Outline

• Introduction to epidemiology: history & definitions
• Descriptive patterns
• Disease models and causation
• Sources of exposure & outcome information
• Study designs
• Introduction to radiation epidemiology
Epidemiology: A scientific discipline that provides quantitative information about human health risks associated with specific exposures
History and Definitions
History: Epidemiology from 1850 - present

Pre-formal Epidemiology
Hippocrates
Graunt
Louis
Farr
Snow
Koch
Lind

Formal epidemiology: infectious diseases
Frost
Langmuir
Francis
Henderson

Formal epidemiology: chronic diseases
Lane-Claypon
Hill
Doll
MacMahon
Lilienfeld
Fraumeni
Susser
Willett

Post-modern epidemiology
Rothman
Consortia studying
- risk factors for many diseases
- genomics (GWAS, The Cancer Genome Atlas)

Modified from AJ McMichael, 2005
Key definitions

• **Epidemiology**: the study of the distribution of a disease or conditions in human populations and the factors that influence the distribution

• **Endemic**: usual prevalence 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
Exposure and Outcomes

- **Exposure**: an agent or substance presumed to be causal of a disease or event (exposure surrogate is a factor indicating exposure potential, e.g., job title)

- **Outcome**: a disease or precursor to a disease
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
Measures of Risk

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

  - **Relative risk**: the incidence of disease in an exposed group divided by the incidence of disease in a non-exposed group.

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

  - **Absolute risk**: the observed or calculated probability of occurrence of an event in a population related to a specific exposure.
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
Descriptive Patterns & Trends and Disease Classification
Descriptive Epidemiology

Why study disease patterns and trends?

• Explain occurrence and natural history
• Provide guidance for health services
• Suggest hypotheses to elucidate causal inferences and mechanisms

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
International Classification of Childhood Cancer

I. Leukemia
II. Lymphomas and reticuloendothelial neoplasms
III. CNS and other intracranial and intraspinal neoplasms
IV. Sympathetic nervous system tumors
V. Retinoblastoma
VI. Renal tumors
VII. Hepatic tumors
VIII. Malignant bone tumors
IX. Soft tissue sarcomas
X. Germ cell, trophoblastic, & other gonadal neoplasms
XI. Carcinomas & other malignant epithelial neoplasms
XII. Other and unspecified malignant neoplasms
Total childhood cancer (ages 0-19) for 2014:

- 15,780 incident cases
- 1,960 deaths
- 5-yr survival 78%
# Pediatric Cancer Types Vary in Age, Gender, and Race Patterns

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Subgroup</th>
<th>↑ Risk by Cancer Types</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 Total U.S. Childhood Cancer Incidence
Children ≤ 20 Years Old, 1975-2012

• Incidence rose about 1% per year for all childhood cancers, 1975-2012

• Rate of increase was lower (e.g., 0.2% per year) during 1990-2006, but subsequently rose

• Mortality steadily declined since chemotherapy in 1960s, but decrease has leveled off
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
- unstable
- incubation period
- symptomatic period
- Outcome
  - recovered
  - -chronic disease
  - deceased

Chronic Diseases

Radiation

Smoking

Specific genes

Incompletely understood carcinogenic mechanisms

Lung Cancer
Steps in Malignant Transformation

- DNA-damaging agents
  - Unspecific (all cells) / Specific (only specific target cells)
  - Metabolic Activation dependent / Independent

  - Indirect action (e.g. radical formation)
  - Direct action (e.g. ionising radiation)

- DNA damage
- Checkpoint agents
- Cell cycle (checkpoint) control
- Replication
- DNA-repair pathways
- Spindle / tubulin interfering agents
- Chromosomal aberration

- Mutation

- Blocker of apoptosis
- Apoptosis
- Proliferation
  - Karotype instability
  - Growth control regulation of gene expression
- Promoters
- Progressors

- Modulating agents
- Tumour/host interaction
- Clonal selection
- Malignancy
Natural History of Chronic Disease

- Risk factor or pre-disease state
- Pathologic changes
- Symptoms
- Diagnosis
- Disease progression or regression
- Cure, chronicity, or death

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

Onset of some familial cases occur at notably younger ages than sporadic cases
Approaches to Identifying Genes Associated with Disease Occurrence or Progression

Population-based association studies
  > Genetic pathways
  > Genome-wide association studies
  > New generation genomic studies
    - germline
    - somatic

Familial aggregation/segregation analysis
## Multi-Factorial Disease Causation

<table>
<thead>
<tr>
<th>Societal Factors</th>
<th>Individual – Level Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neighborhood</td>
<td>Sex</td>
</tr>
<tr>
<td>Cultural</td>
<td>Race/ethnic group</td>
</tr>
<tr>
<td>Economic</td>
<td>Lifestyle, behavioral</td>
</tr>
<tr>
<td>Social</td>
<td>Environmental</td>
</tr>
<tr>
<td></td>
<td>Occupational</td>
</tr>
<tr>
<td></td>
<td>Medical</td>
</tr>
<tr>
<td></td>
<td>Genetic predisposition</td>
</tr>
</tbody>
</table>
Statistical Association versus Disease Causation
Statistical Association

**Definition of association:** 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*

*Modified from Last JM. A Dictionary of Epidemiology, 4th Edition. 2001*
Criteria for Causation* - 1

• Strength of the association
  – Level of risk

• Consistency of the association
  – Repeatedly observed in different populations

• Specificity of the association
  – “If...limited to specific workers and to specific types of disease...then clearly that is a strong argument in favor of causation”

• Plausibility
  – “What is biologically plausible depends on the biological knowledge of the day”

Criteria for Causation* - 2

• Coherence
  – “…the cause and effect interpretation… should not…conflict with the…known… natural history and biology of the disease”

• Experiment
  – “Occasionally is it possible to appeal to experimental or semi-experimental evidence?”

• Analogy
  – “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”

Types of Causal Associations

Common cause: ionizing radiation

Leukemia
Cataracts

Different causes:
Ultraviolet radiation
Ionizing radiation

Common outcome
Cataracts
• **Necessary vs sufficient**
  - Necessary: must be present to cause disease (more common with infections: HIV $\rightarrow$ AIDs)
  - Sufficient: can independently cause disease
  - Example: smoking is neither a necessary or sufficient cause of lung cancer

<table>
<thead>
<tr>
<th></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>
Non-Causal Associations

- Types of non-causal associations
  - Chance association
  - Bias
    > 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)
Sources of Exposure & Outcome Information
Sources of Exposure Information

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

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

- **Administrative records**
  - Birth certificates
  - Job records
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
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

- **Retrospective vs prospective follow-up**

<table>
<thead>
<tr>
<th>Year</th>
<th>1970</th>
<th>2011</th>
<th>2035</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trace &amp; follow up</td>
<td>Select exposed and non-exposed groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retrospective</td>
<td></td>
<td>Prospective</td>
<td></td>
</tr>
</tbody>
</table>
Follow-up: Multiple Axes of Time

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

• **Distinguishing features**
  > compare exposures in cases and controls
  > compare proportion of cases with exposure to proportion of controls with exposure at the time of the study
Introduction to Radiation Epidemiology
Types of Ionizing Radiation

• $\gamma$-rays / X-rays:
  – similar properties
• $\alpha$-particles:
  – nuclei of helium atoms
  – major source of natural background radiation (e.g. radon)
• $\beta$-particles:
  – Electrons ($^{131}$I)
• Neutrons:
  – nuclei with no electrical charge
  – flight crews and frequent flyers
• Heavy charged particles:
  – nuclei of elements (carbon, neon, iron)
  – cosmic radiation, space travel, astronauts

Differ in their penetrating ability & biological effectiveness
- Extremely low frequency magnetic fields/radiofrequency/microwaves: low energy; radiofrequency/microwave heats tissue, not established carcinogens
- Ultraviolet (UV): low energy; skin carcinogen
- Ionizing: high energy, penetrates tissue easily, dislodges electrons creating ions, carcinogen
Penetrating Power

\[ \alpha \text{-radiation} \] Stopped by a sheet of paper

\[ \beta \text{-radiation} \] Stopped by 1.5 cm of aluminum

\[ \gamma \text{-radiation} \] Stopped by inches of lead
Sources of Ionizing Radiation

- Radon: 55%
- Medical X-rays: 11%
- Nuclear Medicine: 4%
- Medical Products: 3%
- Terrestrial: 8%
- Cosmic: 8%
- Internal: 11%

Source: US Nuclear Regulatory Commission 1987
http://www.nrc.gov/reading-rm/basic-ref/glossary/exposure.html
Sources of Ionizing Radiation

2006

Radon 37%
Medical X-rays 36%
Nuclear Medicine 12%
Terrestrial 3%
Consumer Products 2%
Cosmic 5%
Internal 5%

http://www.nrc.gov/reading-rm/basic-ref/glossary/exposure.html
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
## Comparing Doses

**Gray – energy deposited/kg**

<table>
<thead>
<tr>
<th>Activity</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Average, all sources*</td>
<td>6.2 mSv (annual)</td>
</tr>
<tr>
<td>Fallout</td>
<td>0.005 mSv (annual)</td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>0.1 mGy</td>
</tr>
<tr>
<td>Mammogram</td>
<td>0.7 mGy</td>
</tr>
<tr>
<td>CT scan</td>
<td>10 mGy</td>
</tr>
<tr>
<td>A-bomb</td>
<td>100 mSv</td>
</tr>
<tr>
<td>Cancer treatment (tumor)</td>
<td>10,000–70,000 mGy</td>
</tr>
</tbody>
</table>

*US Nuclear Regulatory Commission (2010)*

Radiation Epidemiology Studies

Environmental
- Nuclear discharges
  > A-bomb
  > Nuclear testing
  > Nuclear accidents
- Radon
- Cosmic radiation
- Other natural background

Medical
- Diagnostic
- Therapeutic

Occupational
- Radiologists & radiologic techs
- Uranium miners
- Nuclear facilities
- Chernobyl clean-up workers
Ranges of Effective Dose Levels in Major Study Categories

- **10 Gy**: Low
- **1 Gy**: Chronic
- **100mGy**: Low
- **10mGy**: Protracted
- **1mGy**: Low to Moderate
- **10mGy**: Acute
- **100mGy**: Low to High Local
- **1mGy**: Fractionated

- Natural background
- Nuclear Workers
- A-bomb
- Diagnostic
- Therapeutic

- Low Chronic
- Low Protracted
- Low to Moderate Acute
- Low to High Local Fractionated
Environmental Sources of Radiation

• Protracted exposure to all (natural background) or acute or shorter-term (nuclear discharges)

• Military and nuclear discharges: ↑understanding radiation carcinogenesis & non-cancer diseases
  – A-bomb: ‘gold-standard’ for understanding radiation dose-response and basis of radiation protection
  – Chernobyl: internal exposures and thyroid cancer

• Generally low doses (moderate-to-high in some exposed A-bomb and Chernobyl exposed)
Medical Sources of Radiation

• Fractionated, partial body exposures to growing percent of population with underlying conditions

• Types
  – Diagnostic: x-rays (radiography, CT, fluoroscopy), radionuclides (nuclear heart scans, PET)
  – Therapeutic (low to high doses)

• Cancer and non-cancer outcomes evaluated

• Low, moderate, and high doses
Occupational Sources of Radiation

- Protracted, generally low-dose exposures during working life to millions of workers

- Workers wear monitoring badges to capture exposures for radiation protection purposes

- Epidemiologic studies: risks of all and specific cancers, cataracts, circulatory diseases

- Generally low doses (moderate-to-high exposures before 1950)
Summary - 1

• Epidemiology: provides quantitative information about exposures and associated human health risks

• Key definitions: rates, risks, correlation, statistical association

• Descriptive epidemiology: importance of evaluating patterns and trends

• Disease classification: purpose & importance
Summary-2

• Disease models: infectious & chronic disease
• Natural history of disease: implications for epidemiologic study designs
• Familial occurrence and genetic components of disease
• Multi-factorial disease causation
• Statistical association vs causation; causal criteria; non-causal associations
Summary-3

• Sources of exposure and outcome information

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

• Introduction to radiation epidemiology
  > types of radiation
  > sources and levels of radiation exposures
  > major categories of radiation epidemiologic studies (environmental, medical, occupational)
References

- Radiobiology for the Radiologist, 7th Edition (Eric Hall)
- Health Risks from Exposure to Low Levels of Ionizing Radiation (BEIR VII Report - NAS)
- Effects of Ionizing Radiation (UNSCEAR reports)
References

• Radiation Epidemiology Branch, DCEG, NCI
  http://dceg.cancer.gov/reb

• Radiation Effects Research Foundation (RERF)
  http://www.rerf.or.jp/index_e.html

• Cancer Epidemiology and Prevention (Schottenfeld and Fraumeni)