Chapter 2

Epidemiological and Toxicological Studies
Introduction

• Epidemiological and toxicological studies seek to determine the cause of a particular illness or disease. Etiology is the study of causes.

• Epidemiological studies focus on “real-world” situations and attempt to determine if there is an association between a specific factor and an observed effect.

• Toxicological studies occur in a controlled laboratory environment where a known toxic substance is introduced and a specific effect is measured.
Epidemiological Studies (1)

- Epidemiology is the study of the causative factors that are associated with the incidence and distribution of disease and illness in a specific population.

- Epidemiological studies have been useful in establishing those factors that can cause cancer, heart disease, stroke, and other illnesses. They are particularly useful because large numbers of people can be studies, and the data obtained are representative of exposure and effects that reflect daily reality.
  - cigarette smoking and lung cancer
  - benzene exposure and leukemia in rubber manufacturing workers
Epidemiological Studies (2)

- Important attributes of epidemiological studies
  - Epidemiological studies usually involve a comparison between two groups of individuals.
  - Epidemiological studies often do not provide information in which a clear and specific cause-effect relationship can be established. Instead, the results often suggest an association between some causative factor or factors and the observed effect.
  - Information obtained from epidemiological studies, which attempt to compile information related to past exposures, may be incomplete and inaccurate.
Retrospective and Prospective Epidemiological Studies (1)

Retrospective epidemiological studies evaluate individuals who currently have a specific illness or disease and try to determine the cause by collecting information from past activities.

– Advantages
  • More rapid performance of the study due to the fact that the illness or disease already exists
  • Less costly because it doesn’t require following the individuals until the illness or disease occurs.

– Disadvantages
  • Incomplete records of exposure
  • Inability to completely identify or control confounding factors
  • Higher susceptibility to bias due to data obtained primarily from recall
  • The fact that only a weak to moderate association between the illness or disease and the causative effect may be established.
Retrospective Epidemiological Studies

• Study design
Retrospective and Prospective Epidemiological Studies (2)

Prospective epidemiological studies evaluate the health of individuals who are exposed to a causative agent to determine if the agent will increase the occurrence of an illness or disease in exposed versus nonexposed individuals.

- **Advantages**
  - The exposure data are measurable and more reliable.
  - They can identify and attempt to control confounding factors.
  - They are able to measure the time between initial exposure and occurrence of disease or illness.
  - They may be able to establish a stronger association between the illness or disease and the causative agent.
  - They offer a better control of bias.

- **Disadvantages**
  - The results are not available immediately - this is particularly true in illnesses such as cancer, which does not appear until many years after exposure has occurred.
  - The cost is higher since study may occur over a period of five, ten, or even twenty years.
  - Due to the duration of the study it is difficult to obtain and maintain information from individuals in the population – individuals may move and not be counted in the final evaluation.
Prospective Epidemiological Studies

- Study design

Sample Population

Disease Free Individuals

Exposed to Risk Factor
- With Disease
- Without Disease

Individuals With Disease

Unexposed to Risk Factor
- With Disease
- Without Disease
Measure of Disease Occurrence (1)

- **Prevalence rate**
  - **Number of existing cases of disease**
    - Proportion of individuals in a population with disease or condition at a specific point of time
      - Diabetes prevalence, smoking prevalence
    - Provides estimate of the probability or risk that one will be affected at a point in time
    - Provides an idea of how severe a problem may be – measures overall extent
      - Useful for planning health services (facilities, staff)

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\text{Prevalence rate} = \frac{\text{number of people with attribute during a specific time interval}}{\text{total number of people in specific population during the same time interval}}
\]
Measure of Disease Occurrence (2)

• Incidence rate
  – Measure of new cases of disease (or other events of interest) that develop in a population during a specified period of time
    • For example, annual incidence, five-year incidence
  – Measure of the probability that unaffected persons will develop the disease
  – Used when examining an outbreak of a health problem

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\text{Incidence rate} = \frac{\text{number of new cases in a fixed time period}}{\text{total number of people at risk during the same time period}}
\]
Prevalence varies directly with both incidence and duration.

- If incidence is low, but duration is long (chronic), prevalence will be high in relation to incidence.
- If prevalence is low because of short duration (due to recovery, migration or death), prevalence will be small in relation to incidence.
Measure of Disease Occurrence (4)

- **Prevalence Example**
  - In 1999, a US state reported an estimated 253,040 residents over 20 years of age with diabetes. The US Census Bureau estimated that the 1999 population over 20 in that state was 5,008,863.

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\text{Prevalence rate} = \frac{253,040}{5,008,863} = 0.051
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  - In 1999, the prevalence of diabetes was 5.1%
    - Can also be expressed as 51 cases per 1,000 residents over 20 years of age
Measure of Disease Occurrence (5)

• Incidence example
  
  – A study in 2002 examined depression among persons with dementia. The study recruited 201 adults with dementia admitted to a long-term care facility. Of the 201, 91 had a prior diagnosis of depression. Over the first year, 7 adults developed depression.

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\text{Incidence rate} = \frac{7}{110} = 0.064
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  – The one year incidence of depression among adults with dementia is 6.4%
    • Can also be expressed as 64 cases per 1,000 persons with dementia
Risk

• Definition
  – The probability of an individual developing a response to a given etiological factor.

• Relative risk (RR)
  – It is an estimate of the probability that a given individual will develop a particular effect when exposed to a specific etiological factor compared to a nonexposed individual.

• Attributable risk (AR)
  – It is defined by the number of cases that develop a particular illness or disease and that is associated with a specific etiological factor.

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AR = \text{Incidence in exposed group} - \text{Incidence in unexposed group}
\]
Bias

• Bias may be introduced into an epidemiological study, which could potentially result in a false association being developed between the etiological factor and the measured response.

  – Types of bias
    • Selection bias
      – Distortions that result from procedures used to select subjects and from factors that influence participation in the study.
      – It occurs when groups of individuals are not comparable in all respects except the attribute being studied.
    • Observation bias/information bias
      – A flaw in measuring exposure, covariate, or outcome variables that results in different quality (accuracy) of information between comparison groups.
Confounding (1)

- The distortion of a measure of the effect of an exposure on an outcome due to the association of the exposure with other factors that influence the occurrence of the outcome.

- Confounding occurs when all or part of the apparent association between the exposure and outcome is in fact accounted for by other variables that affect the outcome and are not themselves affected by exposure.
Confounding (2)

- **Confounding factors or confounders**
  - The extraneous factors responsible for differences in disease frequency between the exposed and unexposed.

- **Properties of a confounder**
  - Associated with disease
    - Restriction to association between a potential confounder and disease among unexposed
  - Associated with exposure
    - Restriction to association between a potential confounder and exposure among the source population
  - Association with both disease and exposure alone dose not define a confounder
    - Correlates of a true risk factor
Confounding (3)

Characteristics of Confounders

- Confounders as extraneous risk factors
  - The predictiveness for disease risk involves a mechanism other than the one under study
  - "intermediate" factor not a confounders
- Judging the causal role of a potential confounder
  - On the basis of the best available information, including nonepidemiologic data

Summary: criteria for a confounding factor

- A confounding factor must be a risk factor for the disease.
- A confounding factor must be associated with the exposure under study in the source population (the population at risk from which the cases are derived).
- A confounding factor must not be affected by the exposure or the disease.
Confounding originates from the interrelation of the confounders, exposure and disease in the source population from which the study subjects are selected. By altering the source population, design strategies such as restriction can prevent a variable from becoming a confounder.
Effect Modifier

- An effect modifier is the factor that influences the variation in the magnitude of a measure of exposure effect under study. Effect modification is detected by varying the selected effect measure for the factor under study across levels of another factor.
Toxicological Studies

• Toxicological studies are designed to establish a cause-effect relationship between a specific toxic substance and a measured response.
Acute v.s. Chronic Toxicity Studies

- **Acute toxicity study**
  - It is usually less than 14 days in length.

- **Chronic toxicity study**
  - It is of longer duration, lasting more than 14 days, perhaps weeks, months, or years.
Epidemiological Studies versus Toxicological Studies (1)

• The advantages of epidemiological studies are:
  – The exposure conditions are realistic.
  – There id occurrence of interactive effects among individual chemicals.
  – The effects are measured in humans.
  – The full range in human susceptibility is frequently expressed.

• The disadvantages are:
  – They are costly and time consuming.
  – They are post facto and not protective of health.
  – They pose a difficulty in defining exposure and pose problems with confounding factors.
  – The effects measured are often relatively crude, i.e., mortality.
Epidemiological Studies versus Toxicological Studies (2)

• The advantages of toxicological studies are:
  – The exposure conditions are controlled.
  – They give the ability to measure many types of responses.
  – They give the ability to assess effect of host characteristics (e.g., gender, age, genetics) and other modifiers (e.g., diet) of response.
  – There is the potential to evaluate mechanisms associated with the development of the symptoms.

• The disadvantages are:
  – There are uncertainties in the relevance of animal response to human response.
  – Controlled housing, diet, etc., is of questionable relevance to humans.
  – The exposure concentrations and time of frames are often very different from those experienced by humans.
Epidemiological Studies versus Toxicological Studies (3)

- Epidemiological studies only identify an association or correlation between a toxic substance and some observed effect. Although the association may be strong, a definitive link between cause and effect is difficult to establish, usually because of the number of confounding factors associated with the study. These factors can result in incomplete and misleading information.

- Toxicological studies are designed to establish a direct cause-effect relationship. Usually the test animal is exposed to a single toxic substance and a specific effect recorded. Since most of the other environmental variables are controlled, it is easier to establish the direct cause-effect relationship.
Exposure Routes, Concentration, Duration, and Frequency

- Exposure of the test animals during a toxicological study may occur as a result of inhalation, dermal absorption, ingestion, or as the result of injection.

- Usually only one route is chosen. Regardless of which route is chosen, the variability associated with the concentration of the toxic substance, duration of exposure, and frequency of exposure are all eliminated by strict and controlled laboratory protocol.
Exposure Individuals

- Many different types of test animals are used in toxicological studies. The most frequently used animals are rats and mice.

- Many of the confounding factors such as sex, age, and health – related to the test animal – can be controlled. This helps minimize the number of variables that could affect chemical toxicity as well as the ability to accurately extrapolate animal data to humans.
Extrapolation of Data

• The dose to which a test animal is exposed is usually much higher than the one encountered in the real world.

• In many situations it is not clear whether the toxic substance causes the same response both at low and high exposure levels.

• Conversely, toxic effects observed in epidemiological studies are usually those associated with the lower doses. However, the presence of confounding factors and incomplete information concerning exposure make it difficult to draw definitive conclusions concerning the effects resulting from exposure at these levels.