AACC

Better health through laboratory medicine.

PEARLS OF LABORATORY MEDICINE

Principles of Study Design and Analysis: Cohort Studies

Julie E. Buring, ScD

CCTC Clinical Chemistry Trainee Council

Totality of Evidence

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- Basic Research –laboratory/animal; possible mechanism
- Epidemiologic Studies – in humans
  - Descriptive – who, what, when, where? To raise hypotheses….
    - correlational or ecologic studies
    - case reports and case series
    - cross-sectional studies or surveys
  - Analytic – why? To test hypotheses…
    - observational
      - case-control
      - cohort
    - intervention studies
      - randomized clinical trials

ANALYTIC STUDIES

- Observational studies (exposures are self-selected)
  - Case-control
    (initial selection on basis of disease status)
  - Cohort
    (initial selection on basis of exposure status)
- Intervention studies (exposures are allocated by investigators)
  e.g., randomized clinical trial

Case-Control Study: Observational study, with selection into study on basis of disease status

EXPOSURE **DISEASE**

? ——————————

? ——————————

PRESENT

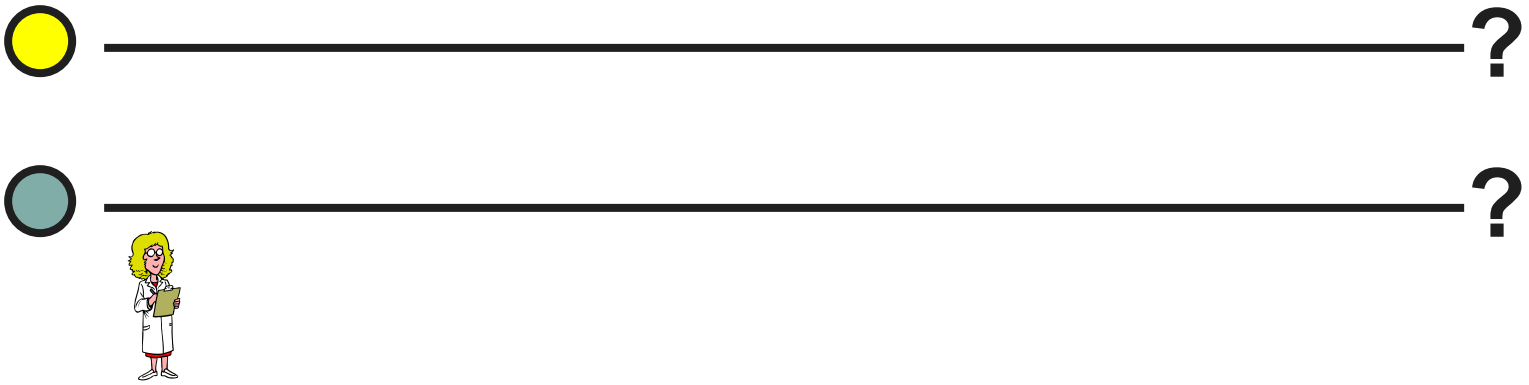
ABSENT

} **Basis on which groups are selected at beginning of study.**

INVESTIGATOR

Cohort Study: Observational study, with selection into study on basis of exposure status

EXPOSURE **DISEASE**



PRESENT

ABSENT

} **Basis on which groups are selected at beginning of study.**

INVESTIGATOR

Cohort Study - Example

QUESTION: What are the adverse effects associated with being exposed to dioxin (Agent Orange) in Vietnam?

EXPOSED: 1,264 Air Force personnel in the "Ranch Hand" project, involved in defoliant spraying in Vietnam between 1962 and 1971.

NONEXPOSED: 1,264 Air Force personnel who flew a variety of cargo missions in Southeast Asian during the same time period, but were not involved in defoliant spraying.

OUTCOMES: dermatologic conditions, adverse pregnancy outcomes, cancer.

Cohort Study - Example

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QUESTION: Are there adverse effects associated with the use of oral contraceptives?

COHORT: Nurses' Health Study - 122,000 female nurses in the U.S., followed since 1976.

EXPOSED: Those who reported use of oral contraceptives at baseline.

NONEXPOSED: Those who reported never use of oral contraceptives at baseline.

OUTCOMES: Breast cancer, myocardial infarction, blood clots.

COHORT STUDIES: DEFINITION

- Group of subjects, free of disease of interest, who are defined or classified by presence or absence of EXPOSURE of interest.
- Followed over time for occurrence of disease of interest.
- Example: women with and without BRCA1 gene mutation, free of cancer, followed for the development of breast cancer.
- Synonyms: follow-up study, longitudinal study.

OPEN COHORT

- Open Cohort: **Members defined by a changeable characteristic**
  - **example: defined by location (living in Boston); by experience (Iraq war vet, students in college); employees in a factory.**
- **New subjects added or eliminated during follow-up (dynamic cohort).**
- **Exposure status may change over time.**

FIXED COHORT

- Fixed Cohort: Members defined by an irrevocable event
  - example: exposure to natural disaster (Japanese earthquake, Katrina)
  - example: inhabitants of a specified location, at specified time (Framingham Heart Study).
- Common starting point, and defined period of follow-up (one year, 10 years, until all cohort dies).
- Exposure defined at start of follow-up, and no new enrollees during follow-up.

NATURE OF COHORT SELECTED

- General cohort versus special exposure cohort?
- Depends on the research question you are asking.

GENERAL COHORTS: EXPOSED SUBJECTS

- General Cohort: Selected based on geography, college attendance, professional groups - nothing special about exposure, enhanced ability to follow-up.
    - example: Framingham Heart Study
    - example: Harvard Alumni Health Study
    - example: Nurses' Health Study
- Provide internal exposed (as well as non-exposed) groups.
- Appropriate when prevalence of exposure is not extremely rare or common.

SPECIAL COHORTS: EXPOSED SUBJECTS

- **Exposed Cohort: Chosen because of higher prevalence of exposure, especially when exposure is rare in the general population.**
  - **example: workers exposed to man-made vitreous fibers**
  - **example: women with breast implants**
  - **example: groups with special lifestyle patterns, such as Seventh Day Adventists (higher prevalence of lower risk factors)**

SELECTION OF NON-EXPOSED SUBJECTS

- **Exposed and non-exposed should be as similar as possible with respect to all factors other than the factor under investigation (i.e., if the null hypothesis is correct, the disease rates of the two populations should be essentially the same).**
- **Need to collect data on any potential baseline differences that could affect the outcome.**

SELECTION OF NON-EXPOSED SUBJECTS

- Internal subgroup of general cohort
  - usually the most comparable group
  - example: women with high vs low intake of fat, or with/without BRCA1, in the Nurses' Health Study
- General population
  - example: mortality in a specific occupational group compared with the general US population
  - problem: "healthy worker effect"
- Comparison cohort
  - example: mortality in a specific occupational group compared to another occupational group
  - avoids healthy worker effect

SOURCES OF INFORMATION ON EXPOSURE

- **Records collected independently of study: occupational, medical, pharmaceutical, education.**
- **Information obtained by research staff: medical exams, biological measurements, electronic devices worn by subjects, environmental or workplace measurements.**
- **Information reported by study subjects (questionnaires, interviews).**

SOURCES OF OUTCOME INFORMATION

- Aim: collect data uniformly from exposed and non-exposed subjects
- Some options:
  - reported by subjects ± validation
  - medical records
  - physical examination
  - links to other pre-existing databases

ANALYSIS OF COHORT STUDY

1. Set up data in 2x2 or rxc table
2. Calculate measures of disease frequency
   - cumulative incidence (CI) if uniform follow-up (denominator is individuals)
   - incidence rate (IR) if variable follow-up (denominator is person-time)
3. Calculate measures of association
   - risk ratio (CI_e/CI_o)
   - rate ratio (IR_e/IR_o)
   - risk difference ($CI_e - CI_o$)
   - rate difference ($IR_e - IR_o$)

SPECIAL ISSUES OF CONCERN IN COHORT STUDIES

1. **Potential for bias due to loss to follow-up.**

2. **External validity (generalizability).**

ADVANTAGES OF COHORT STUDIES

1. Correct temporal sequence:

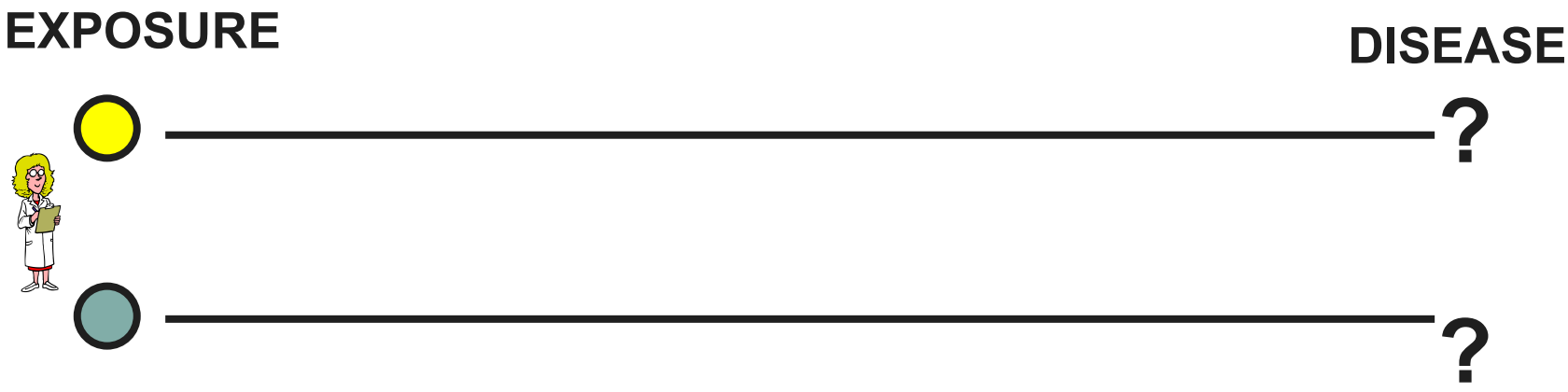
   exposure → outcome

2. Generally involves good information on exposure status.
3. Efficient evaluation when exposures are rare.
4. Can study several outcomes associated with a single exposure.
5. If prospective cohort, can minimize bias in exposure ascertainment.
6. Can directly measure incidence of disease among exposed and non-exposed subjects.

DISADVANTAGES OF COHORT STUDIES

1. Generally inefficient for studying rare diseases.
2. If prospective cohort, time-consuming.
3. Need to minimize loss to follow-up for valid results.
4. If retrospective cohort, requires availability of pre-recorded information on exposure and confounders.

Intervention Study: Structure of cohort study, but exposure is allocated by investigator



PRESENT

ABSENT

} Exposure is allocated to participants at beginning of study. Not self-selected; not observational study.

INVESTIGATOR at beginning of study

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