Epidemiologic Research Methods

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Introduction

The field of epidemiology evolved during the 19th century as researchers developed methods to track disease by neighborhoods in order to control cholera epidemics and other infectious conditions in their communities. John Snow (1813–1858), who practiced medicine in London, has been credited with founding epidemiology. Through careful investigations, he suspected contaminated water was transmitting an agent that caused the massive outbreak of cholera in 1842. When residents were forced to obtain clean water from other sources, the epidemic subsided.1

In 1846 in Vienna, Ignac Semmelweiss (1818–1865), another 19th century physician epidemiologist, observed higher mortality rates from puerperal (childbed) fever among new mothers attended by doctors compared to women whose babies were delivered by midwives. When his colleague, a pathologist, developed the same infection and subsequently died, Semmelweiss hypothesized that the disease was transmitted to patients by doctors from the autopsy laboratory. After requiring doctors to wash their hands in chlorinated water before attending women in labor, maternal mortality from puerperal fever rapidly declined from 12% to 1%.3

Among the most notable contributions of epidemiology to public health in the 20th century was the link between increased cigarette smoking and rising incidence of lung cancer. In 1964, the U.S. Surgeon General reported that lung cancer risk was more than 10 times greater among smokers than nonsmokers. Few epidemiologic studies have observed risk associations of similar magnitude until the recently identified susceptibility genes that strongly predict hereditary cancer syndromes. Recent etiologic studies are benefiting by use of new technology that enables analysis of biospecimens, including blood, urine, saliva, and tissue samples, to search for potential disease-causing organisms, exposures, and biomarkers of disease. The resulting multidisciplinary collaborative studies have stimulated creative and more sophisticated approaches to understanding the causes of complex diseases.2

This chapter reviews established epidemiologic research methods used in many of the studies referenced in this text. Epidemiologists study risk factors for specific conditions and diseases affecting women across the life span. Recent innovative research has identified early life exposures, especially during periods of rapid growth, from prenatal development through early childhood to adolescence, as critical intervals when exposures may influence risk of adult onset diseases. A major public health goal of epidemiologic studies is identification of opportunities for preventing or delaying the development of disabling conditions, thus improving the quality of life among seniors.

Epidemiologic Parameters

Epidemiology is based on the belief that diseases do not occur randomly and opportunities for disease prevention may be provided by identifying potential etiologic agents. Investigations of disease patterns in humans are far more complex to design and conduct than laboratory-based animal studies in which genetic and environment exposures can be controlled. Among humans, our primary goal is to identify factors that differentiate groups of people with a disease from those within the same population who remain unaffected. To adequately study associations between diseases and potential risk factors, multidisciplinary teams are needed to design data collection instruments for measuring biologic, social, and environmental factors and to monitor changes in these parameters over time.5 Although small clinic-based studies may provide etiologic clues, sophisticated statistical methods have been developed to analyze extensive data collected from study participants and collaborating laboratories. Through these challenging investigations, epidemiology has identified public health interventions that are contributing to improved health of all Americans.

Incidence and Prevalence

Essential for public health planning and resource allocation is an understanding of the magnitude of different clinical conditions affecting populations over their life course. Data are collected to determine the incidence of a disease, the number of newly diagnosed cases of disease in a specified interval of time in a defined population. The prevalence of a disease reflects the total number of
affected women at one point in time including newly diagnosed cases and those with longer histories of the disease. An example is prevalence estimates of multiple sclerosis among American women. Distinguishing between incident and prevalent cases is essential; prevalent cases may have unique characteristics that enable long-term survival and, therefore, may not represent the full spectrum of the condition.

**Person, Place, and Time**

Traditional descriptive epidemiology has focused on disease patterns in relation to personal characteristics of the people affected, their geographic diversity and the timing of disease onset. These basic features are addressed in most epidemiology studies of potential causal relationships.

**Person.** Epidemiologic studies classify individuals into groups according to their gender, race/ethnicity, age at disease onset, current knowledge of genetic status, and health behavior patterns among other factors. An example of gender-specific patterns pertains to breast cancer, which primarily affects women. Although differences in incidence and mortality rates have been associated with race/ethnicity, advances in genetic testing and identification of molecular markers may more accurately define person-specific risk patterns, especially among multiracial families.

**Place.** Geographic differences in incidence, prevalence, and clinical course of diseases have been studied for etiologic clues. One example is provided by ecologic studies of multiple sclerosis; the north-south gradient suggests risk may be influence by climate patterns.

**Time.** Rates of death from coronary heart disease (CHD) among Americans ages 35 and older vary considerably by state. CHD mortality rates in some counties of southern states are more than double rates in western and northern sections of the country. The counties with the highest CHD deaths are characterized by disproportionately higher levels of poverty, obesity, and diabetes in addition to sedentary lifestyle.

Migration studies have documented changes in disease patterns among succeeding generations of immigrants who adopt social-cultural patterns, are exposed to new environments, and assume health behaviors prevalent in their new residential and occupational settings. The study of rising breast cancer incidence rates among Hispanic women with each succeeding generation was reported by John and colleagues in California to be among women who immigrated at young ages and had longer residence in the United States.

Geographic assessments have identified disparities associated with close proximity to toxic waste sites and polluting industries primarily affecting residential and employment settings of low-income and minority populations. Some studies have linked environmental contaminants with neurodegenerative conditions detected decades after in utero exposures; children are the most vulnerable members of the population due to their rapid rate of growth. Therefore, research assessing risk factors for adult onset diseases often requires knowledge of early residential exposures.

Timing of exposures may critically influence risk of disease, especially at recognized transition intervals when susceptibility is increased due to rapid cell division. Across the life cycle, women are most vulnerable during prenatal development, puberty, pregnancy, and menopause. Examples include in utero thalidomide exposure that was noted decades ago to cause tragic interruption of fetal limb development. Another drug prescribed to pregnant women, an estrogen called diethylstilbestrol (DES) thought to prevent miscarriage, increased the risk of cancer in both mothers and daughters years later. Risk of breast cancer is increased among mothers more than 30 years after use of DES and among daughters after age 40. In addition, some daughters exposed in utero were prematurely diagnosed with vaginal or cervical cancer soon after puberty, whereas others have experienced gynecologic abnormalities, including infertility.

**Levels of Prevention**

The major goal of public health education is to prevent disease through promotion of healthy lifestyles and avoidance of adverse environmental exposures. Early detection modalities through screening are advocated to avoid diagnosis of diseases at advanced stages. Once a condition has developed, subsequent goals address reduction of disabilities and maintenance of quality of life. These levels of prevention guide public health interventions.

**Primary Prevention**

Avoiding onset of a disease or condition is the goal of primary prevention. Vaccines provide such protection by stimulating the immune system, producing antibodies against an etiologic agent to prevent diseases such as poliomyelitis and measles. Major concerns caused by fear of adverse health effects, especially from erroneous links to autism, have caused some parents to refuse immunizations for their children. Although vaccination is mandated by most states, some provide religious and/or philosophic exemptions. Recently developed vaccines have protected the public against infectious conditions such as flu (H1N1), diseases with infectious and chronic components including liver cancer (HepB) and cervical cancer (human papillomavirus or HPV). Eradication of the bacterial etiologic agent, *H. pylori*, through population-based administration of antibiotic therapy could provide primary prevention of gastric cancer. Personal behaviors such as increased physical exercise and avoidance of smoking may prevent heart disease or delay disease onset.

**Secondary Prevention**

Although screening to identify some diseases or conditions at early stages is often referred to as “prevention,” such secondary prevention procedures do not protect against disease development. However, by altering the natural history through early detection followed by appropriate treatment, risk of death may be reduced or prevented. An example is provided by Berry and colleagues who used...
national data to document improved breast cancer survival due to a combination of screening mammography and adjuvant chemotherapy. A potentially adverse effect of screening is overdiagnosis and unnecessary, aggressive treatment of clinically insignificant disease or borderline conditions.

Tertiary Prevention
The goals of tertiary prevention include prolonging survival and reducing symptoms to improve the quality of life after a condition is diagnosed and appropriate therapy has been received. Self-care guidelines for women with diabetes help lower the risk of blindness or kidney damage by daily monitoring and administration of insulin, which may slow the natural course of the disease. Therefore, tertiary prevention may provide opportunities for rehabilitation through comprehensive and coordinated therapy.

Types of Epidemiologic Studies
Observational studies are conducted when knowledge of a condition or disease is limited. They provide data on the natural history of diseases, incidence rates by ages at diagnosis, race/ethnicity, gender, environmental exposures, and social class, which enable researchers to determine the need for targeted research and public health planning. Data from initial observational studies are essential for the development of hypotheses that are tested in more complex and costly analytic investigations. When appropriate and ethically feasible, randomized clinical trials may be designed to further test suggested avenues for disease interventions. Clinical observations often identify underlying causal factors that stimulate population-based research that may identify causal agents. The sequence of studies that identified the association of endometrial cancer with unopposed postmenopausal estrogen exposure provides an example as noted in Table 2-1.

Observational Studies
Ecologic
Population groups rather than individuals are the focus of ecologic investigations. Changes in disease patterns noted in national data or specific populations may provide important public health clues. For example, the ecologic study published by Austin and Roe in 1982 documented the previously suspected correlation between prescribing patterns of estrogen for menopausal symptoms and rising incidence rates of endometrial cancer. With discontinued use of these medications, diagnosis of endometrial cancer rapidly diminished. A similar response was observed in 2007 as population-based breast cancer incidence rates declined for the first time after decades of steady increases. The authors attributed the downward trend to postmenopausal women discontinuing combined estrogen and progesterone therapy after the 2002 Women’s Health Initiative reports.

Another ecologic analysis of population-based data indicated an inverse association between annual sunlight exposure and breast cancer incidence. Compared with an annual incidence rate of 33 cases per 100,000 women in northern states, breast cancer affected 17–19 per 100,000 women in southern states, suggesting greater exposure to sunlight reduced risk of disease. Although observed correlations identified in ecologic studies may not reflect causal risk factors among individuals, they often guide researchers in developing analytic investigations. Caution is advised in relying on ecologic studies, as excess promotion of the results may result in an “ecologic fallacy,” an inaccurate assumption based on correlations among populations rather than individuals.

Cross-Sectional
The relationship of personal or clinical factors with disease status at one point in time is the focus of cross-sectional

<table>
<thead>
<tr>
<th>Table 2-1</th>
<th>Evolution from a clinical observation to a causal association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation/concepts</td>
<td>Examples</td>
</tr>
<tr>
<td>Clinical observation between factor and condition—personal observation</td>
<td>Estrogen prescribed for menopausal symptoms—unexplained uterine bleeding</td>
</tr>
<tr>
<td>Etiologic studies—population level</td>
<td>Increased menopausal estrogen use was followed by elevated endometrial cancer rates</td>
</tr>
<tr>
<td>Analytic studies using personal data from research participants, consistency of results from numerous studies</td>
<td>Association confirmed in case/control, cohort and nested case control studies</td>
</tr>
<tr>
<td>Understanding the biologic mechanism led to discontinued hormone use that stimulated malignant growth</td>
<td>Rapid decline in endometrial cancer confirmed estrogen as a tumor promoter</td>
</tr>
<tr>
<td>Control of biologic mechanism with additional hormonal treatment</td>
<td>Addition of progesterone to estrogen caused shedding of the endometrial lining of the uterus</td>
</tr>
<tr>
<td>Lower incidence of endometrial cancer in other western countries</td>
<td>Lower frequency of hormone use for menopause in these countries</td>
</tr>
</tbody>
</table>
studies; however, the sequence of disease onset in relation to exposure cannot be determined. A cross-sectional study by Stewart et al. describes a survey mailed to randomly selected households in order to estimate the lifetime incidence of migraine by gender and age group. Repeated cross-sectional surveys provide estimates of changes in disease patterns over time. Individuals with newly diagnosed disease (incident cases) and people who have survived for long intervals after diagnosis (prevalent cases) are included in cross-sectional studies. Although cross-sectional surveys can be useful, prevalent cases may have unique characteristics including more indolent disease enabling longer survival, which may compromise the usefulness of some cross-sectional studies. Tanner and Whitehouse used cross-sectional assessments to identify individual variability of age-specific growth patterns of girls during puberty. However, they supplemented their research with repeated longitudinal assessments of a subset of girls to detect any abnormalities in the rate of maturation.

Analytic Studies

Hypotheses generated by results of descriptive studies guide the design of more complex and costly analytic investigations of individuals. Extensive data collection and appropriate biospecimens are collected from willing study participants. Careful calculations are required to estimate the optimum number of participants to assure adequate statistical power to provide meaningful results. A balanced assessment of study size is essential to achieve precision while being a cost-effective research design. To address some research questions, smaller, targeted investigations may be more manageable and informative than larger, population-based studies. Appropriate selection of a specific analytic study design to address an epidemiologic question depends on the frequency of the condition, the efficiency of recruitment procedures and data collection, and ethical issues affecting biospecimens collection, among other issues.

Case-Control Studies (Retrospective)

A classic study design repeatedly represented in epidemiologic literature referenced in this text is the case-control comparison. Data are collected uniformly from women with a newly diagnosed condition (cases) and unaffected women (controls) by either a personal interview (in person or by phone) or extensive mailed questionnaire. Questions based on prior research or hypotheses ask about exposures and life events preceding diagnosis among cases and during a comparable time interval for controls. These retrospective investigations rely heavily on the cooperation, memory, and honesty of the study participants.

Case-Case Studies (Retrospective)

Case-only studies are a convenient means for understanding risk and/or prognostic factors associated with differing forms of a condition or disease; studies may focus on etiologic or prognostic factors associated with pathologic features, ages at diagnosis, menopausal stage, etc. Research addressing specific case questions such as the impact of maintenance of fertility after breast cancer treatment on prognosis requires case-only recruitment.

Cohort Studies

Cohorts are composed of prospectively recruited healthy women who are followed over time after completing baseline questionnaires, often also providing biosamples and possibly having clinical examinations. Cohort participants are requested to agree to repeated data collection over extended, occasionally undefined, time frames. A famous community-based investigation of heart disease was initiated in Framingham, Massachusetts, in 1948 with approximately one-third of all households represented among the original 15,000 male and female participants. Development of birth cohorts, recruiting pregnant women or women planning to become pregnant, has become a valuable design for epidemiologic studies of prenatal exposures and pregnancy outcomes.

Harvard researchers began recruitment of two cohorts of registered nurses in 1976, focusing on two different age brackets to include pre- and postmenopausal women. Participants in the Nurses’ Health Study cohorts have been followed for several decades by questionnaires mailed biannually. Data collection has included changes in health status and personal behaviors including smoking, hormone use, diet, alcohol intake, and other exposures, providing resources for hundreds of publications on diverse health outcomes affecting women. Some researchers have questioned the representativeness of the nurses enrolled in these cohorts. They may represent a female population biased by the “healthy worker effect” as well as higher education and health consciousness compared with women of similar ages in the general population. Given these concerns, results based on data from the Nurses’ Health Study may be generalizable only to females of similar ages, race/ethnicity, education level, and employment status.

The American Cancer Society (ACS) has created three “prevention cohorts” recruited by county-based ACS volunteers beginning in 1959 with a second cohort added in 1982 and a third currently being planned to assess changes in cancer risk factors over time and among diverse populations. Participants provided baseline and follow-up questionnaire data and are contacted routinely by the ACS volunteers to maintain records of health status changes. Critics of the publications based on data from these cohorts noted that participants were often better educated and less diverse than other members of their communities. Despite these concerns, investigations using ACS-collected data have documented a significant number of cancer risk factors including the changing nature of family history of cancer as relatives grow older and cancer risk increases.

Retrospective Cohort Studies

Cohorts have been created retrospectively through employment records, medical charts, site-specific exposures, birth records, etc. Although the data available on members of a
retrospective cohort may be limited, women with specific exposures assembled retrospectively may be very important for identifying etiologic causes of disease. One study identified radium as the cause of oral cancer among women who painted watch faces many decades ago. Another retrospective cohort that provided important research results was composed of infants exposed to radiation of the thymus in New York State who were found to be at increased risk of breast cancer more than 36 years later. Experimental Studies Randomized Controlled Trials (RCT)
The primary scientific method for reliable, unbiased assessment of an etiologic factor, diagnostic technique, behavioral intervention, or treatment modality is the randomized controlled trial (RCT). Randomization minimizes imbalance of measured and unmeasured personal and behavioral characteristics, a classic means for ensuring comparability of study participants. Women meeting entry criteria and agreeing to participate must be randomly assigned to intervention or control status. Exclusion criteria must be specifically defined and compliance with assignment must be carefully monitored. In order to ensure unbiased study results not influenced by study investigators, neither participants nor research coordinators should know the assigned treatment of participants. An external data monitoring panel must routinely assess study results, applying preset stopping criteria, in order to provide the public with benefits of the research as soon as possible and ensuring safety by prematurely interrupting the trial if negative results are detected, as occurred in a beta carotene trial among smokers.

There may also be limitations in conducting RCTs. Inaccurate results may be recorded if participants fail to adhere to study protocols. For example, inconsistent use of a prescribed medication or placebo may incorrectly suggest a new medication or therapeutic intervention is ineffective. Public health programs may be developed based on inaccurate conclusions. Therefore, carefully designed RCTs should include detective measures for assessing compliance. The RCT conducted by researchers at the Chicago Lying-In Hospital in 1953 reported that diethylstilbestrol did not prevent miscarriage. The prescribed treatment and placebo tablets included an inert chemical marker that was detectable in urine samples collected at each prenatal visit documenting level of adherence to daily pill use.

Randomized controlled trials may be the gold standard for research; however, some questions of special interest cannot be addressed by random assignment due to ethical consideration, willingness of participants to be randomized, etc. Interventions found to be effective in one population may not live up to expectations in other community settings (Table 2-2).

One of the most important RCTs recently conducted among American women assessed the effect of estrogen with and without progestin on several health outcomes. The Women’s Health Initiative (WHI) included several RCTs and observational studies. Hundreds of research reports have been generated and have influenced clinical decisions by many women and their healthcare providers. As previously noted, a downturn in breast cancer has paralleled the reduced hormone use by postmenopausal women.

Table 2-2
Factors that may influence generalizability of clinical trial results

| Diversity of study participants: age distribution, race/ethnicity diversity, comorbid conditions |
| Geographic distribution: regional differences in disease patterns, risk factors, environmental exposures |
| Nature of available clinical settings, including access to health care |
| Interest and willingness of local healthcare providers to recruit participants or permit patients to enter proposed clinical trials |
| Knowledgeable staff with expertise availability to adequately conduct clinical trials to meet research standards |
| Relevance of the intervention to the needs, priorities, and values of study participants and research community |
| Local cultures influencing acceptance of trial results |
Hospital-Based Recruitment

In the past, hospitalized patients were the primary research subjects, especially for studies of less common clinical conditions. Medical records provide documentation of disease status, portions of biospecimens collected for clinical care may also contribute to research, and personal interviews are readily accepted by hospitalized patients. Studies of highly lethal conditions require rapid case ascertainment most conveniently accomplished during initial hospitalization. Medical centers also provide access to women unaffected by the specific conditions being studied to serve as controls. However, hospitalized control subjects may have unique characteristics and comorbid conditions that differ significantly from the larger non-institutionalized female population. Therefore, epidemiologists have avoided hospitalized patients, preferring to recruit population-based study participants. However, recent interest in molecular epidemiology research has stimulated renewed interest in hospital-based recruitment, providing easier access to biospecimens, including tissue.

Birth cohorts provide an opportunity to study the impact of genetic, cultural, and environmental exposures on physical growth and emotional development. Recruitment of pregnant women provides access to information on prenatal exposures, women and babies can be followed through delivery including birth experiences, postnatal exposures, infant feeding, growth rate, psychological development, etc. A unique example is provided by the Dutch birth cohort of babies exposed prenatally to the German-imposed food embargo causing severe malnutrition during pregnancy. Adverse health effects are still being documented in the affected population after 5 decades of follow-up for health outcomes. Diversity of study populations can be ensured by multisite collaborations including mothers of varying races—ethnicities and socioeconomic levels from rural and urban medical centers.

Population-Based Recruitment

Population-based study recruitment is preferred for epidemiologic studies as the study population is more representative of women at risk. Data representative of the broad U.S. population are provided by the National Center for Health Statistics (NCHS), a division of the Centers for Disease Prevention and Control (CDC). The NCHS annually conducts the National Health and Nutrition Examination Survey (NHANES). Using a complex, multistage probability design with oversampling of selected demographic subgroups to provide health and nutrition information from more than 20,000 American women and men of diverse heritages.

In the United States, infectious diseases must be reported to state health departments and the CDC, providing information public health workers use to develop prevention and control programs. Similarly, most states have mandated reporting of all newly diagnosed malignancies. These data enable calculation of incidence and mortality rates by cancer site, gender, age at diagnosis, and length of survival. Researchers, with approval of local institutional review boards and treating physicians, often seek participation of newly diagnosed cancer patients in etiologic and treatment studies. Protection of patient privacy is ensured by mandated procedures, including study descriptions provided in consent to participate forms.

To provide comparison populations for epidemiologic studies, unaffected members of the community are invited to contribute to research as control subjects. Unbiased recruitment of controls is essential. Controls must be drawn from the same base population as the cases. Several appropriate sources of population-based controls include Medicare enrollees, licensed drivers, or individuals contacted by random-digit dialing within specific area codes.

The Internet has provided a means for recruitment of a diverse, interested study population, although self-selected, the subjects are willing to respond to study protocols. This recruitment method provided Lieberman and colleagues with a diverse study population of women and men with a history of bipolar disorder, a serious mental condition of low frequency, who were not readily accessible through alternative recruitment avenues.

Community and Geographic Recruitment

The Framingham Heart Study, noted previously in the discussion of cohort study design, included more than 30% of the population in 1948. Federal funds continue to support the project, enabling follow-up of the original participants and their descendents. Results of the hundreds of studies conducted on data collected during comprehensive physical exams conducted every 4 years and analyses of biospecimens and questionnaire data have identified precursors of heart disease, stroke, and aging. Using these extensive research findings, guidelines for personal health behaviors have been established. In addition to recommended health promotion guidelines, the study findings led to development of medications that have contributed to reduced heart disease mortality over the past 50 years. Recent studies by several social scientists have observed maintenance of healthy behavior patterns among lifelong Framingham friends including smoking cessation, increased physical activity, and optimum weight for height, suggesting a “contagious” nature for healthy lifestyles within the social network of this aging population.

Community-based research became a major component of the American response to the human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) epidemic as the CDC supported local interventions that successfully changed behaviors and contributed to reduced risk of HIV transmission. Concern about localized environmental exposures has increased as incidence rates vary considerably among American cities and states. Investigators have targeted some studies in specific high-risk areas in order to detect potential community-based exposures associated with disease development that may compound individual-level risk factors. New technology has enabled measurement of some adverse exposures, providing scientific evidence of neighborhood contaminants that may increase disease risk many years after initial exposures.

22 SECTION I: INTRODUCTION TO EPIDEMIOLOGY OF WOMEN'S HEALTH
Recruitment Based on Clinical Characteristics

Characteristics of case subjects must be clearly defined and clinically confirmed before they are recruited to case-control studies or are identified in cohort studies. Many clinical factors require consideration when recruiting women for research including reproductive history, menstrual status, genetic susceptibility, among others. Menopausal status may be quite complex to define given the high proportion of hysterectomy at varying ages, accuracy of recall among women reporting natural menopause (not due to radiation, surgery, or medication) and indeterminate status of women using hormone replacement and experiencing menstrual-type bleeding. To correlate self-reported menopausal status with hormonal changes, some studies use biologic measures obtained from serum or vaginal smear cytology.

Twin studies (both monozygotic and dizygotic) provide powerful means for identifying gene-environment interactions. When concordance of a condition is greater among monozygotic than dizygotic twins, the etiologic role of inheritance is strengthened as noted in some studies of social behaviors. Recruitment of families at elevated risk for some diseases has provided resources for identifying specific susceptibility genes and family-specific genetic mutations. Family-based registries provide unique opportunities for gene-environment interaction studies when paired siblings, who shared early life exposures, are discordant for adult onset diseases. Genetic studies must recruit diverse populations to avoid population stratification, a form of bias that may occur when a genotype and the likelihood of disease development compared with mutation carriers from larger, more diverse populations.

Data and Biologic Sample Collection

The quality of data collected is a primary determinant of valid epidemiology studies. Descriptive research is often conducted using information routinely collected by federal agencies, vital statistics, state-based health departments, cancer registries, and hospital admissions (Table 2-3). Most analytic studies collect data directly from study participants by in-person interview, telephone, or mailed questionnaire. Among the data sources noted in Table 2-3 is the Behavioral Risk Factor Surveillance System (BRFSS) created by the CDC in 1984 to routinely assess personal health status and risk behaviors known to affect morbidity and mortality. Increased use of new communication technology has adversely affected BRFSS participation rates as contact is attempted only through landline telephones potentially limiting the representativeness of the data. To overcome these obstacles, the CDC has enhanced the system enabling annual BRFSS cross-sectional surveys to provide reliable data to guide public health policies (Table 2-3).

Accurate recall of the frequency and duration of some important health behaviors is difficult to obtain reliably. Therefore, carefully developed and tested data collection instruments are used to collect information on personal behavior such as physical activity. A team of California investigators designed a self-report questionnaire to capture the broad range and complexity of exercise detailing the frequency, duration, and intensity of the activity which is now routinely used in epidemiologic studies. Reliability of self-reported data has been a constant concern as studies have shown inconsistent recall by women, regardless of their disease status, when asked about specific exposures such as use of prenatal medications, frequency of screening procedures, and extent of family history. In response to questions addressing clinical events, occupational exposures, and other potentially important factors, study subjects must often rely on their memory as efforts to obtain documentation have rarely been successful. The Cancer and Steroid Hormone Study initiated in 1980 by the CDC included a women's health study calendar on which participants recorded dates of major life experiences to facilitate recall of reproductive events, use of contraceptives, etc. In addition, a book of photographs presenting all available brands and dosages of birth control pills were shown to study participants.

Wording of questionnaires may influence the accuracy of responses as noted by Mitchell and colleagues in a pilot study prior to a multisite investigation of an

<p>| Table 2-3 |</p>
<table>
<thead>
<tr>
<th>Sources of population-based data used in epidemiology studies</th>
<th>Sources of Data</th>
<th>Examples Referenced in This Textbook</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phone surveys, in-person interviews or phone contacts, mailed questionnaires</td>
<td>Behavioral Risk Factor Survey System [BRFSS], Health Interview</td>
<td>Survey, investigator-initiated research</td>
</tr>
<tr>
<td>Mandatory laboratory reports</td>
<td>Newly diagnosed HIV &amp; AIDS, sexually transmitted infections</td>
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<tr>
<td>Health maintenance organizations</td>
<td>Kaiser Permanente, Mayo Clinic, Puget Sound Cooperative</td>
<td></td>
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<tr>
<td>Federal and state-based cancer registries</td>
<td>Surveillance, Epidemiology and End Results [SEER], State Registries</td>
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<tr>
<td>Hospital and medical care statistics</td>
<td>Medicare, Medicaid, hospital admissions records</td>
<td></td>
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<tr>
<td>National health surveillance</td>
<td>National Health Center for Health Statistics [NHANES]</td>
<td></td>
</tr>
</tbody>
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association between birth defects and prenatal drug exposure. Responses to open-ended inquiries about drug use generated fewer affirmative responses in contrast to questions naming specific drugs prescribed for common symptoms.\textsuperscript{68} Consistent wording of questionnaires used for more than 40 years by the American Cancer Society Prevention Studies has enabled detection of changing health practices and disease outcomes across decades.\textsuperscript{69}

The source of data, collection methods, and willingness of the study participants have a significant impact on the reliability, completeness, and usefulness of the information collected. When appropriate and feasible, biosamples have been used to compare self-reported behaviors with biochemical measures of exposure. One study measured levels of cotinine in saliva to compare with smoking history reported by adolescent study subjects.\textsuperscript{60} A second technique for detecting inconsistent self-reported smoking by adolescents involved data collected during school and at home from the same participants; 20% who reported smoking on the school-based study denied ever smoking on the survey completed at home.\textsuperscript{67}

**Retrospective versus Prospective Data Collection**

The prospective nature of cohort study data collection is designed to avoid “recall bias” that may influence responses, such as newly diagnosed women blaming specific exposures for their disease.\textsuperscript{7} The potential long latency between enrollment of healthy women and disease detection during follow-up requires cohort studies to include large populations at risk for the condition(s) of interest who are willing to provide baseline data and biospecimens and to be repeatedly contacted for updated personal information.\textsuperscript{33}

Data collected retrospectively during a single interview or survey from participants in case-control studies may result in findings that conflict with analyses of data collected prospectively during years of follow-up after initial cohort recruitment. Factors contributing to the divergent findings should be carefully explored and potentially resolved to avoid miscommunications with healthcare providers and the public. Moffitt and colleagues noted recall bias was avoided when mental health status was assessed prospectively among subjects ages 18 to 32; rates were doubled compared with retrospective reporting.\textsuperscript{86} Although falsely negative findings may appear inappropriately reassuring, falsely positive epidemiologic studies may misguide public health decision making and future governmental funding.\textsuperscript{89} Multiple factors contribute to the frequency of false-positive epidemiologic research, including numerous studies in different populations of potential risk factors leading inevitably to a proportion of false-positive findings, overinterpretation of minimally significant findings, and biased preference for reporting positive findings, among others.\textsuperscript{69}

**Epidemiologic Criteria of Causation**

Epidemiologists conducting etiologic studies search for factors that explain differences in disease incidence between groups of individuals, evaluating potential risk factors, assessing individual susceptibility, and environmental cofactors. Most clinical conditions have multiple causes including both genetic and environmental factors. Some genetic markers or environmental exposures may be necessary for disease to be initiated but may not be sufficient causes without additional adverse events. Analytic assessment of potential etiologic agents is complicated by the long latency known to exist between initial adverse exposures and detection of disease through screening or symptoms. Although risk factors may strongly predict disease in groups with specific characteristics, these may not readily translate to person-specific risk of each individual of the group as genetic and behaviors factors may strongly modify the likelihood of a disease developing.\textsuperscript{72} In 1965, Hill developed the following criteria to guide evaluation of causal inference in epidemiologic studies, one or more of the following criteria are routinely noted in most investigations.\textsuperscript{70}

**Strength of the Association**

The disease must occur with greater frequency among exposed than unexposed women; a larger difference between the groups increases the likelihood of a causal relationship. The first Surgeon General’s report of 1964 based on hundreds of studies stated smoking was the cause of lung cancer, one of the strongest causal associations in public health literature.\textsuperscript{71} The 2010 Surgeon General’s report stated that exposure to active smoking and passive inhalation of cigarette smoke damages coronary arteries, lung tissue, and other organs.\textsuperscript{72}

**Biologic Gradient**

When the frequency of a disease is positively correlated with increasing levels of exposure, a dose-response effect may be detected, strengthening the probability of a causal relationship. Early studies revealed that the risk of lung cancer significantly increased with the number of cigarettes smoked per day and total number of pack years of smoking.\textsuperscript{43}

**Temporality**

Exposure to a potential causal factor must precede the onset of disease. For some conditions with long latency between exposures and disease, accurate timing of exposure may be difficult to document. However, timing may be crucial, as was learned with in utero exposure to DES. Use during the first few weeks of pregnancy was found to cause gynecologic abnormalities not detected until 15 or 20 years after birth.\textsuperscript{11} In contrast to the long latency from administration to detection of adverse effects, the week of gestation when thalidomide was used had specific deforming effects on the developing fetus detected at birth.\textsuperscript{11}

**Specificity**

If an exposure is associated with the emergence of a clinical condition at an unexpected age or frequency, a causal interpretation is strengthened. One historical example is provided by a small matched case-control study.
that identified prenatal exposure to DES as the cause of vaginal cancer diagnosed soon after puberty among young women. Other adverse gynecologic effects of this hormonal exposure have complicated the lives of thousands of exposed women.

**Consistency**

When etiologic studies conducted among different populations repeatedly produce similar findings, the probability of a causal effect is increased. Multiple studies associated lack of pregnancy with increased risk of ovarian cancer. A 1955 report noted ovarian cancer deaths were 50% higher among never-married compared to married women. Subsequent research conducted 20 years later indicated nulliparity rather than marital status was associated with development of ovarian cancer.

**Biologic Plausibility**

The suspected association must be biologically plausible in relation to the natural history of the disease. In DES-exposed women vaginal carcinoma appeared after onset of puberty, when increasing levels of endogenous estrogens stimulated tumor growth in previously initiated vaginal tissue. Cramer suggested the biologic explanation for increased ovarian cancer among nulliparous women was associated with uninterrupted menstrual cycles that raise estrogen levels and potentially stimulate cancer development.

**Coherence of Evidence**

When temporal trends indicate corresponding changes in a disease and an exposure, a causal relationship is more likely to exist, as in the correlation of estrogen use for menopausal symptoms and incidence rates of endometrial cancer observed first in ecologic studies and subsequently in analytic evaluations. Similarly, a decline in both breast cancer incidence and exogenous hormone use has followed the 2002 publication of the Women's Health Initiative clinical trial results that clearly linked combined estrogen and progestin with estrogen-positive breast cancer.

**Statistical Assessment of Early Detection Modalities**

The continuing development of new and costly modalities for early detection of disease has been heralded as a major advance in clinical medicine. Reduction in mortality has led to some screening methods being referred to as “preventive” modalities; however, these procedures must meet secondary prevention criteria. Risk of disease is not reduced by screening. Detection at early, asymptomatic stages increases incidence rates, as can be noted in data from the cancer registries of the Surveillance, Epidemiology and End Results (SEER), a National Cancer Institute program, following expansion of cancer screening programs. Early detection methods have been assessed in case-control studies and among cohorts enrolled in the Breast Cancer Detection Demonstration Project that offered free screening to American women, although the gold standard for unbiased assessment is the randomized controlled trial. Some screening modalities, such as the Pap test for detection of cervical cancer, have been adopted by healthcare providers without confirmatory studies.

To assess the benefit of treatment after screening in contrast to therapy at a later stage after onset of symptoms, investigators must address two potential sources of error: lead-time bias and length bias. Lead-time bias describes a time interval between earlier detection of a condition by screening among presumably healthy women and a diagnostic procedure detecting the condition after clinical evidence or symptoms develop. The duration of lead time varies in relation to the nature of the developing condition as well as personal characteristics of study subjects, including age, hormonal status, immune function, presence of comorbid conditions, etc. Although screen-detected cases may appear to benefit from longer survival time than cases diagnosed with symptoms, the possibility exists for the screened individual to have lived longer with the disease without benefit of improved length of survival. Therefore, the statistic noting the proportion of people with screen-detected cancers surviving 5 years or longer includes the lead time obtained through earlier diagnosis by screening.

Length bias described the recognized problem that screening often detects diseases with long presymptomatic phases; the length of this phase varies considerably with the natural history of the diseases as well as specific patient characteristics. Clinical conditions with short preclinical phases are least likely to benefit from screening. Given that screening detects slower growing lesions, many of which may never become symptomatic, Welch and Black have suggested overdiagnosis has occurred. Highly sensitive screening methods applied to subclinical cases of disease using methods such as mammography and newer procedures, including magnetic resonance imaging (MRI), detected conditions that may not have surfaced during the woman’s lifetime in the absence of screening. In such settings, early diagnosis through screening may be harmful; women potentially receive detrimental treatment for conditions not clinically lethal. Molecular markers are being identified to enable separation of more indolent disease from potentially aggressive lesions in order to avoid morbidity from unnecessary invasive screening and treatment.

Screening tests must meet acceptable standards of accuracy before being applied to presumably healthy women. Four measures used to describe the level of accuracy of screening tests are calculated by comparing the true health status in relation to the test result as noted.

1. **Sensitivity**: the probability of screened women with the condition who test positive

\[
\text{True positives = true positives + false negatives}
\]
2. Specificity: the probability of screened women who do not have the condition and test negative

\[
\text{True negatives} = \frac{\text{true negative}}{\text{true negative + false negative}}
\]

3. Positive predictive value: the proportion of screened women testing positive who have the condition

\[
\text{True positive} = \frac{\text{true positive}}{\text{true positive + false positive}}
\]

4. Negative predictive value: The proportion of screened women testing negative who do not have the condition

\[
\text{True negative} = \frac{\text{true negative}}{\text{true negative + false negative}}
\]

Statistic Measures of Association—Quantifying Risk of Disease

Carefully designed epidemiologic research requires appropriate analytic methods to address specific research questions. An essential component of each investigation is clearly defined statistical procedures that will be applied to assess relationships between “independent” variables and specific disease “outcomes.” Estimates of association are calculated with 95% confidence intervals.

Absolute Risk, Relative Risk, Odds Ratio, and Attributable Risk

Absolute risk (AR) defines the probability of diagnosing a disease in members of a cohort over a defined interval of time. A descriptive example is the incidence of hypertension detected at initial assessment and at a follow-up examination 24 months later in relation to obesity. The strength of the absolute risk of an exposure depends upon its biologic effect and the prevalence of the disease in question.

Relative risk (RR), the ratio of two absolute risks, estimates the strength of the relationship, if one exists, between a defined risk factor and a disease.

\[
\text{Relative Risk} = \frac{\text{Absolute risk of hypertension among obese women}}{\text{Absolute risk of hypertension among nonobese women}}
\]

For example, to determine if obesity, defined as body mass index > 30, is associated with newly detected hypertension 24 months after enrollment of a cohort of older women, the rate of hypertension among obese participants is compared with the rate of among cohort members who were not obese when initially assessed.

Odds ratio (OR) is an alternative measure to RR. Because recruitment for case-control studies begins with disease status, estimates of absolute risk and RR are not possible. Statisticians have proven that ORs provide reliable and valid estimates of RRs when case/control studies enroll incident (newly diagnosed) cases and unbiased representative controls. In this example, appropriately selected controls are assumed to represent normotensive members of the population at large.

Odds Ratio = \[
\frac{\text{Odds of hypertension among newly identified hypertensive (cases) women}}{\text{Odds of hypertension among normotensive (control) women}}
\]

Rather than a single measure, obesity can also be defined by differing levels: normal weight, overweight, obese, and morbidly obese. Using graduated categories of obesity enables calculations of ORs potentially indicating a dose response association with hypertension.

A confounding factor may be associated with obesity but may also be an independent risk factor for hypertension such as a diet high in salt. When confounding factors are suspected, studies require data collection and analyses designed to address potential confounding.

Population Attributable Risk (PAR) is an estimate of the number of cases of a condition that might have been avoided if exposure to a causal factor had not occurred. The magnitude of attributable risk is correlated with the RR or OR associated with the risk factor and the prevalence of the exposure in the population; therefore, the PAR for lung cancer associated with smoking increased in parallel with increasing prevalence of cigarette sales. Although cigarette smoking has declined in recent decades, the residual adverse effect of the behavior continues to influence lung cancer incidence rates, which are beginning to decline in the 21st century.

Interpreting Measures of Association

If the rates of disease are comparable in the exposed and unexposed groups, the relative risk would be approximately 1.0, indicating the exposure is not associated with risk of the disease in the population studied. Calculated relative risks greater than 1.0 indicate an increased likelihood of disease associated with the risk factor, and RR less than 1.0 suggests a decreased probability of disease or a potential protective factor. When the 95% confidence interval (CI) describing the range of possible relative risk or odds ratio estimates includes 1.0, no statistically significant difference exists between exposed and unexposed in relation to the factor being studied.

Some studies may produce relative risks or odds ratios that satisfy the usual criteria of statistical significance denoted by a value less than 0.05 indicating a low probability (less than 1 in 20) of the result being due to chance and the confidence interval does not include 1.0. However, other factors must be considered before research findings are considered important for public health. The magnitude of the estimate, the width of the confidence interval, and the biologic plausibility must be considered before a research result is considered a true and important contribution to public health.

False-positive results may occur due to bias in study design, selection of the study population, instruments used for data collection, etc. Publication bias, the tendency of investigators to submit positive results and the tendency of journals to preferentially publish statistically significant findings, increases attention paid to potentially false-positive results. Therefore, replication studies are essential, as they rarely confirm false-positive findings.
that were due to chance; however, confirmatory studies may produce false-positive results if similar study subjects and data collection materials are used. For these reasons, the diverse results from studies of differing designs must be considered. Greater confidence in research findings should be associated with mutually compatible results obtained from several differently designed studies conducted among diverse populations.**\(^2\)** Many epidemiologists are skeptical of weak relative risks or odds ratios less than 3.0 if the finding is new and unexpected (Table 2-4).**\(^2\)**

> When the results of some investigations meet the expectations or beliefs of advocates and concerned members of the public, the study findings may receive inappropriate overly enthusiastic coverage by the media, often stimulating demands for further research.**\(^2,\)** Although the magnitude of the risk is vital to assess, relatively small differences in adverse exposures may affect the health of many people when a large percentage of the population is exposed.

Examples of risk assessments are included in Table 2-5.

### Table 2-4

<table>
<thead>
<tr>
<th>Cause-effect</th>
<th>Bias</th>
<th>Confounding</th>
<th>Chance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factor is significantly associated with disease, meets one or more causal criteria</td>
<td>Systematic errors distort results – ex. Recall bias, biased study population selected</td>
<td>Finding due to an independent exposure related to the risk factor &amp; condition being studied</td>
<td>(P)-value (&gt;0.05) or (P&lt;0.05) large study population with small, biologically meaningless finding</td>
</tr>
</tbody>
</table>

### Table 2-5

<table>
<thead>
<tr>
<th>Relative Risk</th>
<th>Impact of Risk on Disease</th>
<th>Change in Risk</th>
<th>RR/OR [95% CI]*</th>
<th>Examples from Text Factor &amp; Disease</th>
<th>Chapter &amp; Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.00 &lt;</td>
<td>Extremely increased</td>
<td>(\geq 600 - 1000%) increase</td>
<td>RR=10.0 to RR 32.0</td>
<td>Risk of breast &amp;/or ovarian cancer associated with a BRCA mutation</td>
<td>Ch 41; Ref 16</td>
</tr>
<tr>
<td>5.00 – 9.99</td>
<td>Very great increase</td>
<td>(\geq 500%) increase</td>
<td>RR=7.4 [CI=3.3–16.3]</td>
<td>Alcohol abuse increased risk of bipolar disease in women</td>
<td>Ch 17; Ref 51</td>
</tr>
<tr>
<td>3.00 – 4.99</td>
<td>Large increase</td>
<td>200 – 399% increase</td>
<td>RR=3.9 [CI=2.0–7.7]</td>
<td>Daughter’s risk of ovarian cancer following mother’s diagnosis</td>
<td>Ch 27; Ref 44</td>
</tr>
<tr>
<td>2.00 – 2.99</td>
<td>Moderate increase</td>
<td>100 – 299% increase</td>
<td>RR=2.38 [CI=1.79–3.18]</td>
<td>Diabetes increased the risk of vascular dementia</td>
<td>Ch 24; Ref 91</td>
</tr>
<tr>
<td>1.35 – 1.99</td>
<td>Small increase</td>
<td>35 – 99% increase</td>
<td>RR=1.43 [CI=1.1–1.9]</td>
<td>Poor oral health increased risk of malnutrition in the elderly</td>
<td>Ch 36; Ref 62</td>
</tr>
<tr>
<td>1.21 – 1.34</td>
<td>Minimal increase</td>
<td>10 – 34% increase</td>
<td>RR=1.33 [CI=1.2–1.5]</td>
<td>Secondhand smoke increased risk of lung cancer among non-smokers</td>
<td>Ch 25; Ref 23</td>
</tr>
<tr>
<td>1.01 – 1.20</td>
<td>Slight increase</td>
<td>1 – 9% increase</td>
<td>RR=1.13 [CI=1.02–1.24]</td>
<td>Early menarche (age&lt;12 yrs) increased risk of adult hypertension</td>
<td>Ch 8; Ref 69</td>
</tr>
</tbody>
</table>

(continues)
Multifactorial Research

Early in the 20th century research efforts focused on identifying specific bacterial and viral causes of infectious disease, which eventually enabled vaccines to be developed and diseases prevented. Recently, similar study designs have heralded the discovery of infectious components of several chronic conditions, providing the opportunity to dramatically change the incidence and mortality associated with cervical cancer\(^1\) and stomach cancer\(^2\) among other conditions. Although these single agents may be necessary in the causal pathway to disease development, increased susceptibility is dependent upon more complex cofactors, including physiologic, emotional, and behavioral patterns of women at risk. Therefore, appropriate research must be multidisciplinary, using new measurement technologies and analytic techniques.\(^3\) As biospecimens are relied upon for measurements of exposures and genetic differences among study subjects, ethical and legal issues must be addressed to ethically obtain informed consent while protecting the privacy of research subjects whose invaluable resources are selected for analysis.\(^4\)

Research has repeatedly shown that exposure-disease associations vary among different populations depending on host characteristics such as gender, age at time of exposure, nutrition status, inherited risk, and epigenetic factors. Genetic factors may differ even within families in which inheritance of the susceptibility genotype varies among parents and siblings; differing environmental exposures also contribute to disease risk among blood relatives.\(^5\) Such variation, referred to as interaction or effect modification, raises important questions about the etiologic factors being investigated and emphasizes the individual nature of disease risk and the future of personalized medicine.

Conflicting Epidemiologic Research Findings

Epidemiologic studies of varying designs conducted among diverse populations often produce inconsistent or conflicting findings that confuse the public. Since epidemiologic research often addresses clinically important aspects of health and disease in diverse populations, the findings may not pertain to specific study participants with person-specific genetic and environmental risks of disease. However, clinicians guide individuals based on research results, and the public often responds to media presentations of newly published findings.\(^6\) Therefore, some investigators and journalists caution against quick acceptance of early study results and may suggest that the public delay major health behavior changes until additional data are published.\(^6\)
Differences may be anticipated when results of case-control studies are compared with associations reported from cohort studies in which women are followed over varying intervals of time. Data obtained from newly diagnosed cases may be influenced by disease status and not recalled accurately in comparison to controls, in contrast, cohort studies collect data over time. Risk factors are experienced reducing the likelihood of distorted recall.

Unique susceptibility or protective factors may be active among some members of study populations partially contributing to divergent outcomes, although study methodology may also influence the consistency of results when comparing studies of similar design including: data collection methods, self-reported health status vs. physical examination, conflicting definitions of specific conditions or clinical events, varying dosages and frequency of medication use, etc. Additional larger investigations may be required to accurately determine potential etiologic factors.

Statistical Power
Before a study is launched or funding sought, the number of participants required to ensure adequate power must be determined. The size of the population influences the probability of finding a statistically significant relationship between risk factors and disease outcomes if one truly exists. In a case-control study, the number of women needed for each group is determined by the prevalence of the exposures being studied and their expected effect on risk factors of disease. Similarly, when establishing a cohort study, the frequency and magnitude of exposures to the risk factors and their impact on study outcomes all affect the number of participants required for baseline and follow-up data collection. In addition, the width of the confidence interval from a cohort study provides the range of the true effect and a measure of the study’s power.

Meta-Analyses and Reviews
Many epidemiologic studies are of limited sample size and are conducted in diverse settings often producing weak correlations. To obtain a summary estimate from individual published studies, the statistical technique called meta-analysis was developed and has been frequently applied to major topics of interest. The selection of published investigations to include in these composite analyses may be difficult because not all research reports may be available for inclusion in meta-analyses. To address additional biases that may influence results of meta-analyses, guidelines to improve the quality of these important contributions to epidemiology research were published by a concerned team of investigators. Although well-designed studies of adequate size are preferred to detect meaningful associations of risk factors and disease, pooled analyses can provide meaningful information when collaborators are able to combine raw data from multiple investigations that were similarly conducted providing comparable measures of exposures and disease outcomes.

Future of Epidemiology Studies
Some critics have suggested epidemiologic methods are too imprecise to adequately measure subtle adverse or protective effects of low-level exposures. Others have questioned the reliance on self-reported personal information including imprecise measures of environmental contaminants, which often produce conflicting or falsely positive results. Recently, epidemiology has been accused of creating unnecessary anxiety after repetitive studies produce inconsistent findings that receive extensive attention by the media. However, observational studies remain essential for assessment of health behaviors and clinical outcomes that ethically cannot be randomly assigned for experimental investigations. New technology is being developed to measure endogenous factors as well as past and current environmental exposures. These developing tools have encouraged investigators to assemble data from diverse sources, stimulating development of causal inferences and potentially guiding future public health interventions. As this field of research matures aided by new scientific approaches and techniques, studies will be able to produce more consistent and valuable findings, which will increase respect for and reliance on epidemiology.

Summary
Well-designed epidemiologic studies, whether observational or experimental, contribute to understanding factors associated with disease development and prognosis. Statistical methods enabling assessment of the strength of causal or protective associations have evolved to accommodate multifactorial exposures of interest. The magnitude and biologic plausibility of identified etiologic agents contribute to causal hypotheses. Caution is advised when unexpected results are first presented; replication in different settings is essential to confirm newly identified risk factors. Technology advances have provided less costly molecular studies of biosamples, including blood and tissue specimens, fostering multidisciplinary investigations requiring complex analytic procedures. Gene-environment studies are providing new opportunities for more personalized assessment of health risks with the potential for disease prevention.
Discussion Questions

1. What are the major goals of epidemiology research? What study designs are most useful? Describe the strengths and weaknesses of each.

2. Describe the benefits and risks of early detection. Discuss the conflicts associated with screening methods.

3. To consider a factor an etiologic agent of disease causation, what criteria are used? Provide an example.

4. Methods of selection and recruitment of study participants is extremely important for epidemiologic studies. Describe the most desirable methods.

5. How does assessment of relative risk (RR) differ from calculation of an odds ratio (OR)?

6. When are statistical findings considered significant? How do you determine their public health significance?

References


