>
</tr>
<tr>
<td><strong>Selection bias</strong>: comparison groups may differ from exposed groups (cohort studies) or from the cases (case-control studies)</td>
<td>Controls may be of higher SES than the case-group in case-control studies</td>
</tr>
<tr>
<td><strong>Recall bias</strong>: comparison groups may inaccurately recall more or less than comparable exposed groups (cohort studies) or the cases (case-control studies)</td>
<td>Mothers of children with pediatric leukemia may have enhanced recall of pesticide exposures in pregnancy than mothers of control children</td>
</tr>
</tbody>
</table>
Radiobiology and mechanisms: Key adjuncts to epidemiology

- **Limits of epidemiology, an observational science**
  - Rare outcomes, population size limits, uncertainties, bias
  - Generally consistent exposure-response at moderate-to-high radiation doses, but inconsistent at low (<100 milligray) doses
  - Need for extrapolation from moderate-to-high to low doses (LNT model)

- **Experimental studies**
  - Control dose, dose-rate, timing, population size, species
  - Evaluate effect modification, risks in susceptible subgroups
  - Lifetime follow-up is shorter in animal models

- **New approach needed**
  - Combined approach: biologically-based dose-response models

Combine radiation epidemiology and radiobiology

- New combined approach needed: biologically-based dose-response models that incorporate:
  - Sophisticated exposure assessment with fully validated exposure biomarkers
  - Multiple approaches/data sources for complete follow-up and outcome ascertainment
  - Knowledge of multi-factorial disease causation
  - Efforts to identify effect modifiers and susceptible subgroups
  - Efforts to fully address potential confounders
  - Quantitative mechanistic data into biologically-based disease models
  - Biomathematical disease models

- Future research is needed to identify:
  - Adverse outcome pathways
  - Key events on the pathways

- Objectives: risk protection measures and risk prevention
Summary - 1

- Epidemiology: history and definitions
- Descriptive patterns and trends
- Disease classifications
- Disease models
- Natural history
- Statistical association vs disease causation
Summary - 2

- Epidemiologic study designs: cohort, case-control and cross-sectional studies

- Sources of exposure data, strategies for exposure assessment, and associated errors

- Sources of outcome data, strategies for outcome assessment, and associated errors

- Confounding, selection bias, recall bias

- Radiobiology and mechanisms
References


Questions

What is the definition of relative risk?

1. The maximum proportion of a disease attributable to a given exposures
2. The risk of a certain event happening in one group compared to the risk of the same event happening in another group
3. The observed or calculated probability of occurrence of an event in a population related to a specific exposure
4. The change in a quantity per unit time
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Which one is not a criterion for causation?

1. Plausibility
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- Which one is not a distinguishing feature of cohort studies?

1. Compare proportion of cases with disease with exposure to proportion of controls with exposure
2. Population defined by exposures prior to onset of disease
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