Epidemiologic Study Designs

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Overview

- Classic Study Designs
  - Cohort
  - Case Control
  - Cross-Sectional
  - Ecologic
  - Randomized Clinical Trials
- Newer Study Designs (later lecture)
  - Case-Crossover (self-matched case-control)
  - Time Series (ecologic)

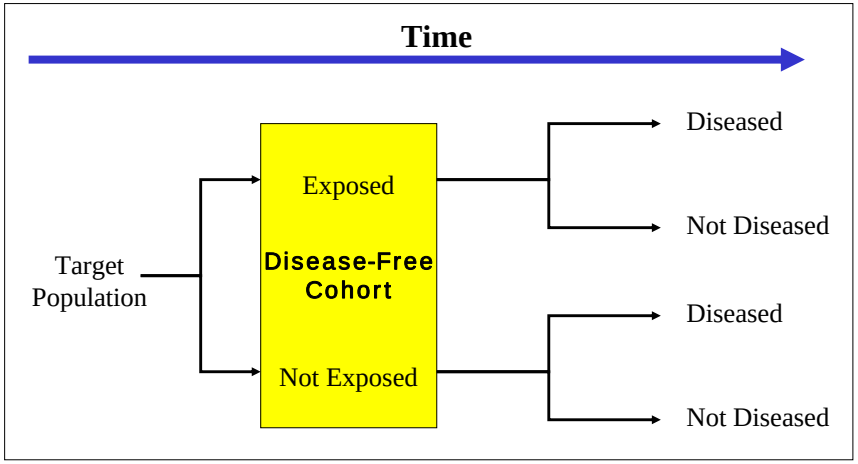
The Cohort Study

- The “What will happen to me?” study
  - Select exposed and unexposed healthy subjects
  - Follow and compare health status
    - example: Are dry cleaners more likely to get kidney cancer?
  - Good for rare exposures/risk factors (<5%)
  - Limitations
    - outcome misclassification
    - loss to follow up

Why Do A Cohort Study?

- Examine common diseases in the general population
  - Causes of death, cancer incidence, births, diabetes,…
- Study a rare exposure (risk) of interest, unusually high levels
  - workers, local pollution,
- Generalize association to the other populations
  - Flight attendants, professional sports, representative sample
- Study special resource groups
  - Doctors, nurses, alumni
- Compare geographical groups
  - Three mile island, specialty care hospitals, NJ

Single Sample Cohort Study Design

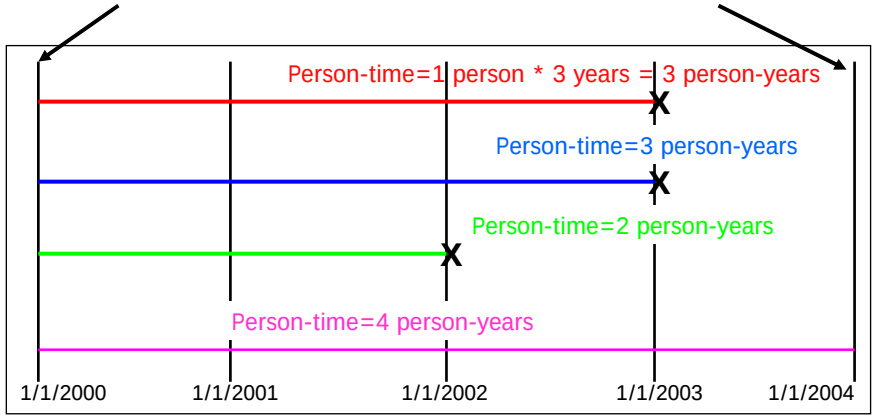


Incidence rate = Number of events that occur from t0 to t1 / Total person-time of observation

Person-time = Sum of total time spent in study for all study subjects

t0 = start of follow-up

t1 = end of follow-up



Determining Exposures/Risk Factors

- Questionnaires/Interviews
- Laboratory tests
- Physical measurements
- Special procedures
- Medical records
- Environmental measurements

Measuring Disease

- Acquiring the Data
  - Routinely collected records
    - Workplace
    - Registries/Surveillance
      - Hospital discharge data
      - National Death Index
      - Special collections: United States Renal Data System
  - Study specific examinations
  - Questionnaires
- Diagnosing Disease
  - Clear, consistent and workable definitions

Most Common Outcome Measures

- Rate Ratio (relative risk)
  - $IR_{Exposed}$ / $IR_{Unexposed}$
    - How many times worse is the rate among exposed than the background (unexposed) rate
- Rate Difference
  - $IR_{Exposed} - IR_{Unexposed}$
    - Size of the (exposed) rate above background (unexposed) rate

Interpreting Rate Ratios or Differences

- RR>1 or RD>0
  - Risk for disease is higher in exposed than in unexposed (or than expected)
  - Risk factor increases risk of disease
- RR=1 or RD=0
  - Risk for disease is equal in exposed and unexposed
  - Exposure is not a risk factor for this disease
- RR<1 or RD <0
  - Risk for disease is lower in exposed than unexposed
  - Risk factor reduces risk of disease (is protective)

The Framingham Study

- Important study of CVD begun in 1948
  - Suburb of Boston; population ~30,000
- Subjects: residents 30-62 years of age

	Men	Women	Total
– Random sample	3,074	3,433	6,507
– Respondents	2,024	2,445	4,469
– Volunteers	312	428	740
– Respondents free of CVD	1,975	2,418	4,393
– Volunteers free of CVD	307	427	734
– Total free of CVD	2,282	2,845	5,127

  - THE FRAMINGHAM STUDY GROUP
- Physical exam every 2 years, questionnaires, and hospital surveillance

Goals of Framingham Study

- Study designed to test:
  - Is an increase of CHD associated with age
    - Does CHD occur earlier and more frequently in males
  - Do persons with hypertension develop CHD at a greater rate than those who are normotensive
  - Is elevated blood cholesterol level is associated with an increased risk of CHD
  - Are tobacco smoking and habitual use of alcohol associated with an increased risk of CHD
  - Is increased physical activity associated with a decrease in development of CHD
  - Does an increase in body weight predispose to CHD
  - Does Diabetes mellitus increase rate of development of CHD

Framingham Exposure Examinations

- Smoking
- Alcohol Use
- Obesity
- Blood Pressure
- Blood Cholesterol
- Level of Physical Activity

- NOTE THAT EXPOSURES LIKELY VARIED CONSIDERABLY AMONG SUBJECTS

- If not, need to identify separate comparison group with lower exposures

Other Examples of Cohort Studies

- Administrative Data Collection
  - Vital records
  - Hospital records
  - Migrant Studies
- Active Data Collection
  - NHANES/HHANES
  - The British Doctors' Study
  - The Nurses Study
  - American Cancer Society CPS I, II
  - Worker cohorts
    - Steel workers
    - Nuclear workers
    - Atomic bomb survivors
    - College alumni

Cohort Study: Strengths and Weaknesses

- Weaknesses
  - Not good for rare disease
  - Misclassification of outcome
  - Information bias
  - Non-participation/non-response
  - Loss to follow up
  - Expensive, slow, logistically difficult
- Strengths
  - Exposure precedes disease
  - Can study rare exposures, multiple outcomes
  - Provide incidence rates as well as rate ratios

Types of Cohort Studies

- Prospective
  - Enroll/identify group of disease-free people
  - Collect exposure data prior to disease occurrence
  - Follow forward in time, noting both exposures and disease occurrence
- Historical (sometimes called retrospective)
  - Identify group of people who were disease-free at a prior, specified date
  - Determine who has disease and who does not
  - Then collect exposure/risk factor data

Example

- Mortality Data from British Physicians Study (Doll and Hill)

Cause of Death	Death Rate Among Non-smokers	Death Rate Among Smokers	Relative Risk	Attributable Risk	Attributable Risk Percent
Lung Cancer	0.07	2.27	32.4	2.20	96.9%
Other Cancers	1.91	2.59	1.4	0.68	26.6%
Chronic Bronchitis	0.05	1.06	21.2	1.01	95.3%
CVD	7.32	9.93	1.4	2.61	26.3%
All Causes	12.06	19.67	1.6	7.61	38.7%

Death rates per 1000 people; data from Doll and Hill

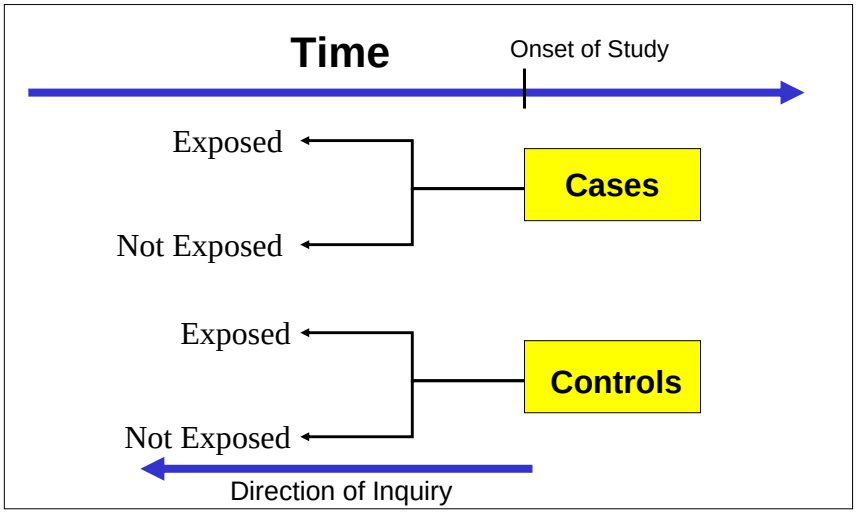
The Case Control Study

- The "Why me?" study
  - Select cases (ill) and controls (healthy) without knowledge of exposure/risks
  - Identify and compare various prior exposure/risks
    - Example: Are people who die from lung cancer more likely to have been smokers?
  - Good for rare diseases (<5%)
  - Limitations
    - exposure misclassification
    - possible control selection bias
    - no temporality

Why Do A Case Control Study?

- Examine a common exposures/risks of interest
  - Personal habits (e.g., smoking), occupation, environment
- Study a rare disease of interest
  - Childhood leukemia, ALS
- Generalize associations to the other populations
  - Power lines (emf), diet
- Why not study in a cohort design?
  - Can complete study more quickly
  - Is less expensive
  - Is easier to implement

Case Control Study Design



Selecting Cases

- Establish case definition
  - symptoms, disease code
- Selected cases should be representative of all cases
  - Typically use a sample
- Incidence cases are preferable to prevalent cases
  - Less likelihood of recall bias
  - Eliminates concern of duration of disease bias

Selecting Controls

- From similar/same population as cases but free of disease
  - (e.g., registry, hospital, lists)
- Sampled to represent exposure/risk distribution in population from which cases have been drawn
- Subjects chosen independently of exposure
- Can match on some variables to remove their influence
  - Cannot assess role of variables on which one matches

Determining Risk Factors/Exposures

- Questionnaires/Interviews
- Medical records
- Other historical records
  - environmental measurements
  - residential histories
  - occupational records

Measuring Exposures

- Acquiring the Data
  - Routinely collected records
    - Workplace monitoring
    - Environmental Surveillance
      - Ambient air quality
      - Drinking water contaminants
    - Study specific examinations
      - Power line location and load
  - Personal interviews/questionnaires

Most Common Outcome Measure

- Odds Ratio (estimate of relative risk)
  - Exposure $Odds_{CASES}$ / Exposure $Odds_{CONTROLS}$
  - How many times worse is exposure rate among cases than exposure rate among controls (background)

Interpreting Odds Ratios

- OR>1
  - Odds (risk) of exposure is higher in cases than in controls (or than expected)
  - Exposure increases risk of disease
- OR=1
  - Odds (risk) for exposure is equal in cases and controls
  - Exposure is not a risk factor for this disease
- OR<1
  - Odds (risk) for exposure is lower in cases than in controls
  - Exposure reduces risk of disease (is protective)

Case-Control Studies: Strengths and Weaknesses

- Weaknesses
  - exposure determination follows disease (temporality)
  - possible control selection, recall, and other biases
  - Inadequate information on confounding factors
  - Possible exposure misclassification
  - no rate information
  - study only one outcome (disease)
- Strengths
  - relatively cheap, easy, fast
  - good for rare disease (<5%)
    - fewer subjects needed
  - good for long latency diseases
  - can look at many exposures (causes)

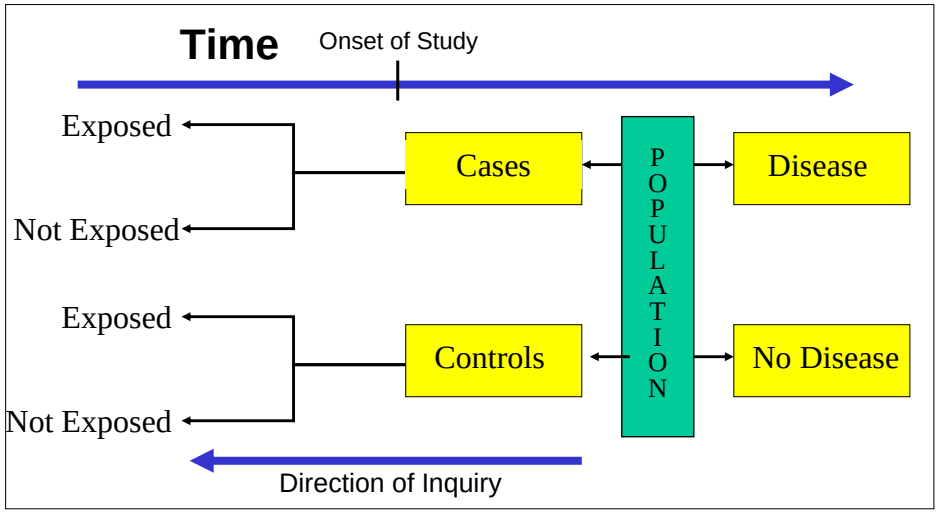
Cohort/Case-Control Comparison

	Cohort	Case Control
Event	Disease	Exposure
Population	Exposed	Diseased
Measure	Disease Rates	Exposure Rates
Advantages	temporality	cheap, quick
	multiple outcomes	multiple exposures
good for:	rare exposures	rare outcomes
	rate information	typically no rate info
Disadvantages	large, slow, costly	lack of temporality
	few exposures	few diseases

Nested Case Control Study

- Instead of Cohort, do Case Control Study within a Cohort
- Why
  - Too difficult/expensive to sample all (cases and) controls
- How
  - Identify cohort for study
  - Follow up outcome of interest
  - Select cases and controls from cohort
    - matched on time and other variables
    - i.e., risk of being a control is proportional to time in cohort—density sampling (via risk set sampling)
  - Assess exposure, analyze interpret
- More efficient than cohort in that only a sample of controls assessed for exposures and confounders

Case Control Study Design



Most Common Outcome Measure

- Odds Ratio (estimate of relative risk)
  - Exposure $Odds_{CASES}$ / Exposure $Odds_{CONTROLS}$
  - How many times worse is exposure rate among cases than exposure rate among controls (background)

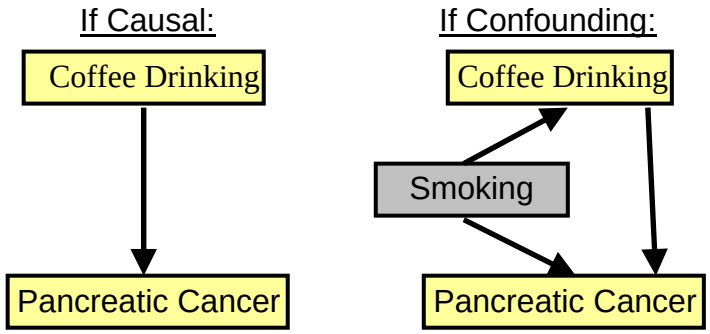
Basic Epidemiologic Questions

- What is the question under study?
- How were the study subjects selected?
- Did most subjects participate?
- How were risk factors assessed?
- Did exposure/risk precede disease?
- What was the size of the observed effect?
- What is the width of the 95% confidence interval?
- Was there adjustment for more than 1 risk factor?
- Are results similar to other studies?

Case-Control: Pancreatic Cancer

- Study by MacMahon et al. 1981
  - N Engl J Med 304: 630-633
- Chair of Epid at Harvard; Top Medical Journal
- Case control study of pancreatic cancer
  - Hypothesis: smoking and alcohol are risk factors
  - Cases diagnosed in any of 11 New England Hospitals
  - Controls other inpatients hospitalized by same doctors who hospitalized cases
  - Collected data on smoking, alcohol, coffee, tea
  - Found association with smoking and coffee
  - Possible explanations for coffee finding
    - Multiple comparison
    - Control selection bias
    - Confounding

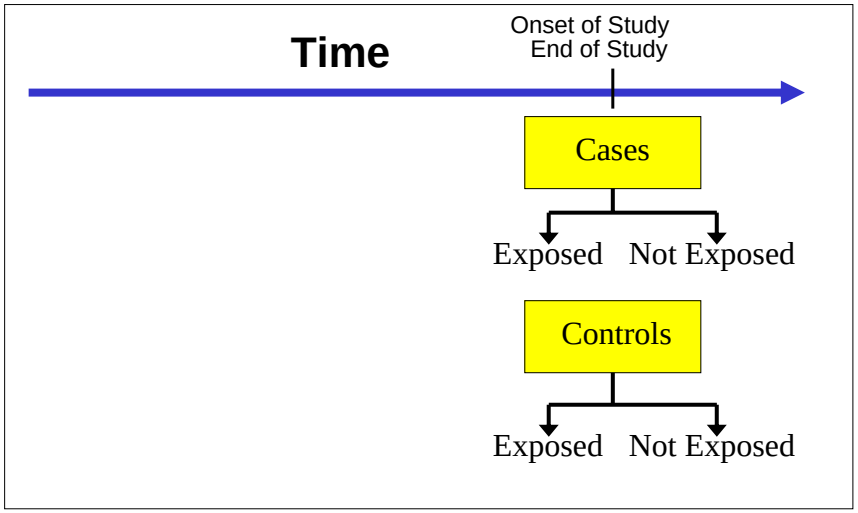
Coffee and Pancreatic Cancer
An Alternative Explanation



The Cross-Sectional Study

- The "Am I like my neighbors?" study
  - Compare health and risks simultaneously—"A Snapshot"
    - example: do vegetarians have lower blood pressure
    - Example: is high serum cholesterol associated with CHD
  - Quick, easy, inexpensive
  - Population-based
  - Often assess prevalence
  - Useful for health service planning
  - Sometimes is used in place of longitudinal data because recall bias is less likely (e.g., diet)
  - Is useful for things that do not change (e.g., blood type)

Cross-Sectional Study Design



Cross-Sectional Study: Strengths and Weaknesses

- Weaknesses
  - Does not address temporality
  - Does not allow for latency
  - Limited to prevalence evaluation—Cannot measure disease incidence
  - Selects for longer lasting diseases (i.e., Neyman bias)
- Strengths
  - quick, easy, inexpensive
  - population-based

The Ecologic Study

- The “Is my town like your town?” study
- Used Aggregate Data
- Group rather than individual is unit of analysis
- Typically cross-sectional (but can be other)
- Usually difficult to control for confounding
- Unable to control for within group variation
- Example: There are high levels of both toxic pollution and cancer in New Jersey, so the toxics must be causing the cancer.
- Example: International comparison of fat in diet and incidence rate of breast cancer
- **Heavily Criticized!!**

A Fully Ecologic Study Example

All data are aggregate (not individual)

Example: Data for Each Study Unit (e.g., town)

individual (*interior*)

	E	NoE	total
D	**4**	**4**	8
NoD	**6**	**16**	20
	10	20	30

OR=(4*16)/(4*6)=2.67

ecologic (*margins*)

	E	NoE	total
D	?	?	**8**
NoD	?	?	**20**
	10	**20**	**30**

D=8/30=27%; E=10/30=33%

Don’t know if those with disease were exposed

Partially Ecologic Study

- Similar to Fully Ecologic but:
  - Have individual outcome data
    - e.g., death certificates, cancer incidence
  - Have aggregate exposure data
    - e.g., regional air pollution monitors
- Most critics do not differentiate from fully ecologic

Strengths of Aggregate Analysis

- Enables analysis of large populations
  - Not easily collectable
  - Facilitates study of relatively small risks
  - Can assess public health impact of an intervention
  - Can be conducted easily and inexpensively with routinely collected databases (surveillance)
- *Statistical inference is valid in spite of biased estimates*
  - Useful for hypothesis generation and prioritization
  - Aggregate sampling variance biases results towards null

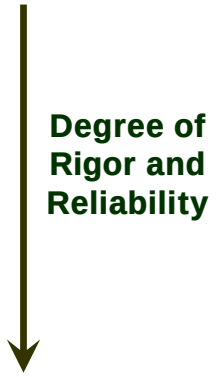
Thompson WD, Wartenberg D. 2007. Additive versus multiplicative models in ecologic regression. Stoch Environ Res Risk Assess (2007) 21:635–646.

The Ecologic Study: Strengths and Weaknesses

- Weaknesses
  - Uses aggregate data (don't know joint distributions)--*Ecologic Fallacy*
  - *Partially Ecologic Studies are better*
  - Data registries are not as reliable as individually collected data
  - Usually difficult to control confounding
  - Unable to control (or assess) within group variation
- Strengths
  - Allows studies of large populations
  - Utilize existing databases
  - Allows study of relatively small risks

Epidemiologic Study Designs

- Case Series (not discussed)
- Cross-Sectional
- Ecologic
- Case-Control
- Cohort
- Randomized Clinical Trial
  - Intervention (more general)



Randomized Clinical/Controlled Trials

- Often used to evaluate treatments
- Experimental study
  - Subjects divided into equivalent groups
    - If randomized, assume other factors equivalent across groups
  - Each group subjected to different treatment
  - Investigator controls intervention
  - Ideally, study is double blinded
  - Subjects followed through time, with outcomes monitored and counted
- Considered the "gold standard" in epidemiology

  (gold standard means best, that against which others are judged)

Example: The Physicians Health Study

- Randomized trial
  - 22,000 US male physicians ages 40-84
    - Aspirin—reduction of cardiovascular mortality
    - Beta-carotene—decrease cancer incidence
  - Large N; moderate risk; good responses
  - Knowledgeable enough to see side-effects
  - Concern about healthy volunteer effect
  - Early results
    - Jan. 1988—daily aspirin reduces risk of MI by 44% (RR=0.56, 95% CI 0.45-0.70)

Critical Issues in an RCT

- What is the hypothesis being studied?
- How was the study population selected?
- Is comparison group explicitly identified?
- Are patients allocated to treatment and control groups without bias?
- How is Intervention Administered?
- Is the Outcome Assessed without Regard to the Treatment Status?

Ethics of RCTs

- Must give people best known treatment
  - cannot withhold proven treatment
- Cannot test an adverse treatment
- Risks must be minimized
- Must be well designed
- Must obtain patients' written consent

Ethics of RCTs—2

- IRBs monitor patients' rights
  - is study scientifically sound
  - does patient understand risks
- Early stopping rules
  - is ethical to withhold beneficial treatment?
  - Is ethical to terminate a study prior to having conclusive scientific data?
    - e.g., AZT studies of AIDS

Elements of Informed Consent

- Research nature of project
- Explanation of procedures
- Explanation of risks and benefits
- Explanation of alternatives
- Explanation about confidentiality
- Name to contact with questions
- Participation voluntary
- Right to withdraw at any time
- Availability and cost of any care necessitated by any complications

Assessing RCTs

- Advantages
  - experimental
  - groups are treated equally
  - no selection bias
  - no confounding
- Disadvantages
  - randomization not perfect
  - blinding is difficult
  - need large sample
  - expensive
  - ethically difficult
  - logistically difficult