CHAPTER

3

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Epidemiology

INTRODUCTION

Cancer epidemiology examines the frequency of cancer in populations, the role of risk factors that contribute to cancer rates, and the interrelationships or associations that exist between the host, the environment, and other conditions that may contribute to the development or inhibition of cancer.[1] The basic premise of epidemiology is that disease does not occur randomly, but rather follows describable patterns that reflect the underlying etiology or causes of cancer. Because disease does not occur randomly, individuals who have cancer must have been exposed to some factor, either voluntarily (through diet, medication, or smoking) or involuntarily (through factors such as cosmic radiation, air pollution, occupational hazards, or genetic constitution), that contributes to the causation of disease.[2] The application of epidemiology to cancer research allows investigators to identify possible causes of disease by elucidating how exposures differ between those persons with and without disease.

The first section of this chapter reviews basic epidemiological concepts. These concepts will help the reader better understand cancer epidemiology, including how to identify groups at higher risk for cancer development and how to conduct research in the field of cancer epidemiology. After reading this chapter, the reader should understand the major issues involved in cancer research, including study design, assessment of cancer risk, and interpretation of research findings. A brief glossary of fundamental terms used in the field of epidemiology is given in **Table 3-1**.[4] **Table 3-2** includes rates and ratios frequently calculated in epidemiological research.[3] Subsequent sections discuss causes of cancer, risk factors that influence cancer susceptibility, and the application of epidemiological principles to nursing practice.

TABLE 3-1

Glossary of Epidemiological Terms

Term	Definition
Agent (of disease)	A factor, such as a microorganism, chemical substance, or form of radiation, whose presence, excessive presence, or (in deficiency disease) relative absence is essential for the occurrence of disease.
Association	Statistical dependence between two or more events, characteristics, or other variables. An association is present if the probability of occurrence of an event or a characteristic, or the quantity of a variable, depends on the occurrence of one or more other events or characteristics, or the quantity of one or more variables.
Bias	Deviation of results or inferences from the truth, or processes leading to such deviation. Any trend in the collection, analysis, interpretation, publication, or review of data that can lead to conclusions that are systematically different from the truth.
Case	In epidemiology, a person in the population or study group identified as having the particular disease, health disorder, or condition under investigation. The epidemiological definition of a case is not necessarily the same as the ordinary clinical definition.
Case-control study	The observational epidemiological study of persons with the disease of interest (cases) and a suitable group of persons without the disease (controls). The relationship of an attribute to the disease is examined by comparing the diseased and nondiseased persons with regard to how frequently the attribute is present, or the levels of the attribute in each group.
Cohort study	The analytic method of epidemiological study in which subsets of a defined population can be identified who are, have been, or in the future may be exposed or not exposed, or exposed to different degrees, to a factor or factors hypothesized to influence the probability of occurrence of a given disease or other outcome. The main feature of a cohort study is the observation of large numbers over a long period (years) with comparison of incidence rates in groups that differ in exposure levels.
Confounding	The distortion of the apparent effect of an exposure on risk brought about by the association with other factors that can influence the outcome. A situation where it is not logically possible to separate the contribution that any single causal factor has made to an effect.
Control	Subjects with whom comparison is made in a case-control study, randomized controlled trial, or other variety of epidemiological study. Selection of controls is crucial to the validity of epidemiological studies.
Ecological analysis	Analysis based on aggregated or grouped data; errors in inference may result because associations may be artifactually created or masked by the aggregation process.
Epidemiology	The study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to control of health problems.

Term	Definition
Etiology	The study of the causes of diseases.
False negative	Negative test result in a person who possesses the attribute for which the test is conducted. The labeling of a diseased person as healthy when screening for the detection of disease.
False positive	Positive test result in a person who does not possess the attribute for which the test is conducted. The labeling of a healthy person as diseased when screening for the detection of disease.
Historical cohort	A study using a cohort defined in the past. This method uses existing records about the health or other relevant aspects of a population as it was at some time in the past, and determines the current (or subsequent) status of members of this population with respect to the condition of interest.
Incidence	The number of new events—for example, new cases of a disease in a defined population—within a specified period of time. Incidence rates can be used to evaluate the changing patterns of disease frequency within a population and to assess the effectiveness of screening programs and treatment modalities on disease development.
Intervention	An investigation involving intentional change in some aspect of the status of the subjects—for example, introduction to a preventive or therapeutic regimen—or designed to test a hypothesized relationship; usually a randomized controlled trial. Community interventions focus on the group or community and evaluate the benefits of new policies and programs, determining which interventions have an effect on the health of those persons who receive the intervention and which do not.
Nested case-control study	A study in which cases and controls are drawn from a population that is already under investigation in a cohort study.
Odds ratio (OR)	Used with case-control data, the ratio of the odds in favor of exposure among the cases to the odds in favor of exposure among the noncases.
Population	The number of persons in a defined group who are capable of developing the disease. Can also refer to the general population; the whole collection of units from which a sample may be drawn; not necessarily a population of persons, the units may be institutions, records or events.
Power	The ability of a study to demonstrate an association if one exists. The power of a study is determined by several factors, including the frequency of the condition under study, the study design, and the sample size.
Prevalence	The number of events—for example, instances of a given disease or other condition—in a given population at a designated time. The prevalence rate is the total number of all individuals who have an attribute or disease at a particular time (or during a particular period) divided by the population at risk of having the attribute or disease at this point in time or midway through the period.
Randomized controlled trial (RCT)	An epidemiological experiment in which subjects in a population are randomly allocated into groups, usually called study and control groups, to receive or not receive an experimental preventive or therapeutic procedure, maneuver, or intervention.
Rate	A measure of the frequency of occurrence of a phenomenon; an expression of the frequency with which an event occurs in a defined population in a specific period of time.
Relative risk (RR)	The ratio of the risk of disease or death among the exposed to the risk among the unexposed. The RR is generally used in cohort studies.
Sensitivity	The proportion of truly diseased persons in the screened population who are identified as diseased by the screening test. A measure of the probability of correctly diagnosing a case.
Specificity	The proportion of truly nondiseased persons who are identified by the screening test. It is a measure of the probability of correctly identifying a nondiseased person with a screening test.
Spurious	As applied to associations between an exposure and outcome, referring to non-causal associations due to chance, bias, or failure to control for extraneous confounding variables.
Validity	An expression of the degree to which a measurement measures what it purports to measure. Internal validity: When the index and comparison groups are selected and compared in such a manner that the observed difference between them on the dependent variables under study may be attributed only to the hypothesized effect under investigation. External validity (generalizability): A study having unbiased inferences regarding a target population (beyond the subjects in the study). For example, a study that uses as its population a specific profession, such as nurses, may yield results that are not relevant to all women in the general population.

Source: Reproduced from Last with permission of Oxford University Press.[4]

TABLE 3-2

Rates and Ratios Commonly Used in Epidemiology

Rate Name	Rate Description	Population Factor
Crude birth rate	Number of live births: average or midyear population	per 1000
Fertility rate	Number of live births: 15- to 41-year-old women at midyear	per 1000
Crude mortality rate	Total number of deaths: total population at midyear	per 1000
Age-specific mortality rate	Deaths in specific age group: midyear population in age group	per 100,000
Cause-specific mortality rate	Deaths from a specific cause: total midyear population	per 100,000
Infant mortality rate	Deaths of children younger than 1 year of age: number of live births	per 1000
Neonatal mortality rate	Deaths of infants younger than 28 days: number of live births	per 1000
Case fatality rate	Number of deaths from a disease in a given period of follow-up: number of diagnosed cases of disease at start of follow-up period	per 1000
Proportional mortality rate	Number of deaths from a given cause: number of deaths from all causes	per 1000
Morbidity rate	Number of cases of the disease that develop in a given period: total population at mid-period	per 100,000

BASIC CONSIDERATIONS IN EPIDEMIOLOGICAL RESEARCH

Multiple components need to be considered when evaluating an epidemiological study: (1) the study design; (2) how study parameters were operationalized, including the disease, the exposure, and the relevant populations; (3) the statistical analysis used to test the association between exposure and disease; and (4) the identification of potential threats to validity, including bias and confounding.[4]

STUDY DESIGN

Epidemiological studies may be categorized as either descriptive or analytic. A descriptive study describes the existing distribution of variables, without regard to a specific hypothesis. Annual statistics on cancer incidence and mortality are descriptive epidemiology. Analytic studies are designed to examine associations between exposures and disease. Analytic studies can be either observational or experimental.[5] The majority of epidemiological studies are observational, as most studies observe the natural course of events, without intervention or experimental influence. Observational studies include case-control studies, cohort studies, cross-sectional studies, and ecologic studies.[5] Experimental epidemiology includes clinical trials and intervention studies, where the investigator influences the natural course of events.

This section discusses the general features of these study designs; however, primary emphasis is placed on the three designs most commonly used in epidemiological cancer research: the case-control, cohort, and clinical trial study designs.[5] In selecting the appropriate study design, several factors must be considered: the frequency of the disease or the exposure in the general population and the defined population to be studied, the length of the latency period for the disease to develop, the anticipated size of the study population, the time allowed for subject recruitment, the diagnostic characteristics of the disease, and the measurability of the exposure.[4]

Case-Control Studies

The hallmark of the case-control study (as illustrated in **Figure 3-1**) is that it begins with people with the disease

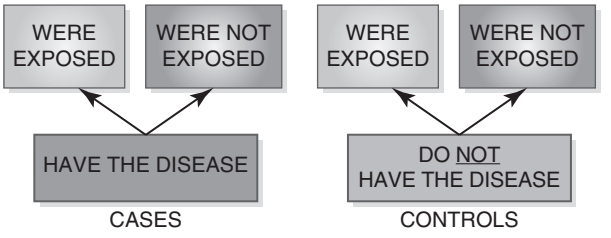

FIGURE 3-1

Design of a case-control study.

Source: Reproduced from Gordis.[5]

(cases) and compares them to people without the disease (controls).[5] Subjects in case-control studies are recruited on the basis of their disease status. Cases of the disease in question can be either preexisting (prevalent) cases or newly developed incident cases. Generally, a strict definition of the disease is used to identify eligible subjects. For example, pathology slides, cytology results, or medical records can be examined to identify the stage or histology of a specific type of cancer. Control subjects, or noncases, are defined as individuals who do not have the disease at present, but who, if the disease did develop, would have the same opportunity to be diagnosed as the case subjects.

The assumption that cases and controls originate from the same hypothetical source population is a critical issue affecting the validity of case-control data. Both cases and controls must originate from populations having similar and relevant characteristics. In this instance, the control group can be regarded as a reasonably representative sample of the case reference population. The selection of an appropriate control group represents the major challenge with case-control studies, and often serves as a source of selection bias in a case-control study.[6]

The information gained from case-control studies does not establish a causal relationship between the disease and the exposure, but it does explore the concurrent association between the two. The case-control study design should be considered if at least one of the following criteria is met: (1) the disease is rare in the general or source population (many forms of cancer meet this criterion); (2) the investigation is preliminary; or (3) time and funding limitations rule out the use of larger, more expensive study designs. If an association is significant in a case-control study, it can be used to justify the use of larger cohort studies or clinical trials to further investigate the causality of the relationship.

When conducting a case-control study, it is important to be aware that cases and controls may differ in characteristics or exposures aside from the ones that are under investigation. As an example, suppose we are interested in conducting a case-control study to determine whether lung cancer is linked to cigarette smoking. With this study design, we would start with the disease outcome (e.g., lung cancer) and retrospectively examine the extent of smoking among cases and controls. Notice that age is related to length of smoking history as well as to cancer of the lung. The confounding effect of age could be avoided by selecting cases and controls of the same age group or matching the two groups by age.[7]

Matching is the process of selecting controls on characteristics beyond the targeted factors of a study, so that the controls are similar to the cases on certain characteristics, such as age, race, sex, socioeconomic status (SES), menopausal status, or occupation.[5] Two matching techniques are used in epidemiological research: frequency matching and individual matching. In frequency matching, the proportion of controls with a certain characteristic is identical to the proportion of cases with the same characteristic. In individual matching (also known as matched pairs), a control is selected for each case based on specific variables or matching factors. If a 50-year-old postmenopausal white woman was enrolled as a case, for example, then a 50-year-old white postmenopausal woman would also be sought as a control. In addition to such 1:1 matching, individual-level matching can be done at any other ratio, such as 1:2 or 1:3. The advantage of matching and analyzing the data for pairs of subjects is that fewer subjects are required in each group to discern a relationship between the exposure and the disease. Matching enhances the ability to substantiate a true association between an exposure and a disease outcome. It is useful when small numbers of case subjects with the disease are available for study and when efficiency is a major issue. Matching also provides a means for controlling for potential confounding introduced by the selection of the control group.

The following example describes a case-control study that used matching to examine breast cancer in relation to occupational exposure to electromagnetic fields (EMF), an exposure about which little is known. The cases were 6213 patients with invasive breast cancer identified from hospitals in Massachusetts, New Hampshire, and Wisconsin that reported to their respective state cancer registry. Eligible cases were between 20 and 69 years old. A total of 7390 controls were identified from lists of licensed drivers and rosters of Medicare beneficiaries. The cases and controls were randomly age-matched within a five-year age strata. Data were collected through phone interviews that included questions on breast cancer risk factors such as smoking, alcohol consumption, menstrual and reproductive history, exogenous hormone use, medical history, diet, physical activity, marital status, and family history. Women were also asked to report their occupational job history beginning at age 14 for any job held for at least 1 year in which the woman worked at least 4 hours per week. Occupational categorization of EMF exposure was based on the *Dictionary of Occupational Titles* classification system. The results illustrated that, when compared to the reference of women with only background exposure, the odds ratio (OR) adjusted for age and state of residence was 1.06 (95% confidence interval [CI]: 0.99–1.14) for women with low exposure, 1.09 (95% CI: 0.96–1.23) for women with medium exposure, and 1.16 (95% CI: 0.90–1.50) for women with high exposure. Women with high EMF exposure were 16% more likely to have breast cancer than unexposed women, while their peers

in the low- and medium-exposure categories were at 6% and 9% greater risk for breast cancer, respectively.[8]

Two problems may arise from matching. First, if an attempt is made to match on too many characteristics, it may prove difficult or impossible to identify an appropriate control for each case. Second, once cases and controls have been matched on a given characteristic, that characteristic cannot be studied in relation to the disease; thus caution is advised on matching for any variable that an investigator may want to analyze in a study.

Cohort Studies

A cohort study seeks to investigate whether the incidence of an event is related to a suspected exposure. That is, a cohort study is an incidence study. It starts with a group of subjects who are at risk for developing a disease, yet are free of the disease at the beginning of the study, as shown in **Figure 3-2**.[5] Cohort studies can be envisioned as going from cause to effect. The exposure of interest is determined for each member of the cohort, and the group is followed to document the incidence of disease in the exposed and nonexposed cohort members.

Cohort studies can be prospective or retrospective. Cohort studies are considered *prospective* or *concurrent* when the cohort is assembled at the present time and the subjects are followed prospectively through calendar time until a point at which either the disease did or did not develop is ascertained. The disadvantages of prospective studies relate to the amount of time and exorbitant costs that are needed to conduct them, and to whether the outcome of interest has had a sufficient length of time appropriate for a specific disease to develop.

The Nurses' Health Study is one of the most prominent examples of a prospective cohort study.[9–12] The first Nurses' Health Study cohort (NHS I) was established in 1976 among 121,701 married female registered nurses from 11 states, ages 30–55 years. Nurses were enrolled in the study and then responded to a questionnaire about their medical histories and lifestyles. Follow-up questionnaires were sent biennially to update information on risk factors and medical events. All included nurses were studied for weight gain, hypertension, dietary intake, reproductive behaviors, menopausal status, family history, hormone replacement therapy (HRT), physical activity, medical history, smoking status, and alcohol consumption. Blood samples have allowed researchers to explore biomarkers and genetic factors. The second wave of this study began in 1989 (Nurses' Health Study II). This study is now in its third wave of data collection, which began in 2010 with the Nurses' Health Study III (NHS III). Data from the NHS have been used to address several hypotheses germane to cancer research, including the association of estrogens, caffeine intake, tubal ligation, night-shift work, plasma inflammatory markers, menopausal status, and weight gain with breast, ovarian, pancreatic, and colorectal cancer risks.[9–12]

An alternative approach to the prospective cohort study design is the nonconcurrent cohort, also known as the *historical* or *retrospective cohort study*. With this design, a previously defined cohort is identified and assembled from the past on the basis of existing records; disease outcome (development or no development of disease) is ascertained at the time when the study began (**Figure 3-3**).[5] Retrospective studies are notably less expensive and can be implemented more expeditiously than prospective studies. Their main disadvantage stems from their reliance on

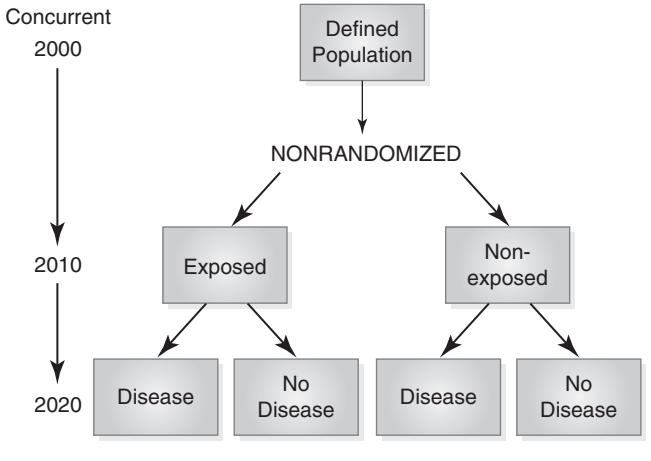

FIGURE 3-2

Design of a cohort study beginning with a defined population.

Source: Reproduced from Gordis.[5]

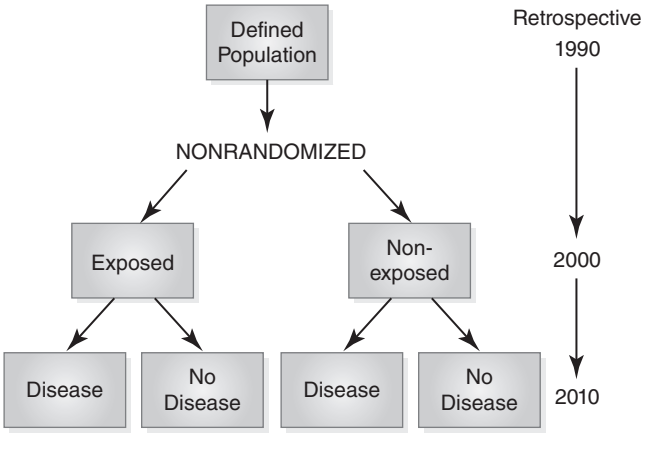

FIGURE 3-3

Time frame for a hypothetical retrospective cohort study begun in 2012.

Source: Reproduced from Gordis.[5]

available information; consequently, the quality of exposure or outcome data is sometimes less than ideal for fulfilling the study objectives. Many occupational cohort studies are conducted retrospectively.

Case-control studies within a cohort study are *ambidirectional studies* known as *nested case-control studies*,[13] because they combine some of the features and advantages of both cohort and case-control designs. The selection of participants is carried out using a case-control approach from a previously established cohort, as shown in **Figure 3-4**.[13] Ambidirectional designs are increasingly being used for cost-efficiency, when analysis of all cohort members would require substantial resources, or to preserve precious biologic specimen.[13]

Cross-Sectional Studies

Cross-sectional studies allow an investigator to study the relationship between an exposure (e.g., EMF) and a disease outcome (e.g., leukemia) by surveying a population, and determining the exposure status and disease outcome status simultaneously (**Figure 3-5**).[14] Cross-sectional studies are referred to as "snapshot" studies because they provide a one-time view of a population's rate of existing (prevalent) cases of the disease, the degree of exposure, and other demographic characteristics of interest at a single point in time. While cross-sectional studies cannot establish a causal relationship between an exposure and a disease, they do provide descriptive statistics for the population and are often used as the preliminary step in establishing disease or exposure status in cohort studies. The unit of analysis in a cross-sectional study is the individual.

Ecological Studies

Ecological studies in epidemiology occupy an intermediate position between descriptive and analytical investigations; they share characteristics with descriptive studies but serve

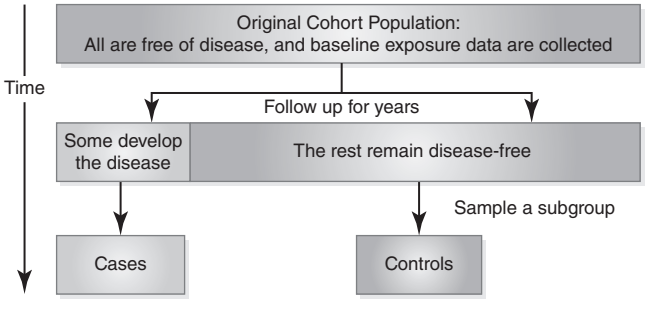

FIGURE 3-4

Schematic of a nested case-control study.

Source: Reproduced from Stanford School of Medicine.[13]

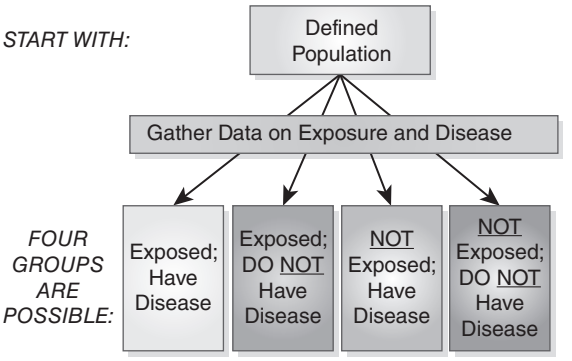

FIGURE 3-5

Design of a cross-sectional study: identification of four subgroups based on presence or absence of exposure and presence or absence of disease.

Source: Reproduced from Gordis.[5]

etiological objectives.[14] These studies are popular because they use existing databases that offer large exposure variations if the data cover broad geographic areas.[15] The exposure and disease under investigation in ecological studies are not ascertained for specific individuals but rather across groups and whole populations.[16] When an exposure is fairly common, such as smoking, sunlight, or fat consumption, ecological studies can elucidate the possible effects of these exposures.[17] For example, skin melanoma is more common in geographic latitudes with more sunshine exposure, and countries with higher per capita intakes of sugar tend to be the same countries with higher rates of prostate cancer mortality.[18]

The caveat of using ecological studies is that they do not prove causality. This is the phenomenon of ecological fallacy—that is, "the bias that occurs because an association observed between variables on an aggregate level does not necessarily represent the association that exists at an individual level."[19] Specifically, ecological data cannot be used to characterize within-area variability in exposures and confounders; the unit of analysis is the population, rather than the individual.

Despite their limitations, ecological studies do have merit within epidemiological research. They are quick, simple to conduct, and inexpensive. When little is known about the association between an exposure and disease, an ecological study is a reasonable place to start for generating hypotheses.[2]

Clinical Trials and Interventions

Experimental studies maintain the greatest control over the research setting. Random allocation is used to assign subjects either to receive or not receive a treatment or to

be assigned to either the exposed or unexposed group. However, it is obviously not acceptable or ethical to expose humans intentionally to a potential carcinogenic agent in an attempt to ascertain causality of an association with cancer.[10] Thus, only after substantial and consistent evidence has accumulated from experimental animal studies should human experimental study designs be employed.

A clinical trial or intervention study is a planned experiment designed to test a specific medical treatment. This type of study seeks to assess the efficacy of a treatment by comparing outcomes for patients who received the test treatment with outcomes for comparable patients who receive the control treatment. Both groups of patients are enrolled, treated, and followed over the same period.[20]

Once clinical trial participants have been screened for eligibility, they are randomly assigned to one of the study groups. Members of the intervention group receive the test treatment, while members of the control group receive a placebo or standard care. A randomized clinical trial may, for example, randomly assign a group of cancer patients to a particular drug regimen and assign a similar group of cancer patients to a course of not receiving the drug. The two groups are monitored over the duration of the study, with researchers comparing the groups' survival, cure ratio, and occurrence of adverse events.

To preserve the objectivity of the data gathered in clinical trials, a blinded approach is used. Participants are blinded as to which group assignment they have—that is, either the treatment or the control group. This prevents attrition from subjects randomized to the placebo arm of a trial deciding to drop out. Additionally, the investigator can be blinded to the subjects' assignments, creating a double-blind design. A double-blind design protects against an investigator influencing a trial's outcome, particularly if a drug manufacturer is financing the trial.[2]

A major benefit of a double-blind, placebo-controlled clinical trial is that the random assignment of patients to treatment groups helps to distribute potential confounding variables evenly between the groups; this serves to minimize the confounding effects on the association between an exposure and an outcome. If this control of confounding is successful and the primary difference between the two treatment groups is the intervention, then a clinical trial can definitively evaluate the efficacy of an intervention.[21]

An example of a clinical trial is the beta-carotene and retinol efficacy trial (CARET), which used random assignment to test the efficacy of a daily combination of 30 mg of carotene and 25,000 international units (IU) of retinyl palmitate (retinol) on the incidence and mortality of lung and other cancers compared to placebo among 18,314 participants who were at high risk for lung cancer because of a positive history of either smoking or asbestos exposure. Participants who were randomly assigned to receive the active intervention were found to have a 28% increase in the incidence of lung cancer, a 17% increase in the incidence of death, and a higher rate of cardiovascular disease mortality compared with participants in the placebo group. CARET was stopped ahead of schedule, and participants returned the study vitamins to their study center and provided a final blood sample. CARET participants continue to be followed annually by telephone interview and self-reported mailed questionnaires.[21,22]

Another example of a randomized clinical trial common to cancer epidemiology is the survivorship study, where a novel treatment is compared to standard care among cancer cases. Metastatic melanoma has a poor prognosis; the median survival for patients with stage IV ranges from 8 to 18 months after diagnosis.[23] Dacarbazine was the only chemotherapeutic agent approved by the Food and Drug Administration (FDA) for the treatment of metastatic melanoma when the BRIM-3 Trial was initiated. This phase III randomized clinical trial compared vemurafenib with dacarbazine in 675 participants with treatment-naïve metastatic melanoma with a specific tumor mutation (*BRAF V600E*). A life expectancy of at least three months, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate hematologic, hepatic, and renal function were required criteria for enrolling patients in the trial. Patients were randomly assigned to receive either vemurafenib (960 mg orally twice daily) or dacarbazine (1000 mg/m² of body surface area intravenously every three weeks).[24,25] Interim analysis for overall survival and progression-free survival showed that vemurafenib was associated with reduced risk of death (hazard ratio [HR]: 0.37, 95% CI: 0.26–0.55, $P < 0.001$) and disease progression (HR: 0.26, 95% CI: 0.20–0.33, $P < 0.001$) as compared with dacarbazine. These results illustrated that single-agent vemurafenib was a superior treatment for *BRAF V600E* mutation–positive metastatic melanoma compared to dacarbazine; vemurafenib has since been approved by the FDA to treat patients with late-stage (metastatic) or unresectable melanoma.

A major limitation of the clinical trial design is that several years of follow-up may be required before significant changes in the rate of disease development or outcomes are observed among treatment groups. The length of follow-up will depend on several factors, including the strength of the treatment's effect on the risk of the outcome. Long-term studies raise patient management issues, such as maintaining active participation of subjects, monitoring subject deaths and adverse events, and tracking subjects lost to follow-up. These factors, if unevenly distributed among the treatment groups, may confound the results of an investigation.

STUDY PARAMETERS

Operationalization of study parameters is critical in epidemiology. Determining how to identify cases of interest and measure exposures, or determine exposure status and then ascertain disease outcome, may sound simple, but in actuality has many nuances. The relevant measurement is indicated by the purpose and aims of a study. For example, a molecular epidemiology study might entail a laboratory assay of a circulating biomarker, whereas a neuro-epidemiological study might include assessment of brain function or imaging.

Whether data are collected by questionnaire, in-person interview, physical exam, biologic assay, or any other approach, it is important to consider the quality of a measure. How good is it? Does it truly capture what it purports to measure? The validity of a measure can be ascertained, and has two primary components: sensitivity and specificity. The *sensitivity* of a test is defined as the ability of the test to correctly identify individuals who have a condition of interest from individuals who do not. The s*pecificity* of a test is defined as the ability of the test to correctly identify those with a specific condition of interest from those with other conditions.[5]

Although commonly used for the validity of a screening test to identify disease, sensitivity and specificity can also be applied to the measure of an exposure of interest.

The Disease

Defining the disease in epidemiological studies is the penultimate task in including and excluding the appropriate subjects in a study population. Disease status may be defined by review of medical records, pathological results, blood test results, physical exam, histological characteristics, or results from a psychological battery of tests. To increase the rigor of this step, two different medical professionals, each unaware of the other's findings, can be used to confirm disease status. Clearly, stating disease definition guidelines at the outset can prevent enrolling subjects who are actually ineligible for a study. Once disease status is confirmed for each subject, only then is he or she eligible for study enrollment.

Study eligibility is determined by a set of criteria that are determined to gather a population of subjects with a sufficient prevalence of disease to test the hypothesis efficiently. Eligibility criteria in cancer research typically consist of age ranges, gender-specific factors, race, stage of disease, life expectancy, absence of other cancers except non-basal cell skin cancer, exposure to certain drugs, treatments, and current health status. A strict definition of exclusion criteria should also be stated as part of the study subject screening process. Exclusion criteria may involve previous medical history, inability to provide informed consent due to mental competency, lack of a permanent address if the study design is conducted via telephone or mail, and proficiency with a particular language if the study materials are written and administered in one language.

The Exposure

An exposure in epidemiology comprises a subject's contact with a variable of interest, which may or may not influence the development of a disease. Exposures run the gamut from microenvironmental exposures on an individual level, such as nutrients, medications, physical activity, and genes, to macroenvironmental exposures that affect an entire community, such as air pollution and environmental conditions.[10]

In epidemiological research, exposures are measured by their frequency and duration as well as their ability to synergistically react with one another. Dose refers to a standardized, measured amount of exposure issued (e.g., standard milligrams, as in the case of drugs; grays [Gy] for radiation; number of packs of cigarettes per year; hours of exercise; drinks of alcohol per day). It is imperative to assess whether the dose has remained constant throughout the exposure or whether certain variables or conditions have affected the dose over time. The likelihood of an association between an exposure and disease being causal is stronger if a more intense dose of the exposure is associated with higher rates of a disease.

The Population

In addition to defining the type of study design appropriate for testing a research hypothesis and defining the specific disease and exposure, the source population for study subjects and the actual study population must be determined. This process clarifies to whom the research results can be generalized (external validity), whether the study population represents the source population, and what the overall characteristics of eligible subjects are.

The source population for a study is the larger group or population from which the study subjects are recruited; it is usually a subgroup of the total population. It might include, for instance, residents in a certain city or neighborhood, university students, or all patients attending a particular hospital. Both the procedure to recruit subjects and the inferences that can be made from the results of a study will be influenced by the selection of a source population.

The study population is the group of subjects actually recruited into an investigation from the source population. Recruitment into a study population, based on defined eligibility and exclusion criteria, is planned to provide equal access to all potential subjects within the source population. It is important to review the types of subjects who

were part of the source population but who were not eligible or not approached for recruitment. For example, if subjects were recruited from phone interviews, we could safely conclude that only subjects with telephones were eligible. Because the presence of a telephone in the household might be related to SES, it is possible that the study population might be biased toward subjects with a higher SES. The relationship of SES to the disease under study may be impossible to evaluate or may be altered by how participants were selected for the study.

STATISTICAL ANALYSIS

The hallmark of epidemiological research is the measurement of the occurrence of events and associations between exposures and disease. Descriptive epidemiology is the measurement of the occurrence of health-related events; these can be either existing (prevalent) or new (incident) events. Both *incidence* and *prevalence* are ratios, defined as the number of relevant events (e.g., diagnoses of ovarian cancer) divided by the possible number of events (e.g., females) for a specific place and time (e.g., U.S. women in 2014); these ratios are frequently called rates. An event can also be measured by its *odds*, defined as the ratio of the probability of the event occurring to the probability of a nonevent. Analytic epidemiology is the measurement of associations between exposures and disease; it requires a comparison group, and depends upon the study design used to identify the association.

Measures of association can be either absolute differences in disease frequencies between groups, or relative differences or ratios. *Absolute differences* are preferred for public health interpretations, and include attributable risk among the exposed and population attributable risk. *Relative differences* are used in etiologic investigations, and include the relative risk or rate ratio, and the relative odds or odds ratio. A *rate ratio (RR)* is the incidence of disease among exposed persons divided by the incidence of disease among unexposed persons; a RR is calculated from a cohort study. The survival study is a special type of cohort study where the incidence of disease recurrence or death is measured; in it, the RR is replaced by a *hazard ratio (HR)*. An *odds ratio (OR)* is the odds of exposure among cases divided by the odds of exposure among controls. The OR, which is calculated from case-control studies, has been shown to be approximately equivalent to the RR. While simple calculations for these measures are provided, they are most frequently determined in epidemiological studies from statistical modeling.

The interpretation of these relative differences is based on their magnitude and significance. A value of 1 means there is no effect or no association. A value greater than 1 means that the exposure is associated with the disease; a value less than 1 means that the exposure is a protective factor for the disease. Significance is determined by a *p*-value threshold; a *p*-value of less than 0.05 means that an association is significant and is unlikely to have occurred by chance.[6]

THREATS TO VALIDITY

Bias

Validity is the extent to which the study measures what it is intended to measure; lack of validity is referred to as "bias" or "systematic error." Two types of study validity exist: internal and external. *External validity*, also known as *generalizability*, refers to whether an exposure–disease relationship in a study is applicable to a larger population.[19,26] An association found among middle-aged white men, for example, may not be generalizable to women, or even to all men. For a study to be externally valid, it must also be internally valid. *Internal validity* occurs when a study is free from bias.

To reasonably assert an uncompromised relationship between an exposure and a disease, we must account for any bias that exists in an epidemiological study design. Three primary threats to validity arise in epidemiological studies: selection bias, information bias, and bias due to confounding.

Selection bias occurs when the relationship between exposure and disease is different for those who participate in the study and those who would be theoretically eligible for the study but do not participate.[27] The common consequence of selection bias is that the association between exposure and outcome among those selected for analysis differs from the association among those eligible.[28] For instance, the healthy worker effect may occur in occupational cohort studies. Only employed individuals are eligible for such a study, and workers who are able to maintain employment are relatvively more healthy people.[2] The characteristics of these individuals are, therefore, not generalizable to the overall population.

Information bias is an observational bias that results from measurement error or a difference in the quality of information between comparison groups. The most common form of information bias in a case-control study is *recall bias*. That is, when cases and controls are queried about exposures in the past, one group may have a more inaccurate level of recollection of past exposures. In a case-control study of congenital malformations, the mother of a case may remember every possible exposure, whereas the mother of a control may not remember possible exposures as clearly. Thus, bias on the selection of subjects or the measurement of study data can lead to a spurious association between an exposure and disease.

Confounding

A third threat to validity is bias due to confounding. Confounding variables prevent study groups from being comparable.[4] For instance, if a case-control study shows an association between alcohol intake and lung cancer, we must investigate whether a third factor might distort the relationship between alcohol and lung cancer. Smoking is another risk factor for lung cancer, and is also associated with drinking alcohol. In this case, smoking confounds the relationship between alcohol and lung cancer. The effects of confounding can be addressed by controlling or adjusting for the effects of smoking during statistical modeling, to try to determine the effect of alcohol on lung cancer that is not distorted by confounding by smoking.

INTERPRETING EPIDEMIOLOGICAL EVIDENCE

A statistical test determines if an association is due to chance, but it does not identify whether an association is real or causal. Both systematic error (bias) and random error (chance) can cause a spurious association; only once these errors are alleviated and adequate control of confounding factors is achieved should an association be considered for causality.[26]

Criteria for judging whether an association is causal were first proposed by Austin Bradford Hill and have been amended over time.[29] A causal association is supported by a temporal sequence where exposure preceded the outcome, a strong magnitude of effect, a consistent association across different studies or populations, and a biological gradient or dose–response relationship between the exposure and the outcome. Further, whether an association is biologically plausible and in agreement with existing experimental evidence must be considered. Thus, results from epidemiological investigations should be scrutinized closely, and the totality of the epidemiological evidence must be considered for public health implementation and clinical application.

ADDITIONAL CONSIDERATIONS

When planning or conducting a study, it is important to include epidemiologists and biostatisticians on the research team. The research team develops the research protocol, a document that describes the objectives, design, methodology, statistical considerations, and organization of a research study. The protocol usually also gives the background and rationale for the research study.

Ideally, the research study will sample a large-enough study group to have the ability to draw causal inferences for the general population and to perform a rigorous statistical analysis. Power calculations need to be conducted to ensure that the planned sample size is adequate. A power calculation allows determination of the sample size required to detect an effect of a given size with a given degree of confidence. Conversely, it allows determination of the probability of detecting an effect of a given size with a given level of confidence, under the sample size constraints. If the probability is unacceptably low, the study recruitment plan may be modified.

When conducting and analyzing a study, the goal is to minimize potential errors. Validation of measurements, whether from questionnaires or laboratory assays, will serve to reduce bias. An appropriate and well-conducted analysis is imperative to ensure valid study results. A variety of statistical techniques can be used to prevent or minimize the effects of confounding, including randomization, matching, and statistical adjustment.

Note that this section is intended to serve as a general introduction to key concepts in epidemiology. The reader is referred to numerous excellent texts for further information on epidemiological[2,5,7,10,28] and statistical[19,26] methods and practice.

CAUSES OF CANCER

The causes of cancer discussed here are actually factors associated with cancer risk. Notably, not all factors associated with cancer risk have been proved to directly cause cancer in laboratory experiments. Further, cancer is a multifactorial disease that is influenced by host factors, behaviors, and environmental exposures. For example, not all smokers develop lung cancer, indicating that individual susceptibility also plays a role. Not all people with lung cancer have ever smoked, indicating that other exposures also contribute to the disease. In 1981, Doll and Peto published seminal work that attempted to quantify the avoidable causes of cancer in the United States.[30] More recently, causes of deaths in the United States were attributed to specific behaviors and exposures; the actual top causes of death in the country were found to include tobacco, poor diet/physical inactivity, and alcohol consumption.[31]

Currently in the United States, cancer is the second leading cause of death, second to heart disease.[31] Thus, cancer epidemiologists seek to identify associations between factors of interest and either cancer development or survival.

HOST FACTORS

Age

Age is a major risk factor for many health outcomes. For most cancers, increasing age corresponds to an increasing

risk of disease. As shown in **Table 3-3**, the probability of developing breast cancer is higher (1 in 15) in older women (age > 70) than in younger women; conversely, the probability of developing cervical cancer is higher (1 in 348) in younger women (age < 50) than in older women.[32] Age is also frequently associated with numerous exposures. Even if the effect of age is not among the primary objectives of a study, it is important to assess its relationship with both the exposure and the outcome of interest, given that age can potentially confound a relationship and alter the association detected. Because age is such an important determinant of cancer risk, it is critical in epidemiological studies to make adjustments for age in the statistical analysis, unless comparison groups have the same age distribution.

Sex

The incidence and mortality of cancers in the United States by sex are shown in **Figure 3-6**.[33] The greatest number of cancer deaths predicted for males and females in 2014 were expected from lung cancer (28% and 26% of estimated deaths, respectively). The leading site of incident cancers in men is prostate cancer, followed by lung and bronchus and colorectal cancers. The leading site of incident cancers in women is breast cancer, followed by lung and bronchus and colorectal cancers.[33] In addition to cancers common to both sexes, note that some cancers are specific to only one sex, such as ovarian cancer in women, which is not a top 10 site for incidence, but is the fifth most common cause of cancer deaths among U.S. women.

Race and Ethnicity

Race is generally based on biological constitution. The U.S. Bureau of the Census classifies race into categories such as white, African American, Asian or Pacific Islander, Mexican American, and Native American. Ethnicity is generally based on cultural identity. Race and ethnicity can be difficult to separate, as people who come from a particular racial background may share a common ethnic identification. Further, caution should be used when trying to classify individuals with mixed racial parentage into a specific racial group. Race does have implications for differences in the incidence and prevalence of disease. Racial or ethnic groups may differ in their attitudes toward illness, care seeking, and prevention behaviors.

An illustration of the variation in cancer incidence and mortality from the Surveillance, Epidemiology, and End Results (SEER) data by race appears in **Table 3-4**. The data on prostate cancer, which can be detected by physical exam and prostate-specific antigen test (PSA), reveal how cancer mortality adversely affects African Americans. Approximately 49.8 prostate cancer deaths per

TABLE 3-3

Probability (%) of Developing Invasive Cancers During Selected Age Intervals,* Females, United States, 2008–2010

	Birth to 49	50 to 59	60 to 69	70 and Older
All sites†	5.4 (1 in 19)	6.0 (1 in 17)	10.1 (1 in 10)	26.7 (1 in 4)
Kidney and renal pelvis	0.1 (1 in 753)	0.2 (1 in 586)	0.3 (1 in 317)	0.7 (1 in 134)
Breast	1.9 (1 in 53)	2.3 (1 in 43)	3.5 (1 in 29)	6.7 (1 in 15)
Colon and rectum	0.3 (1 in 334)	0.5 (1 in 189)	0.9 (1 in 109)	3.7 (1 in 27)
Leukemia	0.2 (1 in 526)	0.1 (1 in 979)	0.2 (1 in 475)	0.8 (1 in 120)
Lung and bronchus	0.2 (1 in 522)	0.6 (1 in 171)	1.6 (1 in 62)	4.9 (1 in 20)
Melanoma of the skin§	0.5 (1 in 206)	0.3 (1 in 313)	0.4 (1 in 243)	0.9 (1 in 113)
Non-Hodgkin lymphoma	0.2 (1 in 537)	0.2 (1 in 475)	0.4 (1 in 233)	1.4 (1 in 71)
Uterine cervix	0.3 (1 in 348)	0.1 (1 in 812)	0.1 (1 in 824)	0.2 (1 in 619)
Uterine corpus	0.3 (1 in 370)	0.6 (1 in 171)	0.9 (1 in 111)	1.3 (1 in 78)

*For those who are cancer free at the beginning of each age interval.

†All sites exclude basal cell and squamous cell skin cancers and in situ cancers except urinary bladder.

§Statistic is for whites only.

Source: Data from *DevCan: Probability of Developing or Dying of Cancer Software, Version 6.7.03*; 2015 http://surveillance.cancer.gov/devcan/.[32]

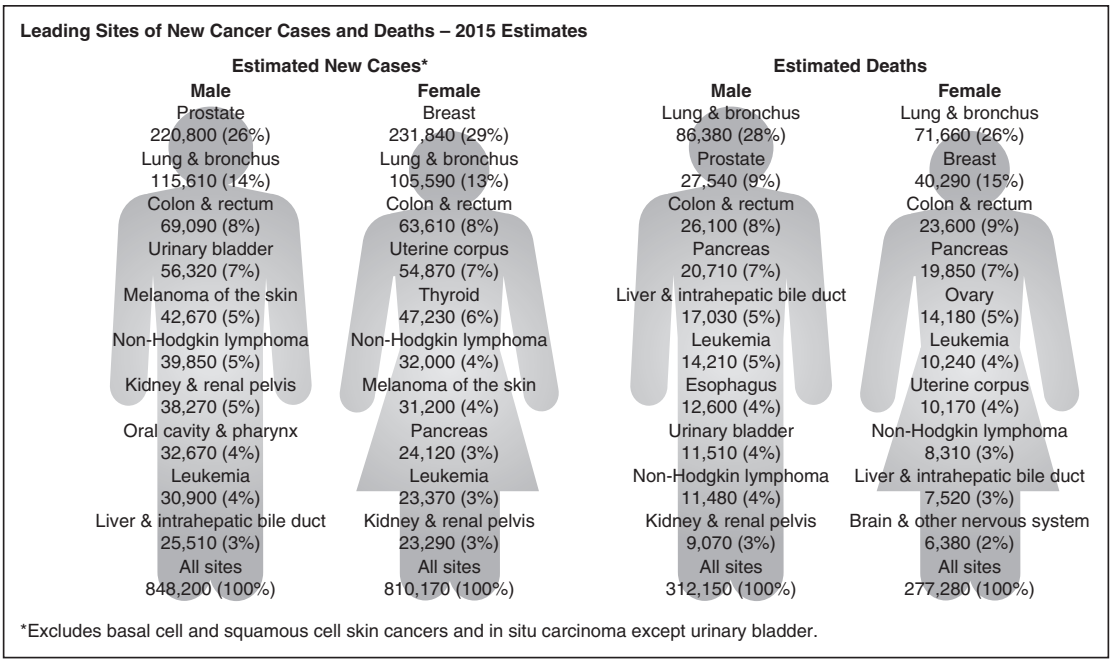

FIGURE 3-6

Leading sites of new cancer cases and deaths in the United States, 2015.
Source: Reproduced from American Cancer Society.[33]

100,000 occurred in African American males, compared to approximately 20.7 prostate cancer deaths per 100,000 white males.[33]

Socioeconomic Factors

Socioeconomic status of an individual is determined by income, education, or occupation; SES of a region is classified by the percentage of people living below the poverty level. Lower SES is related to excess mortality, morbidity, and disability rates. Higher-poverty areas are characterized by later stage of disease at diagnosis, poorer survival, and higher mortality rates. A substantial decline in mortality has occurred over time for all socioeconomic groups, but a considerable lag in improvement is still evident for lower-SES groups or regions.

Racial and ethnic disparities in cancer mortality stratified by SES were examined using data from 1990 to 2000 from the National Cancer Institute (NCI) SEER program.[34] SES was categorized into three levels: less than 10% of the population in a county living below the poverty level, counties with 10% to less than 20% of the population living below the poverty level, and counties with more than 20% of the population living below the poverty level.[34,35] Disparities in this analysis were defined as a ratio of mortality rates for a specific cancer, sex, and SES group. Results of this analysis indicated that African Americans have greater disparities in cancer mortality relative to whites for each cancer site examined except for female lung cancer. Further, these disparities had larger declining trends for higher-SES groups, and small declining trends for the lowest-SES group. Other racial/ethnic groups, including American Indian/Alaskan Natives (AI/ANs), Asians and Pacific Islanders (Asian/PIs), and Hispanics had greater disparities for cervical cancer. For the majority of the other cancers evaluated, AI/ANs had worse trends for the middle-SES group, while Hispanics had the best trends for the middle-SES group. This indicates that cancer mortality is certainly influenced by SES, but that factors other than SES, especially for AIs/ANs, Asian/PIs, and Hispanics, also influence cancer mortality. Culture in its many manifestations, such as access to health care on tribal reservations, acculturation to American lifestyles and diet, and cancer literacy, needs to be considered in understanding the differences in cancer incidence and mortality that occur in the United States.[34,35]

Genetic Susceptibility

The cumulative body of evidence indicates that genetic factors contribute to the development of most cancers, including those without a clear familial aggregation. Epidemiological

TABLE 3-4

Cancer Incidence and Death Rates* for Selected Cancers by Race, and Ethnicity, United States, 2007–2011

Incidence	Non-Hispanic White	African American	Asian American or Pacific Islander	American Indian and Alaska Native§	Hispanic/Latino
All sites					
Male	540.8	606.2	322.3	432.2	420.9
Female	435.8	406.3	283.7	368.3	330.1
Breast (female)	127.6	123.0	86.0	91.7	91.6
Colon and rectum					
Male	49.2	61.9	39.9	50.9	45.9
Female	37.4	45.6	30.0	41.1	31.6
Kidney and renal pelvis					
Male	21.6	24.1	10.7	30.1	20.6
Female	11.3	12.9	5.0	17.8	11.6
Liver and bile duct					
Male	8.9	16.0	21.2	18.4	19.1
Female	3.0	4.6	8.0	8.6	6.9
Lung and bronchus					
Male	81.3	95.4	48.0	68.5	45.0
Female	59.3	51.7	28.0	52.5	26.3
Prostate (male)	133.2	219.8	72.5	97.9	120.2
Stomach					
Male	7.8	15.4	15.3	12.0	13.8
Female	3.5	8.1	8.6	6.5	7.9
Uterine cervix (female)	7.1	10.2	6.4	9.5	10.5

Mortality	Non-Hispanic White	African American	Asian American or Pacific Islander	American Indian and Alaska Native§	Hispanic/Latino
All sites					
Male	214.0	275.5	131.0	190.0	150.1
Female	151.2	173.0	91.5	135.2	99.9
Breast (female)	22.2	31.4	11.3	15.2	14.5
Colon and rectum					
Male	18.7	28.4	13.1	19.2	15.8
Female	13.2	18.9	9.5	15.6	9.9
Kidney and renal pelvis					
Male	5.9	5.8	3.0	9.5	5.1
Female	2.6	2.7	1.3	4.4	2.3
Liver and bile duct					
Male	7.3	12.4	14.5	13.8	12.6
Female	3.0	4.3	6.0	6.0	5.5
Lung and bronchus					
Male	63.9	77.5	34.7	50.0	30.5
Female	42.1	37.4	18.4	32.4	14.0

Mortality	Non-Hispanic White	African American	Asian American or Pacific Islander	American Indian and Alaska Native[§]	Hispanic/Latino
Prostate (male)	20.7	49.8	10.0	21.2	18.5
Stomach					
Male	3.8	9.8	8.3	7.0	7.5
Female	1.9	4.6	4.8	3.8	4.2
Uterine cervix (female)	2.0	4.2	1.8	3.4	2.8

Hispanic origin is not mutually exclusive from Asia/Pacific Islander or American Indian/Alaskan Native.

*Per 100,000, age adjusted to the 2000 U.S. standard population.

[§]Data are based on Indian Health Service Contract Health Service Delivery Areas (CHSDA). Incidence rates exclude Kansas.

Source: Data from American Cancer Society.[33]

studies of genetic factors in cancer etiology include family studies and case-control studies. Family studies can provide information on the role and/or inheritance pattern of genetic factors in the etiology of disease. Case-control studies that evaluate genetic factors or other biomarkers can either target specific variants, genes, or pathways, or agnostically evaluate the entire genome in a genome-wide association study (GWAS). GWASs have been conducted to identify genetic variants or single-nucleotide polymorphisms (SNPs) associated with a variety of cancers, diseases, and other traits.[36] Thousands of genetic variants have been identified by GWAS, each explaining only a small part of genetic susceptibility.[36,37]

Breast cancer—most common malignancy in women—is a good example for discussing genetic susceptibility.[38] Approximately 15% of breast cancer cases have a positive family history of disease. Mutations in *BRCA1* and *BRCA2* confer a very high risk of developing breast cancer (high penetrance); mutations in other genes have also been found to confer a moderate lifetime risk of breast cancer. More than 70 SNPs have been associated with breast cancer by GWAS; together, these account for 28% of familial breast cancer risk. Such GWAS-identified SNPs have low penetrance, and confer small increases in cancer risk. Thus, the current challenge in this post-GWAS era is to identify the missing heritability of complex diseases.[36]

Epidemiological investigation into the genetic causes of cancer has expanded rapidly, due to developments in molecular biology that have made it possible to study genetic markers in large populations.[39] The Human Genome Project was spearheaded by the National Institutes of Health (NIH) and the Department of Energy to sequence all 3 billion letters, or base pairs, in the human genome, which is the complete set of DNA in a human body. The Human Genome Project's goal was to provide researchers with powerful tools to understand the genetic factors in human disease, paving the way for new strategies for their diagnosis, treatment, and prevention. The Human Genome Project was completed in 2003.

An ambitious new initiative, The Cancer Genome Atlas (TCGA), was then initiated in 2006. Funded by the NIH's National Cancer Institute and National Human Genome Research Institute, TCGA aims to identify genomic abnormalities in 30 different types of cancers.[40] TCGA has compiled information on both host and tumor samples; in addition to genetic susceptibility variants, data include exome sequencing (for all protein coding regions of DNA), mRNA (gene expression), methylation (an epigenetic alteration that influences gene expression), microRNA (small non-coding RNA genes implicated in genetic regulation), and de-identified clinical information from patients.

Genetic epidemiology in cancer research aims to identify factors that can be used for the primary, secondary, or tertiary prevention of cancer.[41] For example, the identification of *BRCA1* and *BRCA2* susceptibility genes means that genetic screening can be used to identify women with a high likelihood of developing breast or ovarian cancer. At-risk individuals can then choose to modify their behaviors or select prophylactic options, such as taking tamoxifen or undergoing surgical removal of the breasts and/or ovaries. Such decisions are highly personal, and it is important for trained genetic counselors to be available for subjects choosing to undergo genetic testing for cancer prevention. Personalized medicine based on tumor genetics may be thought of as tertiary cancer prevention. For example, 20% to 25% of breast cancers are positive for the expression of the *HER2* oncogene; targeted treatment for these tumors with the humanized monoclonal antibody trastuzumab has been shown to result in improved survival outcomes among women with *HER*-positive breast cancer.

BEHAVIORAL FACTORS

Energy Balance

A positive energy balance is the state achieved when energy intake exceeds expenditure.[42] Under chronic conditions, positive energy balance will manifest as overweight and obesity.[42] Epidemiological studies have provided compelling evidence that obesity is associated with increased risks of colon, endometrial, esophageal, renal, pancreatic, and postmenopausal breast cancer.[43] Probable evidence exists for associations of obesity with gallbladder and hepatocellular carcinomas, and evidence is also suggestive for associations with ovarian and thyroid cancers.[44,45] The total number of cancer cases attributed to obesity is estimated at 20%, with the increased risk being influenced by diet, weight change, body fat distribution, and physical activity.[46] However, the precise biological mechanisms underlying the relationship between obesity and cancer are not well understood.

While there is a clear association between obesity and cancer, it is frequently difficult to distinguish the consequences of diet composition from those of obesity. Research on specific components of the diet in relation to cancer has flourished in recent years, with many micronutrients (vitamins and minerals) and some macronutrients (proteins, fats, and carbohydrates) being investigated for adverse or protective effects.[47,48] Studies in humans include mostly observational research, such as international differences in dietary fat consumption and cancer incidence.[49] Additional epidemiological evidence, including both case-control and cohort studies for multiple dietary components, is presented here, but readers should keep in mind that it is difficult to disentangle the effects of obesity from specific dietary components. For most associations, results across studies are generally mixed; whether an association truly exists must be inferred from the totality of the evidence, rather than by focusing on any one specific study. Further, while laboratory and epidemiological evidence has linked diet and dietary components to increased risk for numerous cancers, few etiologic relationships have been definitively established.[43,50–52]

The role of dietary fat in the development of cancer has received extensive attention. The cancer sites most frequently studied, and for which associations have been most consistently observed, include breast, colon, and prostate cancer.[53] For breast cancer, several case-control studies have shown an association between dietary fat and increased risk, while evidence from cohort studies is inconsistent.[54–58] Analysis of data from seven cohort studies in four countries showed no evidence of a positive association between total dietary fat and breast cancer risk.[55,59] Two of the largest landmark cohort studies, the Nurses' Health Study[60] and the Iowa Women's Study,[61] showed no relationship between dietary fat intake and breast cancer risk. Results from the Women's Health Initiative (WHI) randomized dietary modification trial showed a reduction in breast cancer risk among postmenopausal women who reduced their total fat intake, although the association was not statistically significant (HR: 0.91, 95% CI: 0.83–1.01).[62] This evidence is particularly compelling, given the experimental—rather than observational—study design.

In addition to total fat, many studies have examined particular types of fat, such as saturated fatty acids (SFAs) and omega-3 polyunsaturated fatty acids (ω-3 PUFAs). Both inverse[63–66] and null associations[67,68] with breast cancer risk have been reported for SFAs and PUFAs. Similarly, the relationship between monounsatured fatty acids (MUFAs) and breast cancer risk is conflicting, with both positive[67] and inverse[69,70] associations reported. Narrow ranges of fat intake among populations, measurement error, high correlation between specific types of dietary fat, confounding variables like body type and energy intake, and possibly other dietary components, such as fiber and antioxidants, may contribute to these inconsistent findings.[71] Thus, the relationship between total or specific types of dietary fat and cancer is not definitive.

Currently, the American Cancer Society considers dietary fat recommendations for the general population for heart disease prevention to also be appropriate for cancer survivors due to shared risk factors between cancer and heart disease.[72] A 2012 report from the American Cancer Society recommends that cancer survivors consume 20% to 35% of their energy from fat, and limit their intake of saturated fat.[72]

Extensive research on fruit and vegetable intake in relation to cancer development has also been conducted. However, fruits and vegetables include many important nutrients, including antioxidants and fiber, and increased fruit and vegetable intake frequently correlates with lower dietary fat intake and increased physical activity. Thus, while increased fruit and vegetable intake has shown protective associations with cancer, which particular nutrient, vitamin, or combination of fruits and vegetables actually confers protection against cancer remains under investigation. In a 2007 report from the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR), evidence for an association between fruit and vegetable intake was determined to be too limited for a conclusion to be drawn in relation to breast cancer, while evidence for colorectal cancer protection was deemed limited.[73] More recently, a meta-analysis of 15 prospective studies found a weak inverse association when comparing the highest category of fruit intake versus the lowest (RR: 0.92, 95% CI: 0.86–0.98) in terms

of breast cancer risk; no association was found for vegetable intake.[73,74] A protective dose–response relationship was found with 100 g/day increasing vegetable intake (RR: 0.98, 95% CI: 0.97–0.99), and when comparing the highest versus the lowest categories of exposure (RR: 0.91, 95% CI: 0.86–0.96) for colorectal cancer risk. These estimates were based on data from the Continuous Update Project (CUP), a large database containing results from published cohort studies and randomized trials that conducts ongoing systematic literature reviews on food, nutrition, physical activity, and body fatness in relation to cancer risk.[73]

Dietary fiber from fruits, vegetables, and grains has also been studied in relation to cancer risk. A meta-analysis of 16 prospective studies confirmed that the risk of colorectal cancer is inversely related to the intake of dietary fiber from cereals (RR per 10 g/day: 0.90, 95% CI: 0.86–0.94).[74] A CUP 2011 report included foods containing dietary fiber as having convincing evidence for an association with decreased colorectal cancer risk.[73] One theory for this risk reduction is that carcinogens may have a decreased transit time through the body when an individual consumes a high-fiber diet.

Vitamins and minerals are additional dietary components that have been investigated in relation to cancer. For example, a protective role for high calcium intake against colon cancer has been reported in several studies[75–79] but not in all.[80] Calcium may inhibit colorectal carcinogenesis because of the molecule's ability to bind toxic bile acids, thereby rendering them inert, or by directly exerting effects on the cell cycle.[81] Data suggest that a 30% to 50% reduction in risk for developing colorectal cancer can be achieved by increasing vitamin D intake to least 1000 IU/day,[82] although randomized intervention trials have produced mixed results in regard to this regimen.[83–86]

Studies of associations between dietary components and cancer risk present some important problems for consideration. First, the distribution of dietary components among individual foods varies greatly. The interactive roles of dietary components are not completely understood, particularly when several components are present in individual foods.[87] Disentangling the effects of specific dietary components from those of a generally healthier dietary pattern are extremely difficult.

Second, recall bias may be present if dietary assessment was conducted after the presentation of the disease, as in a case-control study. In essence, individuals' recall of their past diet may be affected by their knowledge that they have the disease.[88] To avoid the problems associated with self-reported dietary intake methods, direct assessment of some micronutrients has been developed, involving measuring serum micronutrient levels. Several observational studies have reported stronger associations between diet and disease endpoints when using biomarkers of diet, rather than data from questionnaires.[89–91] This suggests that some diet–disease associations may be underestimated due to measurement error.[92]

Third, randomized controlled trials (RCTs) are the ideal study design for establishing the cause–effect relationship that is required to demonstrate cancer prevention by dietary modifications; however, methodological issues and their prohibitive costs make RCTs generally rare. Trials limited to specific nutrients may be useful to investigate biological pathways of interest and mechanisms for the identification of biomarkers of nutrient availability. Without RCTs, findings from case-control and cohort studies should be examined carefully. Differences in methods between studies should be considered, and it should be recognized that prospective studies generally provide stronger evidence than case-control studies. Further, meta-analyses are particularly useful for discerning the totality of current evidence for a specific association.

Energy balance is a result of both dietary intake and physical activity. Epidemiological investigations on physical activity and cancer risk are also abundant. Convincing evidence indicates that exercise plays a key role in the primary prevention of colon cancer,[93–98] precancerous colon polyps,[99] breast cancer,[50–52,100–103] and endometrial cancer.[93,104–107] Weaker evidence suggests that physical activity is protective against prostate cancer,[108,109] lung cancer among nonsmokers,[110,111] ovarian cancer,[112] and kidney cancer.[109,113,114] The associations between physical activity and hematologic, cervical, rectal, gastric, esophageal, pancreatic,[94] and some genitourinary cancers are either null or considered insufficient due to a lack of published research. Physical activity may protect against cancer through reduced lifetime exposure to sex steroid hormones, reduced exposure to insulin and insulin-like growth factors, and prevention of overweight and obesity—factors collectively referred to as positive energy balance.[115,116] Physical activity is one of the few known modifiable risk factors related to cancer, and is implicated in both cancer risk and cancer survival.[100,117]

In summary, the most authoritative review on the epidemiological evidence for the relationship of food, nutrition, and physical activity to cancer risk to date is the WCFR/AICR's *Second Expert Report*.[118–120] Nine academic or research institutions from the United States and Europe examined epidemiological evidence for 17 cancer sites and presented eight general recommendations and two special recommendations for personal cancer prevention and general public health, as shown in **Table 3-5**.[73] Recommendations will continue to be updated as new research is conducted and CUP incorporates new findings on diet and physical activity into its reviews.

TABLE 3-5

Personal Recommendations for Cancer Prevention: World Cancer Research Fund and American Institute for Cancer Research, 2007

Recommendations
Body Fatnesss
Be as lean as possible within the normal range of body weight.
Ensure that body weight throughout childhood and adolescent growth projects toward the lower end of the normal body mass index (BMI) range at age 21.
Maintain body weight within normal range from age 21.
Avoid weight gain and increases in waist circumference throughout adulthood.
Physical Activity
Be physically active as part of everyday life.
Be moderately physically active, equivalent to brisk walking, for at least 30 minutes every day.
As fitness improves, aim for ≥ 60 minutes of moderate or for ≥ 30 minutes of vigorous physical activity every day.
Limit sedentary habits such as watching television.
Foods and Drinks That Promote Weight Gain
Limit consumption of energy-dense foods. Avoid sugary drinks.
Consume energy-dense foods sparingly.
Consume "fast foods" sparingly, if at all.
Plant Foods
Eat mostly foods of plant origin.
Eat at least five portions/servings (at least 400 g or 14 oz) of a variety of nonstarchy vegetables and fruits every day.
Eat relatively unprocessed cereals (grains) and/or pulses (legumes) with every meal.
Limit refined starchy foods.
People who consume starchy roots or tubers as staples also need to ensure intake of sufficient nonstarchy vegetables, fruits, and pulses (legumes).
Animal Foods
Limit intake of red meat and avoid processed meat.
People who eat red meat should consume less than 500 g (18 oz) per week, little if any of which is processed.
Alcoholic Drinks
Limit alcoholic drinks.
If alcoholic drinks are consumed, limit consumption to no more than two drinks per day for men and one drink per day for women.
Preservation, Processing, and Preparation
Limit consumption of salt.
Avoid moldy cereals (grains) or pulses (legumes).
Avoid salt-preserved, salted, or salty foods; preserve foods without using salt.
Limit consumption of processed foods with added salt to ensure an intake of less than 6 g (2.4 g sodium) per day.
Dietary Supplements
Aim to meet nutritional needs through diet alone.
Dietary supplements are not recommended for cancer prevention.
Breastfeeding
Mothers to breastfeed; children to be breastfed.
Aim to breastfeed infants exclusively up to six months, and continue with complementary feeding thereafter.
Cancer Survivors
Follow the recommendations for cancer prevention.
All cancer survivors should receive nutritional care from an appropriately trained professional.
If able to do so, and unless otherwise advised, aim to follow the recommendations for diet, healthy weight, and physical activity.

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Alcohol Consumption

Alcohol is an acknowledged carcinogen, both by the International Agency for Research on Cancer (IARC) and the World Health Organization (WHO).[121,122] Experimental evidence suggests that alcohol interferes with folate absorption, transport, and metabolism, potentially limiting tissue folate stores. Folate deficiency is implicated in carcinogenesis through interference with DNA synthesis.[123,124] Globally, the average amount of alcohol consumed per day is approximately 17 g; intake greater than 20 g/day is considered harmful.[125]

Alcoholic beverages consist primarily of ethanol, water, and both volatile and nonvolatile compounds. Numerous additives are also used in the production of alcoholic beverages, such as hops, synthetic flavor enhancers, preservatives, and trace elements.[126] Certain contaminants with proven mutagenic and carcinogenic properties that interfere with DNA synthesis, repair, and tumor development have also been detected in alcoholic beverages, such as N-nitrosamines, asbestos, arsenic compounds, pesticides, and acetaldehyde.[127]

Alcohol is the only established dietary factor consistently related to breast cancer risk.[124,127–136] A majority of findings from epidemiological studies have shown moderately increased breast cancer risk among women who consume moderate to high levels of alcohol.[127,130,131,133,135,137] A meta-analysis of 89 published studies found a significantly increased risk when comparing drinkers to nondrinkers (OR: 1.11, 95% CI: 1.06–1.17); further, each 10 g ethanol/day was associated with a 12% excess risk of breast cancer in a dose–response analysis among drinkers from 71 studies.[138] Both the minimum level of alcohol consumption required to significantly increase breast cancer risk and the age at which exposure to alcohol exposure becomes important are unclear, and remain under investigation.[136,137,139]

Convincing evidence also indicates that alcohol consumption increases the risk of several other cancers in addition to breast cancer. A meta-analysis of 27 cohort studies and 34 case-control studies found significantly elevated risks of colorectal cancer; risk was increased only 7% for those who drank 10 g/day (95% CI: 1.04–1.10), whereas risk was more than 80% increased for those who drank 100 g/day (95% CI: 1.41–2.35).[139] A meta-analysis of 19 cohort studies with 4445 liver cancer cases found that compared to nondrinkers, moderate (<3 drinks/day) drinking was not associated with liver cancer risk, but heavy drinking (≥3 drinks/day) was associated with significantly increased risk (RR: 1.16, 95% CI: 1.01–1.34).[140] Conversely, alcohol intake has been inversely associated with renal cell cancer. A meta-analysis of 24 studies found that those persons who consumed alcohol had lower risk of renal cell cancer; this reduction was observed for both men and women, and for different types of beverages.[141] Another meta-analysis on renal cell cancer also found significantly protective effects associated with any, light, moderate, and heavy drinking.[142] Finally, no association was observed between alcohol intake and ovarian cancer risk in a meta-analysis of 27 studies that included a total of 16,554 ovarian cancer cases.[143]

To better understand the association between alcohol intake and cancer risk, researchers recently reviewed published meta-analyses as well as mortality data and national surveys of alcohol consumption and sales in the United States. Deaths for seven malignancies previously linked to alcohol intake were examined: cancers of the oral cavity and pharynx, larynx, esophagus, colon, rectum, liver, and breast. Alcohol use was estimated to account for 3.5% of all cancer deaths, representing 19,500 deaths in the United States each year. Among females, the highest attributable fraction of cancer deaths due to alcohol was from breast cancer, whereas the highest attributable fraction among men was for upper airway and esophageal cancer deaths.[144,145]

Tobacco Exposures

A causal relationship between tobacco use and multiple types of cancer is primarily derived from epidemiological research; the best-known association is with lung cancer. In 1950, Doll and Hill[146] published epidemiological evidence that the risk of lung cancer was very high among cigarette smokers, and was also elevated among pipe and tobacco smokers. Results from cohort studies then confirmed these case-control findings, and in 1964, the U.S. Surgeon General issued a landmark report on the health effects of smoking.[147] Cigarette smoking has now been confirmed as the most predominant cause of the epidemic of lung cancer that occurred in the 20th century and as the single leading preventable cause of death in the United States.[148,149] Smoking tobacco is associated with malignancies of the lung, larynx, mouth, esophagus, bladder, pancreas, kidney, cervix, and stomach, as well as acute myeloid leukemia.[148] In addition to cancer, cigarette smoking is associated with coronary heart disease, atherosclerosis, chronic obstructive pulmonary disease, sudden infant death syndrome, cataracts, hip fractures, and numerous other negative health outcomes.[148]

Given the rising costs of tobacco cigarettes, bans on smoking in occupational and recreational settings, and health concerns, smokeless tobacco products seem like an obvious substitution for active smoking tobacco.[150–152] Smokeless forms of tobacco include chewing tobacco, dipping tobacco, snuff, and snus, a moist snuff that originated in Sweden. Electronic cigarettes (e-cigarettes) are a popular new substitute for traditional cigarettes; these devices vaporize nicotine

without combusting tobacco.[150] Particle emissions of pollutant concentrations from mainstream tobacco smoke of traditional cigarettes have been compared to the emissions from e-cigarettes, including formaldehyde, acetaldehyde, toluene, nicotine-derived nitrosamine ketones (NNK) and *n*-nitrosonornicotine (NNN).[153] Not only were pollutant concentrations significantly lower in the e-cigarette emissions, but the average ratio of toxic substances in e-cigarette vapors to those in conventional cigarette smoke ranged from 9 to 450 times lower.[153] Further, several clinical and psychological studies have demonstrated that "vaping" may be a very promising harm reduction tool.[154] However, due to the extreme paucity of empirical research investigating the presence of vaping-induced health hazards and benefits, additional research is essential before any conclusions can be drawn about the dangers or efficacy of e-cigarettes. Research is needed on both the acute and long-term cardiopulmonary effects of vaping, especially investigations comparing the effects of vaping with those of smoking.

While active tobacco smoking is accepted to be detrimental to health, the effects of passive smoking or exposure to environmental tobacco smoke (ETS) have been hotly debated during the past decade. ETS can be defined as sidestream and mainstream smoke that is exhaled by active smokers. Sidestream smoke represents approximately 85% of total ETS; mainstream smoke constitutes less than 15% of total ETS. Once released into the environment, ETS can further aggregate with existing air pollutants, a phenomenon that further changes the physiochemistry of ETS from that of mainstream smoke.[155] Both sidestream and mainstream smoke contain about 40 different chemicals that are either suspected or proven carcinogens. [2,156]

Several epidemiological studies have investigated the relationship between ETS and cancer. The European Prospective Investigation into Cancer and Nutrition (EPIC) is the largest cohort analysis of smoking and breast cancer risk to date. In this study, compared to women who never smoked and who had no work or home ETS exposure, current smokers (HR: 1.16, 95% CI: 1.05–1.28), former smokers (HR: 1.14, 95% CI: 1.04–1.25), and passive smokers (HR: 1.10, 95% CI: 1.01–1.20) all had significantly increased risks of breast cancer.[157] Additional epidemiological evidence is supportive, but not conclusive for an association between ETS and cancers of the nasopharynx and cervix, while evidence for lung cancer is sufficient to infer a causal relationship.[158,159] For example, a meta-analysis of 55 studies found that never-smoking women exposed to passive smoking from spouses had a significantly increased risk of lung cancer (RR: 1.27, 95% CI: 1.17–1.37).[160] In fact, passive smoking is estimated to cause 3000 lung cancer deaths per year in the United States, and 21,400 deaths per year globally.[158,161]

Reproductive History

Factors related to reproduction and sexual behaviors may influence cancer risk. This section focuses on choices and activities that result in hormonal exposures; sexual behaviors that may result in viral exposures and virus-associated cancers are discussed in the "Environmental Factors" section.

Reproductive choices and behaviors influence cancer risk through modulation of hormone levels. Hormones are chemical messengers that influence cell growth and function; they can be either endogenous or exogenous. Endogenous sex steroid hormones in women are produced primarily by the ovary, and include estrogens and androgens. Convincing epidemiological evidence shows that numerous reproductive factors are associated with breast cancer risk, including age at menarche, age at menopause, parity, age at first live birth, and breast feeding. The cumulative number of ovulatory menstrual cycles in a woman's life is strongly associated with breast cancer risk, and all of these factors influence total years of ovulation. Age at first live birth is important for breast cancer, as the undifferentiated tissue of the breast undergoes significant changes during pregnancy and lactation.[162] In addition to their implications for breast cancer, ovarian hormones and reproductive history are important for endometrial and ovarian cancer. While increasing parity provides protection against all three of these cancers, obesity is most strongly associated with increased endometrial cancer risk, whereas hysterectomy and tubal ligation are protective for ovarian cancer.

Exogenous hormones also influence cancer risk. Sources of these hormones include oral contraceptives (OCs) and postmenopausal hormone replacement therapy (HRT). Combined OCs contain both estradiol and a progestin. The role of OCs in breast cancer risk is not fully determined, with some studies showing no relationship and others showing a significant increase in breast cancer risk with long-term use.[163–166] The most definitive work on this topic to date is a pooled analysis of 54 studies by the Collaborative Group on Hormonal Factors in Breast Cancer; a significantly elevated risk was found for women taking OCs (RR: 1.24, 95% CI: 1.15–1.33), and this elevated risk persisted up to 10 years after taking OCs.[167] Research on the duration of use, timing of use, and effects of different formulations will clarify the association between OCs and breast cancer risk. In regard to other cancers, OC use is consistently associated with reduced risk of ovarian and endometrial cancers[168,169] as well as with protection from colorectal cancer.[168]

An association between HRT use and breast cancer is of great public health importance, given the increasing size of the older female population. The composition of hormones in HRT has been used to classify therapeutic

options as estrogen-only therapy, estrogen–progesterone therapy, progesterone-only therapy, estrogen–testosterone therapy, or testosterone-only therapy. Numerous epidemiological studies have been conducted, and differences in hormone compositions and durations of use have also been examined. A pooled analysis of 51 studies conducted by the Collaborative Group on Hormonal Factors in Breast Cancer found a small but significant increase in breast cancer risk (RR: 1.023, 95% CI: 1.011–1.036) per year of HRT use.[170] The most definitive evidence of the association between HRT and breast cancer risk came from the WHI randomized trial; women taking estrogen plus progesterone were found to have significantly increased risks of invasive breast cancer (HR: 1.26, 95% CI: 1.00–1.59), and cardiovascular outcomes (HR: 1.29, 95% CI: 1.02–1.63), and the trial was stopped early.[171] Even the results of large trials can be controversial, however, and debate over the health effects of HRT has continued; critics believe that bias and confounding have distorted the true results. However, based on the totality of the evidence, the U.S. Preventive Services Task Force recommended against the routine use of estrogen-plus-progestin therapy and unopposed estrogen therapies for the prevention of chronic conditions in women, which has resulted in a substantial reduction in HRT use among postmenopausal women.

Medication Use

Despite the vast array of chemicals discovered to cause cancer in animals, few chemicals (other than tobacco) exist for which there is strong causal evidence for cancers in humans.[172,173] However, numerous medications have been evaluated in epidemiological studies, and associations with numerous cancers have been reported. Discussed here are two interesting examples: (1) diabetes mellitus (DM) and metformin (an oral insulin-sensitizing agent) and (2) aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), which are commonly used as analgesics.

Epidemiological studies indicate that patients with DM have increased risks for several cancers, including hepatocellular, pancreatic, endometrial, colorectal, breast, kidney, bladder, gastric, and ovarian cancer, non-Hodgkin lymphoma, T-cell lymphoma, and leukemia.[174] DM is not a singular disease, but rather a complex constellation of metabolic disorders that affect patients differently. Many factors associated with DM, including hyperglycemia, hyperinsulinemia, obesity, and high-fat diet, are also independent risk factors for cancer, illustrating a close correlation between these two prevalent diseases.[175] Mechanisms that account for accelerated tumor growth in people with DM include the downstream actions of insulin, a potent growth factor that promotes cellular proliferation. Insulin signaling results in direct modulation of metabolic pathways, including activation of insulin receptors (IRs) in epithelial tissues. Indirectly, insulin influences the levels of other modulators of cell growth, such as the insulin-like growth factors (IGFs). When free from insulin-like growth factor binding proteins (IGFBPs), IGFs can decrease apoptosis and promote tumor growth and cancer progression.

In contrast, several epidemiological reports have indicated that metformin use is associated with a decreased risk of cancer among those persons with DM. Metformin is an inexpensive, well-tolerated oral agent, which is used as the first-line treatment for type 2 diabetes. The primary effects of metformin are a reduction in plasma insulin and glucose levels, followed by an enhancement of blood glucose control.[176,177] Metformin is thought to act as an anticancer agent either by a direct effect of reducing growth in cancer cells or an indirect effect of reducing the impact of endogenous hyperinsulinemia or other metabolic abnormalities on the development and progression of cancer.[174] Thus, not only are cell growth and proliferation influenced, but metformin also plays a role in metabolic reprogramming, now considered a hallmark of cancer development.[178]

Over the past decade, epidemiological observations have suggested that metformin use correlates with a reduction in cancer incidence in patients diagnosed with type 2 diabetes.[176,179–183] A meta-analysis of 12 randomized trials and 41 observational studies found that metformin use was associated with a significant reduction in cancer deaths in observational studies (OR: 0.65, 95% CI: 0.53–0.80), whereas no effect was seen in randomized trials. Similarly, results from observational studies indicate a reduced risk of any malignancy (OR: 0.73, 95% CI: 0.61–0.88); again, no effect was seen in randomized trials. Individual cancers for which individuals had a significantly reduced risk with metformin use included colorectal, liver, pancreatic, stomach, and esophageal cancer. The authors concluded that the trials had not been designed to evaluate the relationship between metformin and cancer, and that the anticancer effects of metformin warrant further research, including trials specifically designed to address this question.[184]

The use of metformin as an anticancer drug appears very promising, but some limitations need to be considered. Notably, the majority of the studies on metformin were retrospective, with researchers relying on clinical and hospital data, rather than prospective population-based data. The studies conducted on metformin and cancer did not use randomization of the patient population for the administration of metformin versus other treatments; for example, hospital patients with a history of cancer may have been included in some studies. Several types of bias might also have influenced these results, including selection of appropriate comparison groups (subjects with DM) and confounding due to shorter durations of diabetes among

metformin users. Regardless of these shortcomings, such observational studies have provided compelling data that suggest a plausible antitumor effect with metformin use, and they are paving the way for prospective clinical trials to directly address this important issue.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most frequently used medications in the United States. NSAIDs create a variety of effects in the body, including analgesic (pain reduction), antipyretic (fever reduction), and anti-inflammatory effects. Aspirin and other NSAIDS inhibit the activity of the cyclooxygenase (COX) family of enzymes, thereby preventing the production of certain eicosanoids (a large family of intracellular signaling molecules) in response to inflammatory or mitogenic stimuli. NSAIDs are linked to the inhibition of COX-2, an enzyme associated with tissue regulation of inflammation. COX-2 is found wherever inflammation is present; it is markedly upregulated in major epithelial cancers, including colon, esophagus, lung, breast, and prostate cancer.[185,186] The anticancer effects of aspirin and NSAIDs have been extensively studied. Numerous observational and case-control studies indicate that regular NSAID use is associated with a reduced risk of colorectal adenomatous polyps, cancer, and cancer mortality.[187] An overview of reviews that focused on one NSAID, aspirin, found that the benefits of aspirin included reduced all-cause mortality, reduced incidence of major cardiovascular events, and reduced cancer incidence and mortality; however, important increased risks were also found, including the incidence of gastrointestinal (GI) bleeding and strokes.[188]

Selective inhibitors of COX-2, known as COXIBs, are another type of NSAID that are attractive candidates as means of cancer prevention.[189] Data from approximately 40 observational studies demonstrated the utility of COXIBs as chemopreventive agents in patients with familial adenomatous polyposis (FAP). Three randomized trials were conducted between 1999 and 2000 to assess the incidence of adenomas, advanced adenomas (including carcinoma in situ and invasive carcinoma), and the number and size of polyps in patients with FAP who were randomized to COXIB use. These studies resulted in relative risks (RR) ranging from 0.64 to 0.76 for adenoma incidence; however, each of these studies was terminated after safety analyses revealed RRs for cardiovascular events ranging from 1.92 to 3.40.[190,191] COXIBs appear to have a greater effect as chemopreventive agents in colorectal cancer, and additional research on this indication is under way. However, given the major cardiovascular side effects of COXIBs, their use will be greatly limited. Rather than focusing on their utility for cancer prevention in the general population, investigations on aspirin and other NSAIDs are now examining whether these agents can improve outcomes, such as reduced disease recurrence, among subjects already diagnosed with cancer.

ENVIRONMENTAL FACTORS

Pollution

Environmental pollution includes contamination of the land, water, and air. One form of air pollution, already discussed, is passive smoke exposure. Environmental carcinogens may also act through occupational or dietary exposures. Some environmental pollutants interact with hormone receptors and interfere with normal signaling; these endocrine disruptors have received attention in regard to hormonally related cancers, such as breast, prostate, and endometrial cancer.

For example, exposure to some pesticides and inorganic arsenic (As) has been linked to increased prostate cancer risk.[192] Exposure to inorganic arsenic through drinking water is a major international public health issue. Evidence clearly illustrates statistically significant, more than fivefold increased risk for bladder cancer and more than twofold risk for lung cancer among those persons exposed to high concentrations of inorganic arsenic (>50 μg/L).[193–195]

Another common pollutant of drinking water, which is also found in swimming pools, is trihalomethane; it may be linked to rectal and bladder cancer risk.[196,197] This compound is produced by the action of chlorine on organic waste. Drinking water may also contain other chlorination by-products, as well as other contaminants, such as metals, nitrates, and other potentially carcinogenic compounds, but epidemiological evidence for increased cancer risk due to contaminants other than inorganic arsenic remains lacking.

Assessing associations between air pollution and cancer risk in epidemiological studies is more challenging than performing the same sort of analysis for water pollution. It is complicated to measure past exposures to the relevant pollutant as well as the level of the exposure. Exposure to air pollution has been evaluated based on residence near a major pollution source. These data mainly take into account suspended particulates, sulfur oxides, and nitrogen oxides, which are not the agents responsible for the carcinogenic effect of air pollution.[198] Moreover, exposure to air pollution may also be addressed by occupational epidemiology, such as the diesel exhaust encountered by truck drivers, as described further in the "Occupational Exposures" section.

Nocturnal Light Exposure

The benefits of electricity are obvious, although the benefit of artificial light may not be completely innocuous when exposure is inappropriately timed. Exposure to light at night in the form of occupational exposure resulting from night-shift work or as a personal lifestyle choice is experienced by numerous night-active members of society.[199] Light at night, regardless of its duration or intensity,

inhibits melatonin secretion and shifts the normal circadian clock; alteration of the circadian rhythm may, in turn, result in altered cell growth rates.

Evidence from experimental studies has suggested a link between melatonin and tumor suppression. Reports show that melatonin is oncostatic in a variety of tumor cells; multiple actions of melatonin counteract tumor growth. Physiologic and pharmacologic blood concentrations of melatonin have been shown to inhibit tumorigenesis in a variety of experimental models. Several clinical studies have confirmed the potential of melatonin, either alone or in combination with standard treatment regimens, to generate more favorable responses during the treatment of several human cancers.[200–202]

Observational studies investigating the effects of occupational light exposure at night have focused on breast cancer. The mechanistic framework of nocturnal light exposure and breast cancer risk was refined in the classic research study by Steven and Davis,[203] who suggested that decreased melatonin production due to exposure to light at night leads to a rise in the levels of reproductive hormones such as estrogens, thereby inducing hormone-sensitive tumors in the breast.[202,204] Numerous additional epidemiological investigations have ensued to examine this purported link. For example, the Nurses' Health Study found a positive association between extended periods of rotating night work and breast cancer risk for postmenopausal women with more than 30 years of rotating night work (RR: 1.36, 95% CI: 1.04–1.78).[199] Epidemiological evidence is generally supportive of the hypothesis that altered lighting causally contributes to breast cancer risk, with the best evidence indicating that women with an occupational history of night-shift work have a higher risk of breast cancer.[202,203,205–208] As such, shift work has been classified as a 2A probable human carcinogen by the International Agency for Research on Cancer (IARC).[209]

Additional research is needed to determine the biological mechanisms connecting disruption of circadian rhythms, melatonin suppression, and cancer etiology. The long-term goal is to identify mechanisms by which the consequences of circadian disruption from exposure to light at night may be altered, so as to protect those persons who engage in night-shift work. Notably, exposure to light at night may be viewed as a form of pollution.

Radiation

No other environmental carcinogen, with the possible exception of tobacco smoke, has been studied as extensively as ionizing radiation. Background radiation includes naturally occurring cosmic rays and radiation from ground sources, such as uranium, radon, potassium, and other substances. It is problematic to conduct epidemiological studies of potential cancer risk due to naturally occurring background radiation due to the difficulty of measuring an individual's lifetime or cumulative exposure.[210] Consequently, epidemiological studies of radiation generally focus on environmental, occupational, or medical sources of exposures. Differences in sources and doses of exposures have been determined to be too great to perform a formal meta-analysis, but a review of epidemiological studies found that 7 of 19 studies with more than 400 cases showed significantly increased risks across all solid cancers, and 10 of 16 studies with at least 30 cases demonstrated significant associations of radiation exposure with increased risk of leukemia.[211]

Radon is responsible for the majority of public exposure to ionizing radiation; this naturally occurring inert gas has radioactive isotopes. Radon exposure has been shown to increase the risk of lung cancer among underground miners, and in 1987, the IARC listed radon as a human carcinogen. An extremely large investigation of residential radon exposure in the American Cancer Society cohort study included 811,961 subjects and 3493 lung cancer deaths; the analysis revealed a significant positive linear trend between increasing radon concentrations and lung cancer mortality (P = 0.02), with a 15% increase in lung cancer mortality (HR: 1.15, 95% CI: 1.01–1.31) per 100 Bq/m^3 increase in radon exposure.[212] Participants with mean radon concentrations above the Environmental Protection Agency's (EPA) guideline value (148 Bq/m^3) experienced a 34% increase in lung cancer mortality relative to those below the guideline value (HR: 1.34, 95% CI: 1.07–1.68).[212] Radon exposure was determined to be the second leading cause of lung cancer in the United States.

Further, radon and smoking may have a synergistic effect on lung cancer.[158] A multiplicative interaction has been proposed, meaning that for the same level of radon exposure, the risk of lung cancer is substantially greater for smokers than for nonsmokers.[213] A pooled analysis of seven case-control studies that included 3226 lung cancer cases and 4966 controls showed that the risk of lung cancer increased approximately 11% for every 100 Bq/m^3 increase in radon concentration.[214] However, the relative risk of lung cancer did not differ by smoking status in this study, contrary to the findings from early research conducted on uranium miners. If the interaction is ultimately proved to exist, then stopping smoking actually has the greatest potential for preventing radiation-induced lung cancer, rather than preventing exposure to radon itself.

Another form of ionizing radiation that has been studied by epidemiologists is that given to patients during cancer treatment. Numerous studies have demonstrated that patients who receive radiotherapy are at risk for radiation-related second cancers, and this risk persists for decades following exposure. The risk for most radiation-sensitive malignancies increases with increasing radiation dose, and the tissues in or near the radiotherapy treatment fields

typically have the highest risks because they receive the highest doses.[215] Ionizing radiation from medical therapy is a known risk factor for numerous malignancies, particularly cancers of the thyroid, breast, brain, gastrointestinal tract, lung, bladder, and bone, as well as non-melanoma skin cancer (NMSC), sarcomas, and myeloid leukemias.[215,216] Further research is needed to evaluate radiation-related second-cancer risks associated with newer radiotherapy techniques (e.g., intensity-modulated radiation therapy), proton therapy, and new efforts to reduce treatment doses and volumes.[217]

Medical radiologists have also been the subject of epidemiological investigations on ionizing radiation, and other relevant occupations include underground uranium miners, commercial nuclear power plant workers, fuel fabricators, physicians, flight crews and flight attendants, industrial radiographers, and well loggers. Finally, other populations of interest for research on ionizing radiation are the survivors of the atomic bombings that occurred in World War II at Nagasaki and Hiroshima, Japan.

Radiation from sunlight has a complicated role in cancer. Sunlight is known to contribute to the development of skin cancer, which includes both melanoma and non-melanoma (basal cell carcinoma and squamous cell carcinoma) cancers. Both cumulative ultraviolet (UV) exposure and number of lifetime sunburns are predictive of increased melanoma risk.[218–220] Evidence now implicates UV-B radiation as being critical to the initiation of melanoma, and chronic exposure to UV-A radiation in the progression of cutaneous malignant melanoma.[221,222] For non-melanoma skin cancers, exposure to UV-B radiation is the predominant environmental risk factor.[221] For squamous cell carcinoma of the skin, cumulative lifetime sun exposure and occupational sun exposure are the most important risk factors; for basal cell carcinomas of the skin, multiple factors have been identified, all implicating the midrange of radiation from UV-B.

Notably, radiation from sunlight may be an effect of increased air pollution, as chlorofluorocarbons (CFCs) are destroying the ozone layer in the stratosphere.[223] Destruction of the ozone layer will allow more ultraviolet light to reach the earth's surface, and is predicted to increase the risk of both non-melanoma and melanoma skin cancer. In the United States, the incidence of malignant melanoma of the skin increased approximately 2.9% per year between 1973 and 2003, suggesting this prediction may be coming true.[224,225]

Other cancers, such as ocular melanomas, are also associated with exposure to UV-B radiation.[226] The incidence of these eye cancers follows an inverse gradient with latitude among non-Hispanic whites in the United States, presumably due to higher ambient UV radiation.[221]

Despite UV radiation's link to skin cancer, sunlight is also implicated in protection from cancer, via vitamin D. Sunlight skin exposure, especially to high-energy UV-blue light (UV-B) photons, results in the photoconversion of a cholesterol metabolite in the skin (7-dehydrocholesterol) to provitamin D, which is then converted through a series of oxidation reactions in the liver and kidney to its biologically active form, 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D$).[227,228] Vitamin D is a potent antiproliferative factor that can inhibit cellular proliferation and angiogenesis and induce differentiation or apoptosis in cells and tissues that have the vitamin D receptor (VDR). Several lines of experimental evidence are consistent with a protective influence for vitamin D in cancer. Individual studies have associated increased UV-B exposure with reduced risks of breast, colon, endometrial, prostate and renal cancers, as well as non-Hodgkin lymphoma.[229] Review of all published studies on either sunlight exposure or vitamin D in relation to cancer risk revealed that the evidence was generally consistent in supporting a protective effect for colorectal and prostate cancer, while evidence related to protection from breast cancer and non-Hodgkin lymphoma was mixed.[230] Meta-analyses for specific associations are also generally supportive of an inverse relationship between sunlight activation of vitamin D and a reduced cancer incidence and mortality. For example, a 10 ng/mL increase in blood 25(OH)D levels was associated with a 26% reduced colorectal cancer risk in one meta-analysis of 2767 cases and 3948 controls; another meta-analysis found no benefit for prostate cancer, but a 7% reduction in aggressive prostate cancer per 10 ng/mL of serum vitamin D.

Non-ionizing radiation includes microwaves, radio waves, and extremely low doses of electromagnetic forces (EMF). Early epidemiological studies observed that residential exposure to the weak EMF surrounding power lines was associated with a small elevated risk of childhood cancers. Of all outcomes evaluated in relation to EMF, childhood leukemia from postnatal exposures greater than 0.4 μT has the most convincing evidence supporting an association. The relative risk was estimated to be double that with smaller exposures (RR: 2.0, 95% CI: 1.27–3.13) by a large pooled analysis. However, only 0.8% of all children were exposed to more than 0.4 mT of EMF in this analysis. Further studies designed to test specific hypotheses, such as aspects of selection bias or exposure of EMF on childhood cancers, remain to be conducted.[231]

The rapid increase in cellular phone use has resulted in recent attention to the possible health risks of radio frequency (RF)/microwave (MW) radiation exposures.[232] In 2011, the IARC concluded that RF/MW radiation should be listed as a possible carcinogen for humans (group 2B).[233] The INTERPHONE Study, the largest health-related case-control study of cell phone use, found no statistically significant association in brain cancers with increasing cell phone use.[234] Although some studies have found marginally increased risks associated with cell phone use,[235] overall published findings are mixed, and no consistently significant associations between cell phone use and cancers

of the head, neck, or brain (glioma or meningioma) have been identified.[236–240] As cellular telephones are a relatively new technology, no long-term follow-up on their biological effects is available yet; future studies on negative health effects due to long-term cell phone use will be needed.

Viruses and Other Biological Agents

Viruses encode proteins that reprogram the host cellular signaling pathways that control cells' proliferation, differentiation, death, genomic integrity, and recognition by the immune system. Both DNA and RNA viruses have been shown to be capable of causing cancer in humans. DNA viruses include the Epstein-Barr virus (EBV), human papillomavirus (HPV), hepatitis B virus (HBV), and human herpes virus-8, while the human T-lymphotrophic virus type 1 and hepatitis C virus (HCV) are RNA viruses that contribute to human cancers.[241] Viruses result in cancer in the host only after a substantial incubation or latency period, which usually extends for years; the long-term nature of this process hinders studies from linking particular viral exposures with particular cancers. When the initial infection with a candidate virus is subclinical, verification of infection status after clinical features have emerged will result in compromised determination of the exact time of infection.

Viruses that are associated with different cancers are listed in **Table 3-6**.[242] Viruses have been etiologically linked to approximately 20% of all malignancies worldwide.[243]

Human immunodeficiency virus-1 (HIV-1) accounts for a significant cancer burden. Kaposi's sarcoma (KS) is a very rare tumor except among individuals infected with HIV-1; the incidence of KS is magnified approximately 70,000-fold among HIV-infected homosexual men. Human herpes virus-8 (HHV-8), also known as Kaposi's sarcoma–associated virus (KSHV), is an essential cofactor for the development of KS, and is also believed to have a role in primary effusion lymphoma.[241] A dramatic decline in KS incidence has occurred in recent years, due to the introduction of highly active antiretroviral therapy (HAART) for those persons infected with HIV. Other cancers that may occur secondary to HIV infection include B-cell non-Hodgkin lymphoma (which affects 3%–4% of patients infected with HIV) and Hodgkin lymphoma.

Human papillomaviruses (HPV) are DNA viruses that have been causally linked to cancers of the cervix, vulva, and vagina in women; cancers of the penis in men; and anal cancers and anogenital hyperproliferative lesions or warts in both women and men. Passed through sexual intercourse, HPV infections have a prevalence of more than 50% and are considered to be the most common sexually transmitted disease.[244] A major risk factor for cervical cancer is having multiple sexual partners; this relationship arises because the number of sexual partners is a measure of the likelihood of exposure to HPV.[9,226,227] Two HPV subtypes (16 and 18) are causally responsible for the vast majority of all cervical cancers.

Two vaccines to protect against HPV infection have been developed and were licensed in the United States in 2006; both the bivalent (against HPV-16 and -18) and quadrivalent (against HPV-16, -18, -6, and -11) vaccines have been shown to be nearly 100% effective against both wart and cancer development. However, because the vaccine is associated with a sexually transmitted disease,[244] its use, especially in youths, has been met with some social and political resistance.[245] Given that approximately 4.8% of incident cancers are attributable to HPV infection worldwide, vaccination is extremely important. One paradigm to prevent cervical and other HPV-associated cancers recommends that all women in all countries receive routine HPV vaccination. Further, people are urged to consider the broader spectrum of diseases preventable by HPV vaccination.[245]

TABLE 3-6

Cancers Associated with Viruses or Other Biological Agents

Virus or Biological Agent	Cancer
Hepatitis B virus	Hepatocellular carcinoma
Human papillomavirus (types 16 and 18)	Cervical cancer, esophageal squamous cell carcinoma
Epstein-Barr virus	Burkitt's lymphoma
Human T-cell lymphotrophic virus type 1	Adult T-cell leukemia/lymphoma
Human immunodeficiency virus	Kaposi's sarcoma: non-Hodgkin lymphoma
Schistosoma	Bladder cancer
Helicobacter pylori	Gastric cancer

Source: Data from American Cancer Society.[242]

Other viruses associated with human cancer include the human T-cell lymphotropic virus (HTLV-1), which is endemic to Japan, South America, Africa, and the Caribbean.[246] This virus is primarily spread from males to females, with transmission in semen, and from mother to child, with likely transmission through breast milk. After a long latent period, adult T-cell leukemia/lymphoma (ATL) occurs in 1 per 1000 carriers per year, resulting in 2500–3000 cases per year worldwide and more than half of all adult lymphoid malignancies in endemic areas.[241,243]

Epstein-Barr virus is a ubiquitous virus that has been linked to Burkitt's lymphoma and other B- and T-cell lymphomas, leiomyosarcomas, and nasopharyngeal carcinomas, as well as to the development of Hodgkin disease.[243,247]

Occupational Exposures

At least 10% of cancer deaths in the United States are attributable to workplace exposures. Examples of detrimental occupation exposures already provided in this chapter include light at night for shift workers, diesel exhaust for truck drivers, and radiation for people with numerous occupations. Reasons to study occupational causes of cancer include the following:

- An immense number of individuals spend large amounts of time at their jobs, and a growing repertoire of chemicals and physical factors are found across diverse workplaces.
- Workers are generally exposed to much higher levels of potentially hazardous chemical and physical factors than individuals who are exposed to similar hazards in nonoccupational settings.
- Cancer resulting from occupational exposures should be considered preventable. Evidence from epidemiological research that confirms the dangers posed by causal cancer agents should prompt the removal of those agents or adequate prevention of potential exposed workers.[248]

Additional literature on occupational carcinogens is available for interested readers.[3,249,250]

BIOMARKERS

Approximately 80% of cancers are theoretically preventable because the causative factors are exogenous rather than inborn or inherent. In the absence of external carcinogenic exposures from behaviors, occupation, and the ambient environment, it is estimated that 400,000 of the annual 500,000 cancer-related deaths in the United States could be averted. More effective methods are needed to identify groups and individuals at greatest risk of developing cancer when intervention is still a possibility.

Molecular epidemiology offers a powerful tool for cancer prevention by combining biomarkers with epidemiological methods. A biomarker is a substance, structure, or process that can be measured in the human body or whose products may influence the incidence or outcome of disease in human populations.[251] Examples include chemical, physical, radiological, or immunological assays conducted on blood, urine, or tissue. There are four main classes of biomarkers, though the distinction between these classes may be somewhat arbitrary: biomarkers of exposure, intermediate biomarkers, biomarkers of disease, and susceptibility biomarkers.[252]

- Biomarkers of exposure may be helpful in determining the accuracy of epidemiological exposure measurements and can overcome the potential recall bias inherent in the use of questionnaires on diet, alcohol intake, or smoking status.[89,253] These biomarkers may measure exogenous agents (e.g., pollutants), agents formed endogenously (e.g., hormones), metabolites of either endogenous or exogenous agents, products from interactions with metabolites (e.g., DNA adducts), or physiological responses due to exposures (e.g. antibodies).[252]
- Intermediate biomarkers measure biological events that take place in the continuum between exposure and disease; they include cytogenetic abnormalities and DNA adducts.[252]
- Biomarkers of disease aim to increase the validity of the defined outcome.[252] For example, mutations in the tumor suppressor gene *TP53* have been identified in the majority of serous papillary ovarian cancers; it is now believed that if an ovarian cancer does not have a *TP53* mutation, it is most likely a histologic subtype other than serous papillary.[254]
- Biomarkers of susceptibility include genetic markers such as single nucleotide polymorphisms and phenotypic or functional markers, such as DNA repair capacity.[252]

Goals of using biomarkers in cancer epidemiological studies include improved exposure assessment, documenting early changes preceding or during disease, and identifying subgroups of the population with greater susceptibility to cancer, thereby enabling investigators to identify causes and mechanisms important in the development and progression of cancer.[255] This is schematically represented in **Figure 3-7**.

One type of exposure biomarker is measurement of internal dose. For biomarkers of internal dose, investigators may examine how well a biomarker correlates with assessment by administering a questionnaire. Accuracy can be assessed by measuring burden levels of the actual compound or a stable metabolite in human tissues.[28] Examples of such biomarkers include plasma or salivary cotine from

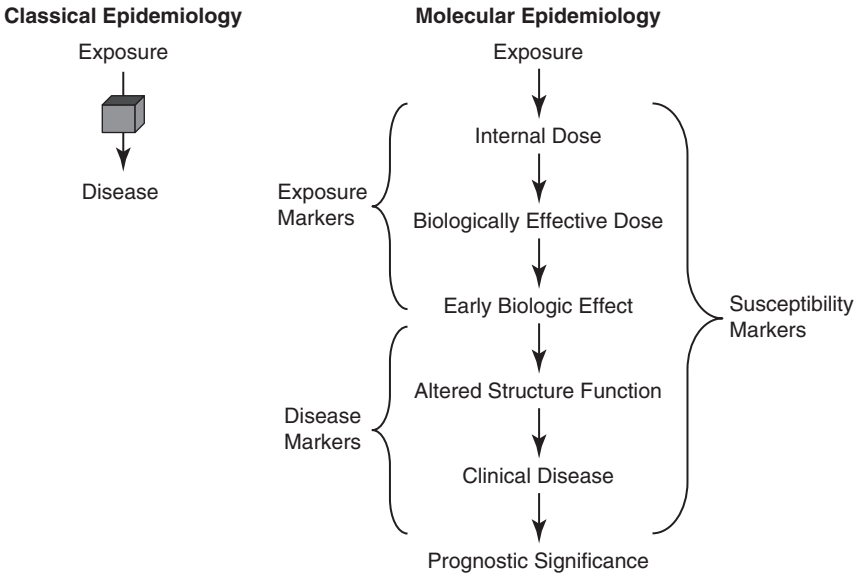

FIGURE 3-7

Schematic representation of the application of biomarkers in molecular cancer epidemiology.

cigarette smoke, urinary aflatoxin from fungal contamination of certain cereals or nuts, and urinary N-nitroso compounds from dietary sources and cigarette smoke.[256] Additional examples of biomarkers of internal dose are listed in **Table 3-7**.

Molecular epidemiology was first named as a discipline in 1982, and the field has rapidly and substantially evolved over the last three decades. Successful examples where molecular epidemiology has contributed to the understanding of human cancer are many, and include assessment of aflatoxin exposure and its causal role in liver cancer, determination of a causal role of smoking in lung cancer, and identification of cancer-associated genetic susceptibility variants by genome-wide association studies. As technology continues to advance, molecular epidemiology will continue to investigate and advance our understanding of the development and progression of cancer and other diseases in human populations.

APPLICATION OF EPIDEMIOLOGY TO NURSING PRACTICE

As cancer prevention, early detection, and cancer treatment are a priority for oncology professionals and the institutions, nurses will continue to play a critical role in the development, management, and success of cancer-control programs. Specific areas of nursing focus discussed in this section include cancer risk assessment, cancer survivorship, and palliative care, although nurses can have an impact anywhere across the spectrum of cancer research and care.

RISK ASSESSMENT

Assessing a patient's risk of cancer, assisting in determining the course of treatment, and monitoring response to treatment define the priorities of the oncology nurse.[257] The requisite knowledge and expectations of the oncology nurse in assessing cancer risks have changed dramatically over the past decade. Palpating a tumor or visualizing it on an x-ray may help diagnose cancer, but provides insufficient additional information. Rather, determining the course of treatment and monitoring the response requires learning about the tumor at the molecular level.[258] An oncology nurse with a basic understanding of the differences between types of cancers at the mechanistic level will allow a patient's cancer care team to proceed with clear determination of the best course of treatment.[259] The advent of whole-genome sequencing and risk analysis engenders precision in cancer risk prediction and cancer prevention.

TABLE 3-7

Examples of Biomarkers of Internal Dose

Biomarker	Source of Exposure	Biological Sample
Aflatoxin	Contaminated food	Urine
Bacterial mutations	Cigarette smoke	Cervical fluids
Benzene, toluene	Cigarette smoke	Urine, breath concentration
CFA (3-chloro-4-fluoroaniline)	Occupational exposure	Urine
Cotine	Cigarette smoke	Serum, urine, saliva
DNA sequences	Human papillomavirus	Cervicovaginal lavage
Fatty acids	Diet	Subcutaneous adipose tissue, serum lipids
High-density lipoprotein (HDL), alkaline phosphatase	Alcohol	Serum
Mutagens	Cigarette smoke	Bone, soft tissues
Nitrosamine acids, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), N′-nitrosonornicotine (NNN)	N-nitroso compounds, diet, tobacco	Urine
Potassium	Diet	Urine
Selenium	Diet	Hair, toenails
Vitamin level	Diet	Serum

Source: Data from Nasca;[28] Bingham et al;[89] Arab and Akbar.[253]

Nurses who function as navigators during risk assessment may call upon their deeper understanding of cancer epidemiology to interpret test results from assays applied to their patients' biospecimens. Nurses can convey knowledge to their patients and empower both patients and their families to understand test results. Goals may include targeted prevention or selecting an appropriate treatment plan with minimal negative sequela.[258]

CANCER SURVIVORSHIP

Advances in early detection, supportive care, and cancer treatment have resulted in five-year survival rates exceeding 65% for all cancers combined. There are more than 13.7 million cancer survivors in the United States, accounting for approximately 4% of the population; this number is expected to increase by 2% annually, leading to a potential population of 18 million cancer survivors by 2022.[33] While this increase in cancer survivors is positive, more individuals than ever before are living with the chronic and late-emerging effects of cancer treatment. Cancer survivors continue to face challenges and symptoms long after treatment is complete. A cross-sectional study of 377 cancer survivors examined the self-reported concerns and quality-of-life issues of cancer survivors; fatigue, fear of recurrence, and living with uncertainty were identified as high-ranking concerns among this population.[260]

Nurses should thus take a proactive role in assessing the physical, social, emotional, and spiritual needs of all cancer survivors, regardless of the cancer type or time since diagnosis of their patients. Priority should be placed on addressing ongoing educational, informational, and resource needs of cancer survivors throughout their continuum of care. The approach for each cancer survivor should be individually tailored, understanding that all survivors' needs are not the same.

PALLIATIVE AND END-OF-LIFE CARE

The goals of high-quality palliative care are to optimize patient function and comfort, enhance quality of life (QOL) for both patients and family/caregivers, and assist with medical and end-of-life (EOL) decision making.[261] Patients who require palliative care may be defined as those with a serious illness or advanced disease (such as people living with advanced cancer) who are unlikely to be cured, recover, or stabilize.[262] Cancer patients are in particular need of palliative care services, a fact recognized by both a 2001 Institute of Medicine report[263] and the American Society of Clinical

Oncology (ASCO) vision for 2020.[264] The Institute of Medicine report specifically recommended that all National Cancer Institute–designated comprehensive cancer centers offer patients and their families palliative care.[263]

Palliative care service models range from those that provide total care for the patient (home or inpatient) to those that provide only consultations with specific clinical professionals. Systematic reviews on the state of the science of quality improvements in palliative care have yielded intriguing results.[265] A broad range of settings, interventions, and clinical conditions were evaluated across 90 studies with a focus on improving the quality of palliative care through critical assessment of relevant evidence. Studies that included patient-centered quality improvement, such as education and self-management, had the strongest evidence supporting their effectiveness in patient- and family-centered domains, such as satisfaction and quality of life. Of five studies that focused on facilitated relay of clinical data to providers, only one study demonstrated a statistically significant improvement in quality of life or satisfaction. These results provide a framework for using patient-centered interventions to improve patient satisfaction in palliative and EOL care.[266]

Nurses may need to navigate across multiple settings and providers when providing EOL or palliative care. In addition, research is needed that follows large patient populations over sufficient periods of time to evaluate quality of care and disease outcomes for cancer patients who receive palliative care.

CONCLUSION

Much of the progress that has been made in cancer control has stemmed from epidemiological research results that can be used to pursue environmental, genetic, and population risks for developing specific cancer(s). Nurses are constantly challenged to construct and understand cancer risk assessments, interpret associations from new research findings, and aid in diagnoses and treatment plans for patients and their families. These efforts demand that nurses be able to accurately interpret epidemiological studies of cancer that are relevant across the continuum of care, from deciding whether a new exposure is causally associated with cancer risk to deciding whether a new treatment shows benefit over the current standard of care. This chapter provides a foundation in epidemiology, and highlights many of the advances in our understanding of cancer made by the field of epidemiology. Nurses may use their knowledge of cancer epidemiology to contribute to research, coordinate and implement education services and other components critical for cancer control, and improve the care provided to cancer patients and their families.[267]

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