

# CHAPTER 9: EPIDEMIOLOGY OF CANCER

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## CHAPTER 9

# *Epidemiology of Cancer*

Epidemiology is the study of variations in disease frequency among population groups and the factors that influence these variations. Its principal objective is the finding of causes so that, ideally, preventive measures may be applied. By focusing on events that necessarily precede the onset of disease, epidemiology contrasts to clinical medicine, in which the primary concern is the diagnosis and treatment of individual patients. In epidemiology, the perennial reference point for individual patients is the population from which they come. This approach encompasses not only unaffected members of the group in question, which may be useful for comparison purposes, but also all affected persons in that population, avoiding the selection factors that can determine the experience of individual clinicians.

After dramatic improvements in the control of infectious disease during this century, the attention of epidemiologists has increasingly turned toward the study of chronic illnesses. The resulting advances include some of the most important discoveries in the cause and prevention of cancer. The impact of epidemiology on cancer touches the clinician, experimentalist, policy maker, and even the lay public, whose attention is often drawn to epidemiologic observations and environmental issues by the news media, sometimes in an unbalanced way.

Practicing physicians must often interpret epidemiologic findings for their patients. They have opportunities to use epidemiologic data that will protect high-risk individuals, to collaborate in epidemiologic studies, and to make clinical observations relevant to etiology. The large volume of research into the origins of cancer and its prevention makes it increasingly important for the clinical oncologist to understand the principles and methods of epidemiology.

### HISTORICAL PERSPECTIVE

Epidemiologic observations in cancer have a long and fascinating history.<sup>1</sup> In 1700, the Italian occupational physician Bernardino Ramazzini observed that breast cancer was more common in nuns than other women, and he suggested the influence of celibacy. In 1775, the British surgeon Percivall Pott reported the first description of occupational carcinogenesis in the form of scrotal cancer among chimney sweeps. In the 18th century there were also reports of cancer risks associated with tobacco, namely snuff taking and nasal cancer by Hill in 1761 and pipe smoking and lip cancer by von Soemmering in 1795. Perhaps the first modern epidemiologic study of cancer was in 1842 by Rigoni-Stern, who attempted to quantify the risks of uterine cancer in the city of Verona among nuns and other women and showed that the disease was significantly less common in the former group. Important occupational cancers were also observed in the 19th century: lung cancer (first described as "mediastinal lymphoma") among the metal miners of Schneeberg and Joachimsthal by Harting and Hesse in 1879 and bladder cancer among aniline dye workers by Rehn in 1895. In 1888, Hutchinson reported the first suggestion of drug-induced cancer with an account of skin cancers in patients treated with an arsenic-containing solution.

These historical observations and many others that followed illustrate the importance of clinical observations as a source of new discoveries in cancer etiology.<sup>2,3</sup> They also include an early indication of the long latent interval in human carcinogenesis, because Pott observed that some of the men with scrotal cancer had not worked as chimney sweeps since boyhood. Furthermore, they show how some causes can be de-

tected (and diseases prevented) before specific agents and mechanisms are elucidated by laboratory investigators. Many decades elapsed before evidence was available to indicate that polycyclic hydrocarbons, radioactive substances, and aromatic amines explained some of the early findings described previously.

## AIMS OF EPIDEMIOLOGY

Several words are key to the definition of the term *epidemiology*, which is the study of the distribution and determinants of disease frequency in human populations.<sup>4</sup> The word *humans* differentiates the approach from laboratory disciplines in cancer research that use animals and other test systems in their experiments. The study of *populations* stands in contrast to clinical research, which usually involves investigations at the individual patient or case series level. The term *frequency* indicates the orientation of epidemiology towards quantifying the occurrence of disease and the risks attributable to various causes. The phrase *distribution and determinants* points to the two major approaches of epidemiology. In general, descriptive studies examine the distribution of disease frequency in populations that can be useful in generating etiologic hypotheses, whereas analytic studies test hypotheses by pursuing differences in the personal characteristics or exposures among individuals.

The main contribution of cancer epidemiology is the detection and quantification of the risks associated with specific environmental exposures and host factors. These associations may lead to causal inferences, providing the basis for instituting preventive measures. Epidemiologic data support the concept that carcinogenesis is a lengthy multistage process that is affected by a wide variety of factors.<sup>5-7</sup> Some factors appear to act early as initiators, others later as promoters, and still others at both early and late stages. Certain agents act together to accelerate the carcinogenic process, such as the way smoking combines synergistically with asbestos to produce lung cancer or with alcohol to produce oral and esophageal cancers. Furthermore, the process may be retarded by dietary factors, such as certain micronutrients that appear to diminish the risk of various cancer sites including smoking-related lung cancer.

The aims of epidemiology are to uncover new etiologic leads through peculiarities in the distribution of cancer, quantify the risks associated with different exposures (some of which may be protective), promote insights into the mechanisms of carcinogenesis, and assess the efficacy of preventive measures. Although the usual observational methods of epidemiology have succeeded in identifying many causes of cancer, future progress may depend to a considerable degree on innovative strategies that employ laboratory techniques in epidemiologic investigations.

## DESCRIPTIVE STUDIES

There is perhaps no disorder that shows a uniform incidence in all human groups. Cancers are striking in the variations they show according to such factors as age, sex, race, time,

socioeconomic class, marital status, and geographic location. Descriptive (or demographic) studies, by revealing the patterns of disease in populations, have provided many clues to cancer causes. Variations by age, area, and time are often remarkable, even allowing for the fluctuations that might be expected as a result of chance and differences in diagnostic and reporting practices.<sup>6</sup> The descriptive patterns are useful also in monitoring variations and trends that might point to new environmental hazards, in evaluating the effects of cancer prevention, screening, and treatment activities and in predicting future trends that may help set priorities in various aspects of oncology.<sup>8</sup>

## MEASURES OF CANCER FREQUENCY

Descriptive studies measure rates, which are based on three items of information: the number of persons affected by the disease (numerator), the length of the period covered (time), and the population from which they are derived (denominator). The expression of disease in this manner allows the rates in one population to be compared with the rates in another. Often these rates must be adjusted for such factors as age, race, and social class, which might otherwise spuriously influence the comparison.<sup>9</sup> The rates most often used in cancer epidemiology concern incidence, mortality, and prevalence, with each having its particular uses and limitations. When measures of occurrence are not based on populations at risk, they usually represent proportions, even though sometimes labeled as rates (*e.g.*, case-fatality rates). Sample calculations of these measures are derived from numbers given in Table 9-1.

The incidence rate provides a direct measure of the probability of developing cancer, and it is defined as the

$$\frac{\text{Number of persons developing cancer in a unit of time}}{\text{Total population living at that time}}$$

Most often the unit of time is 1 year, with the midyear population serving as the denominator. The rates are usually expressed per 100,000 or per million persons. For example, from the data in Table 9-1 the annual occurrence of Hodgkin disease per 100,000 residents in Connecticut is calculated as follows:

$$\begin{aligned} \text{Incidence rate} &= \frac{120}{3,126,488} \times 100,000 \\ &= 3.8 \text{ per } 100,000 \text{ per year} \end{aligned}$$

Incidence rates may be crude (all ages), as in this example, or age-specific. Because of the great dependence of cancer incidence on age, age-specific rates are more informative. However, when summary figures are necessary to compare rates between population groups with different age distributions, they should be age-adjusted; this is done by multiplying each age-specific rate by the percent of individuals in a standard population (*e.g.*, the 1970 U.S. population) with the same ages, and then summing to produce a single value. For etiologic studies, incidence rates tend to be more informative than mortality rates, because they cover all diagnosed cases (not merely the fatal ones) at a time which is closer to the point of causation. The information on incident cancers is usually

**TABLE 9-1.** Patients With Hodgkin's Disease and Pancreatic Cancer, Connecticut, 1982

Type of Cancer	Patients Alive at Start of Year*	New Cases in Year†	Deaths in Year‡
Hodgkin's disease	1151	120	26
Pancreatic cancer	220	326	297

\* Prevalence data estimated from data of Feldman AR, et al. The prevalence of cancer. *N Engl J Med* 1986;315:1394.  
 † Incidence data from Connecticut Tumor Registry.  
 ‡ Mortality data from National Center for Health Statistics. Estimated populations were 3,112,469 on January 1, 1982, for prevalence and 3,126,488 on July 1, 1982, for incidence and mortality.

more extensive and reliable, with details often available on histologic type and stage.

The mortality or death rate is defined as the

$$\frac{\text{Number of persons dying of cancer in a unit of time}}{\text{Total population living at that time}}$$

From data in Table 9-1, the mortality rate for Hodgkin disease is computed as follows:

$$\begin{aligned} \text{Mortality rate} &= \frac{26}{3,126,488} \times 100,000 \\ &= 0.8 \text{ per } 100,000 \text{ per year} \end{aligned}$$

For etiologic research, mortality rates most clearly reflect the occurrence of those cancer sites with the worst prognosis, and are vulnerable to well-known inaccuracies and variations in death-certificate reporting of diagnoses. However, mortality data are often the only statistics available in certain locations and periods, and they have been especially useful for evaluation of long-term trends and geographic variations on a national or international scale. For several cancers with poor survival, mortality rates nearly equal incidence rates. Even with improvements in survival of many cancers, mortality rates help in clarifying incidence trends for certain cancers (*e.g.*, breast and prostate) that may be distorted by heightened efforts at case finding.<sup>6,8</sup> Mortality rates are also useful in evaluating the impact of advances in cancer prevention and treatment on the general population. The combined analyses of incidence, mortality, and survival statistics that comprise the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) provide valuable data on the patterns of cancer in the United States.<sup>10</sup> When comparing cancer incidence or mortality rates in different countries, investigators sometimes use truncated age groups (*e.g.*, 35-64 years) to exclude the elderly whose rates are most subject to variations in medical care and reporting.

The case-fatality rate is a measure of the severity or lethality of disease. A proportion rather than a true rate, it is usually expressed as a percentage and defined as the

$$\frac{\text{Number of deaths from cancer}}{\text{Number of persons developing cancer}} \times 100\%$$

From data in Table 9-1, case-fatality rates are estimated as follows:

$$\text{Case fatality (Hodgkin's disease)} = \frac{26}{120} \times 100\% = 21.7\%$$

$$\text{Case fatality (pancreatic cancer)} = \frac{297}{326} \times 100\% = 91.1\%$$

Because the cases and deaths usually refer to the same period of time, this concept is less meaningful in chronic than in acute diseases and is generally replaced by survival rates that are discussed later.

The prevalence rate is seldom used in etiologic studies of cancer, but provides a useful measure for planning health services by estimating the burden of disease in the population.<sup>11</sup> Also called *point prevalence*, it is defined as the

$$\frac{\text{Number of persons with cancer at a given point in time}}{\text{Total population living at that time}}$$

From the data in Table 9-1, the prevalence of Hodgkin's disease on January 1, 1982 is calculated as follows:

$$\begin{aligned} \text{Prevalence} &= \frac{1,115}{3,112,469} \times 100,000 \\ &= 37.0 \text{ per } 100,000 \end{aligned}$$

Table 9-2 summarizes the various kinds of rates for Hodgkin's disease and pancreatic cancer. Hodgkin's disease displays lower incidence and mortality rates than pancreatic cancer, but a higher prevalence rate due to its much lower case-fatality rate (or conversely, higher survival rate).

Proportional rates or relative frequencies are used when details of the population that produce a series of cancer cases

**TABLE 9-2.** Measures of Frequency for Hodgkin's Disease and Pancreatic Cancer, Connecticut, 1982

Rate	Hodgkin's Disease	Pancreatic Cancer
Mortality	0.8	9.5
Incidence	3.8	10.4
Prevalence	37.0	7.1

Crude rates per 100,000 population per year are calculated from data in Table 9-1.

or deaths are unknown. This may occur in surveys of hospital patients or death certificates, in which the proportions of different cancers may be compared with those in the general population for each sex and age group. Proportional mortality ratios are sometimes used in studies of occupational groups.<sup>12</sup> Because the denominator refers to total deaths rather than the population at risk, the magnitude of the ratio for a particular cancer may be misleading, because it also fluctuates according to the number of deaths from other causes. Positive findings emerging from this type of survey should be interpreted cautiously and pursued by more definitive investigation.

## CORRELATIONAL STUDIES

Descriptive studies may use the correlational (or ecologic) approach, in which the rates of disease in populations are compared with the geographic or temporal distribution of suspected risk factors.<sup>13</sup> The association is often expressed in terms of correlation or regression coefficients. Although a correlational study may be helpful in formulating hypotheses about carcinogenic risks, it falls short of establishing causal relations. Correlational studies have the advantage of being inexpensive and quick because they often use statistics assembled for other purposes.<sup>13</sup>

The primary weakness of such studies for etiologic research, as with descriptive studies generally, is that the exposures concern populations rather than individuals. Moreover, the exposure measures are usually crude and subject to confounding factors. For example, in early surveys of lung cancer, the temporal increases among men were consistent with the effects of an increasing prevalence of cigarette smoking, but this correlation by itself provided only weak evidence of causation, because other factors such as air pollution and improvements in diagnosis showed a similar pattern. It required analytic studies that pursued these leads to establish the cause-and-effect relation between smoking and lung cancer. Correlational studies also may provide supporting evidence in evaluating relations detected by analytic or laboratory studies. This is illustrated by the more recent temporal increases in lung cancer among women, who have lagged about 25 years behind men in their adoption of smoking habits. Another example is the geographic correlation in developing countries between primary liver cancer and intake of foodstuffs contaminated by aflatoxin, a potent hepatocarcinogen in laboratory animals.<sup>6</sup> Although correlational data may provide clues to the causes, an investigator must be careful not to draw a premature or inappropriate conclusion, sometimes referred to as an *ecologic fallacy*.<sup>13</sup>

## SOURCES OF DATA

Descriptive studies employ mainly population-based statistics on mortality, incidence, and survival to calculate rates, although clinical series from hospital-based registries or other sources may also provide clues to the cause and natural history of cancer.

### *Death Certificates*

In many countries, a death certificate is prepared for legal purposes for each person who dies.<sup>14</sup> In addition to demo-

graphic variables, the certificate usually includes the underlying and secondary causes of death. Although in 1900 only 11 states in the United States contributed to the national registration system, by 1933 all 48 states were included. Alaska and Hawaii were added in 1959 and 1960 with their entry into the Union. The National Center for Health Statistics tabulates the deaths annually and calculates rates using population estimates provided by the Census Bureau. The data are also made available on computer magnetic tape for research purposes. A national death registry for the United States was established in 1979. This National Death Index is frequently used to identify persons in epidemiologic studies who have died.

The NCI has examined the national cancer mortality data in several periods. An early tabulation by age, race, sex, and form of cancer included deaths starting in 1930 and continuing through 1955.<sup>15</sup> Geographic variations in cancer mortality at the state level were evaluated for the years 1950 to 1967.<sup>16</sup> Analyses at the county level for 1950 to 1969<sup>17</sup> formed the basis for computer-generated color atlases portraying geographic patterns on a small-area scale for whites and non-whites.<sup>18,19</sup> More recently, cancer mortality was tabulated at the county level by decade from 1950 through 1979.<sup>20</sup> Using data through 1980, maps of cancer mortality were prepared according to state economic area to examine trends in the geographic patterns.<sup>21,22</sup> Computer graphics have also been used to display national trends by age, race, and sex for 1950 to 1977.<sup>23</sup> Long-term trends in U.S. cancer mortality and incidence were examined for 1935 to 1974<sup>24</sup> and more recently for 1947 to 1984.<sup>25</sup> The geographic and temporal variations of cancer mortality have also been analyzed on an international scale.<sup>26</sup>

Despite the value of mortality data for epidemiologic study, reservations are often expressed about the quality of diagnoses reported on death certificates, even though most cancers diagnosed before death are properly recorded on the certificates.<sup>27</sup> Changes in diagnostic and certification practices and in coding rules may produce spurious trends, and it is prudent to consider each observation on its merits. Death certificates are also of great value to epidemiologists in comparing the mortality of a specific group under study with that of the general population. However, the death certificates of the study group must be coded according to the same rules as for the standard or reference population.

### *Population-Based Registries*

The complete ascertainment of all newly diagnosed cases of cancer in a defined population is a difficult and expensive task. There is no system for gathering incidence data for the entire United States, but such data have been collected for specific areas in different time periods. The longest ongoing population-based resource is the Connecticut Tumor Registry, which has incidence data available from 1935.<sup>28</sup> Several other registries covering states or cities have been in existence for varying periods.

The NCI has coordinated several periodic surveys of cancer incidence in selected areas of the country. The first survey was in 1937 to 1939 and the second in 1947 to 1948,<sup>29</sup> with both covering the same 10 metropolitan areas and referred

to as the Ten-Cities Surveys. Information was gathered on cases diagnosed during 1 calendar year in each of the areas, although the specific year varied among the areas. A special survey of cases diagnosed during 1950 was conducted in Iowa to compare cancer incidence patterns among rural and urban residents.<sup>30</sup> The Third National Cancer Survey included cases diagnosed during 1969 to 1971 in two states and seven cities.<sup>31</sup> Since 1973, the SEER program has included several population-based cancer registries that continuously gather information on cancer incidence, mortality, and survival.<sup>10,32,33</sup> The SEER registries cover more than 10% of the U.S. population. Although not a probability sample of the entire population, considerable geographic and ethnic variations are represented. It has been possible to evaluate the long-term trends in cancer incidence by focusing on the geographic areas common to the various surveys.<sup>24,25</sup> In other countries, cancer reporting systems have been in existence for varying periods, starting with the Danish Cancer Registry in 1942. The International Agency for Research on Cancer has compiled data from many of the registries in five successive volumes of *Cancer Incidence in Five Continents*, the most recent providing data generally for 1978 to 1982.<sup>34</sup> This resource has been immensely valuable for proposing etiologic hypotheses.

In conjunction with the operation of a cancer registry, patients may be followed to ascertain their medical condition and vital status. Such survival data are useful in understanding incidence and mortality trends, and in measuring the dissemination and effect of treatment improvements in the general population. Although not population-based, the End Results Group of the NCI compiled survival data starting in 1950.<sup>35,36</sup> Since the advent of the SEER program in 1973, it has been possible to continuously monitor population-based survival

### Hospital-Based Registries

Although hospital-based cancer registries are valuable for clinical, administrative, and educational purposes, the data have limited use for epidemiologic studies.<sup>39</sup> However, such a registry may be an important component of a population-based cancer reporting system, and provides a means of identifying patients for case-control studies. In addition, a hospital registry may be useful in investigating the natural history of cancer and the risk of developing second primary cancers, and in assembling a clinical series that may provide clues to environmental or genetic factors in carcinogenesis.

## PATTERNS OF CANCER OCCURRENCE

### MAGNITUDE OF THE PROBLEM

In the United States, cancer is second only to heart disease as a cause of death and accounts for 22% of all deaths.<sup>40</sup> Among women aged 35 to 74, it is the leading cause of death. More than 1 million newly diagnosed cases of cancer and 500,000 deaths due to cancer are predicted for the United States during 1992 (Table 9-3). Lung cancer is the most common form, accounting for 15% of the cases and 28% of the deaths. Almost as many cases of colorectal cancer occur as lung cancer, but there are more than twice as many deaths from lung cancer. The next most common are cancers of the breast and prostate, so that these four cancers account for 56% and 55% of the

**TABLE 9-3.** Estimated New Cases and Deaths in the United States for Major Forms of Cancer—1992

Type of Cancer	Number of Cases	Number of Deaths
All sites	1,130,000	520,000
Lung	168,000	146,000
Colon and rectum	156,000	58,300
Breast	181,000*	46,300
Prostate	132,000	34,000
Urinary tract	78,100	20,200
Uterus	45,500*	10,000
Oral cavity and pharynx	30,300	7,950
Skin	32,000†	8,800‡
Pancreas	28,300	25,000
Leukemia	28,200	18,200
Ovary	21,000	13,000
All other sites	229,600	132,250

\* Invasive cancers only; more than 20,000 carcinomas in situ of the breast and 55,000 carcinomas in situ of the cervix are estimated.

† Melanoma only; more than 600,000 nonmelanoma skin cancers are estimated.

‡ Melanoma 6700; other skin cancers 2100.

(Boring CC, Squires TS, Tong T. Cancer statistics, 1992. CA 1992; 42:19. Based on incidence data from National Cancer Institute SEER program 1986-1988 and mortality data from the National Center for Health Statistics. All figures are rounded.)

total cancer cases and deaths, respectively. The 11 sites shown in Table 9-3 comprise 80% of all cancer cases and 75% of cancer deaths.

Table 9-4 presents the age-adjusted incidence and mortality rates for 44 specific forms of cancer among white males and females in the United States for the period 1984 to 1988. Among males the mortality rate is highest for lung cancer, followed by colorectal and prostate cancers, whereas among females the rates are highest for lung and breast cancers, followed by colorectal cancer. However, the highest incidence rates are for prostate and breast cancers among males and females, respectively, survival rates for which are both considerably better than for lung cancer. All cancers show higher rates among men except for those of the breast, gallbladder, and thyroid.

### INTERNATIONAL VARIATION

It has been estimated that about 75% to 80% of all cancer in the United States is due to environmental factors.<sup>6</sup> To obtain this estimate, rates for the lowest-risk countries were subtracted from rates prevailing in the United States. The lowest risk is considered the baseline level for so-called *spontaneous tumors* that in theory cannot be prevented.

Table 9-5 shows in rank form the international variation for a number of cancers based on recent statistics from volume 5 of *Cancer Incidence in Five Continents*.<sup>34</sup> The variation ranges from 155-fold for melanoma to fivefold for leukemia and is not believed to be greatly affected by differences in diagnostic and reporting practices between countries.<sup>3,6</sup> Although genetic

**TABLE 9-4.** Average Annual Age-Adjusted Incidence and Mortality Rates Per 100,000 Among U.S. Whites by Primary Cancer Site, 1984-1988

Type of Cancer	Incidence (SEER)		Mortality (U.S.)	
	Males	Females	Males	Females
All sites	433.1	339.8	212.7	138.3
Lip	2.8	0.3	0.1	0.0
Salivary gland	1.3	0.8	0.3	0.1
Nasopharynx	0.6	0.3	0.3	0.1
Other oral cavity and pharynx	11.6	5.0	3.7	1.5
Esophagus	5.2	1.6	4.9	1.2
Stomach	10.6	4.5	6.6	3.0
Small intestine	1.3	0.9	0.4	0.2
Colon	42.3	31.4	20.9	14.8
Rectum	19.3	11.3	3.6	2.1
Liver	2.9	1.2	2.9	1.3
Gallbladder	0.8	1.4	0.5	1.0
Other biliary	1.4	1.0	0.8	0.6
Pancreas	10.7	7.9	9.8	6.9
Larynx	8.3	1.6	2.3	0.4
Lung and bronchus	82.5	37.8	72.5	27.6
Pleura	1.4	0.2	0.3	0.1
Nasal cavity and sinuses	0.8	0.5	0.2	0.1
Bones and joints	1.0	0.7	0.5	0.3
Soft tissue	2.5	1.8	1.2	1.0
Melanoma of skin	12.6	9.7	3.2	1.7
Other nonepithelial skin	5.2	0.8	1.3	0.3
Breast	0.8	108.8	0.2	27.3
Cervix uteri	—	7.8	—	2.7
Uterus excluding cervix	—	22.7	—	3.4
Ovary	—	14.6	—	7.9
Vagina	—	0.6	—	4.2
Vulva	—	0.6	—	0.3
Prostate	92.2	—	22.2	—
Testis	4.7	—	0.3	—
Penis	0.8	—	0.2	—
Bladder	32.1	7.8	6.0	1.7
Kidney	11.6	5.6	4.8	2.2
Ureter	0.9	0.3	0.1	0.1
Eye and orbit	0.8	0.6	0.1	0.1
Brain and other nervous system	7.6	5.5	5.2	3.5
Thyroid	2.5	6.0	0.3	0.4
Hodgkin's disease	3.5	2.7	0.9	0.5
Non-Hodgkin's lymphoma	16.6	11.2	7.3	5.0
Multiple myeloma	4.7	3.2	3.2	2.2
Acute lymphocytic leukemia	1.8	1.2	0.8	0.5
Chronic lymphocytic leukemia	4.2	2.0	1.7	0.7
Acute myeloid leukemia	2.8	1.9	2.2	1.5
Chronic myeloid leukemia	1.7	1.0	1.0	0.6
Other leukemias	2.8	1.7	2.8	1.7
All other sites	15.9	12.2	17.0	11.5

Rates are age-adjusted based on the 1970 U.S. standard population. Incidence data are from the National Cancer Institute SEER program, and national mortality data are from the National Center for Health Statistics.

factors may play some role (*e.g.*, in melanoma, which tends to affect fair-skinned populations), evidence suggests that the international differences are mainly due to environmental factors. The patterns observed in Table 9-5 are in fact likely to underestimate the true global variation, because some regions with exceptionally high rates of certain cancers are not covered by registries (*e.g.*, esophageal cancer in parts of China and Iran, liver cancer in parts of Africa and Asia, and urinary tract cancer in areas endemic with schistosomiasis or Balkan nephropathy).<sup>3</sup> Furthermore, the differences would be more pronounced if data were available for certain subtypes of cancer such as Burkitt's lymphoma and Kaposi's sarcoma, or subsites such as the gingival-buccal mucosa which comes in contact with smokeless tobacco and related products.

#### MIGRANT PATTERNS

Further evidence for environmental factors can be found in studies of migrant populations, such as the Japanese who moved to Hawaii and California. After migration, with the adoption of new habits, the risk of various cancers has moved away from the rate prevailing in the country of origin toward that of the new country.<sup>41</sup> Among Japanese migrants, increases in the risk of large bowel cancer were evident within a few decades of migration, whereas changes in breast cancer rates continue for generations. In contrast to general environmental exposures, lifestyle practices may change slowly among migrants, depending on the speed and extent of acculturation.

Migrant patterns have been studied by comparing the cancer mortality rates in the U.S. white population by country of birth with the corresponding rates in the country of origin.<sup>42</sup> Figure 9-1 shows the age-adjusted mortality rates for colorectal and stomach cancers.<sup>43</sup> Stomach cancer rates among migrants are generally lower than in the country of origin, but higher than among whites born in the United States. In contrast, colorectal cancer mortality in most countries is lower than in the United States, but the rates among migrants not only approach those of the U.S.-born whites but even exceed them in some instances. Those born in Mexico, however, have retained rates that are about 50% those of native-born white Americans. In addition, colorectal cancer mortality among the foreign-born has not reached U.S. rates as frequently for women as for men. When mortality from other cancers among the U.S. foreign-born is compared with statistics in the countries of origin, the rates for breast, corpus uteri, and prostate cancers are generally more closely aligned with those of U.S. native-born whites. Analytic studies among migrants should provide insights into lifestyle factors in cancer causation.

#### CANCER MAPS

Although variations within countries are not as great as those seen internationally, the computer-generated mapping of cancer death rates in the United States at the county level for the period 1950 to 1969 revealed several high-risk areas that have led to the investigation of environmental exposures.<sup>18,19</sup> For example, the elevated rates for lung cancer among men along the eastern seaboard drew attention to the unexpected scale and impact of asbestos exposures in shipyards during World War II (Fig. 9-2).<sup>44</sup> Similarly, a clustering of high-risk

**TABLE 9-5.** International Variation in Cancer Incidence\*

Type of Cancer	Ratio (H/L)	High (H) Incidence Area	Rate†	Low (L) Incidence Area	Rate†
Melanoma	155	Australia (Queensland)	30.9	Japan (Osaka)	0.2
Lip	151	Canada (Newfoundland)	15.1	Japan (Osaka)	0.1
Nasopharynx	100	Hong Kong	30.0	U.K. (South Western)	0.3
Prostate	70	U.S. (Atlanta, black)	91.2	China (Tianjin)	1.3
Liver	49	China (Shanghai)	34.4	Canada (Nova Scotia)	0.7
Penis	42	Brazil (Recife)	8.3	Israel (Born Eur. and Am.)	0.2
Oral cavity	34	France (Bas-Rhin)	13.5	India (Poona)	0.4
Cervix uteri (F)	28	Brazil (Recife)	83.2	Israel (non-Jews)	3.0
Esophagus	27	France (Calvados)	29.9	Romania (Urban Cluj)	1.1
Stomach	22	Japan (Nagasaki)	82.0	Kuwait (Kuwaitis)	3.7
Thyroid	22	Hawaii (Chinese)	8.8	Poland (Warsaw City)	0.4
Multiple myeloma	22	U.S. (Alameda, black)	8.8	Phillipines (Rural)	0.4
Kidney	21	Canada (NWT and Yukon)	15.0	India (Poona)	0.7
Corpus uteri (F)	21	U.S. (Bay Area, white)	25.7	India (Nagpur)	1.2
Lung	19	U.S. (New Orleans, black)	110.0	India (Madras)	5.8
Colon	19	U.S. (Connecticut, white)	34.1	India (Madras)	1.8
Testis	17	Switzerland (Urban Vaud)	10.0	China (Tianjin)	0.6
Bladder	16	Switzerland (Basel)	27.8	India (Nagpur)	1.7
Lymphosarcoma	12	Switzerland (Basel)	9.2	Japan (Rural Miyagi)	0.8
Pancreas	11	U.S. (Los Angeles, Korean)	16.4	India (Poona)	1.5
Hodgkin's disease	10	Canada (Quebec)	4.8	Japan (Miyagi)	0.5
Brain	9	N.Z. (Polynesian Islanders)	9.7	India (Nagpur)	1.1
Larynx	8	Brazil (Sao Paulo)	17.8	Japan (Rural Miyagi)	2.1
Ovary (F)	8	N.Z. (Polynesian Islanders)	25.8	Kuwait (Kuwaitis)	3.3
Rectum	8	Israel (Born Eur. and Am.)	22.6	Kuwait (Kuwaitis)	3.0
Breast (F)	7	Hawaii (Hawaiian)	93.9	Israel (non-Jews)	14.1
Leukemia	5	Canada (Ontario)	11.6	India (Nagpur)	2.2

\* Among males unless specified as females (F); rates based on less than 10 cases are excluded.

† Average annual rate per 100,000, age-adjusted based on the world standard population; rates generally are for the period 1978-1982.

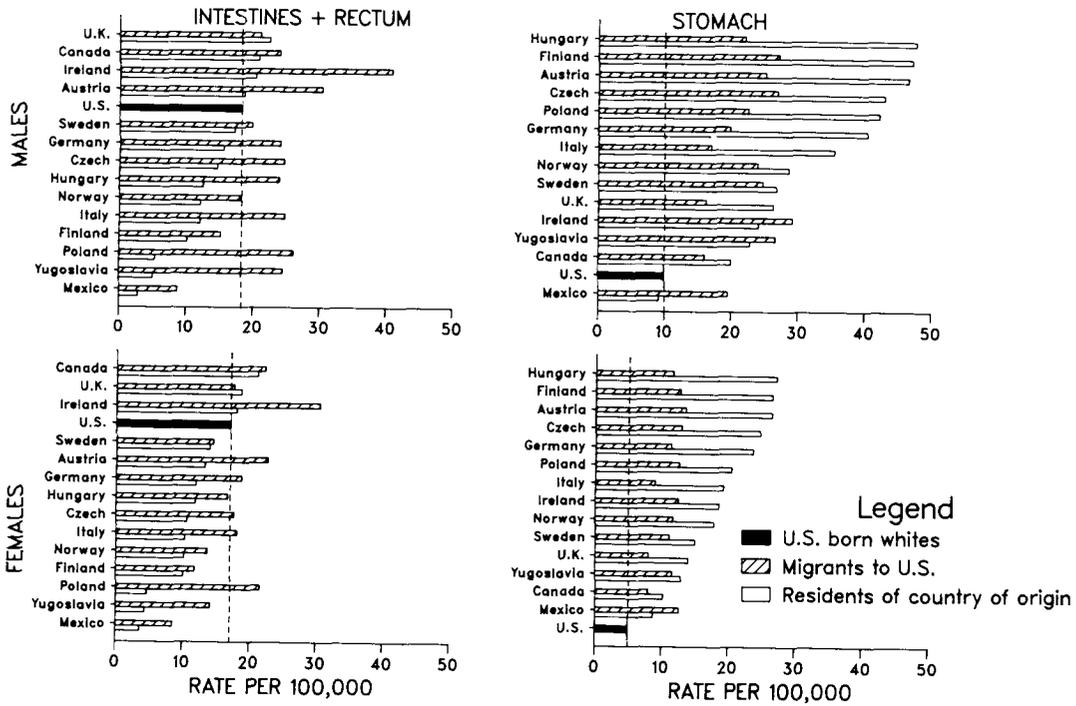
(Muir C, Parkin M. International Agency for Research on Cancer, based on data abstracted from Muir C, Waterhouse J, Mack T, et al. eds. Cancer incidence in five continents, vol 5. Lyon: International Agency for Research on Cancer, 1987)

areas in Louisiana was traced in part to heavy smoking by the Cajun population.<sup>45</sup> Furthermore, studies of the elevated rates for oral cancer among women in the rural south have pointed to the hazards associated with the practice of snuff dipping (Fig. 9-3).<sup>46</sup> A recent update of the cancer maps through the period 1970 to 1980 has revealed patterns resembling those in the earlier atlas, but with a tendency toward greater uniformity of rates around the country.<sup>21,22</sup> Yet some new clustering emerged, including elevated rates of lung and oral cancers among women in Florida and along the Pacific coast that seem related to smoking habits, and high rates of non-Hodgkin's lymphoma in central regions that may be associated with agricultural exposure to herbicides.<sup>47</sup> The U.S. cancer maps were soon followed by similar atlases from other countries, the total reaching 22 at last count.<sup>48</sup> Most remarkable are the maps from China that have disclosed dramatic variations in mortality and have stimulated analytic studies in areas with exceptionally high rates.<sup>49</sup> In Scandinavian countries that have national cancer registries, atlases based on

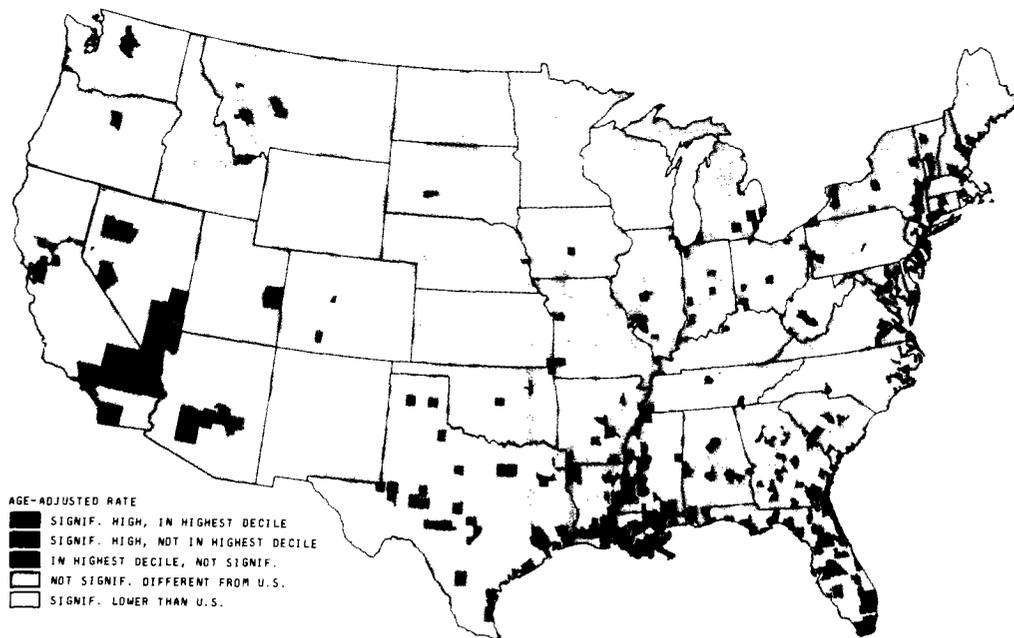
incidence data have been useful in identifying high-risk communities, particularly for less lethal tumors (*e.g.*, endometrium) that are not measured well by mortality statistics.

#### TIME TRENDS

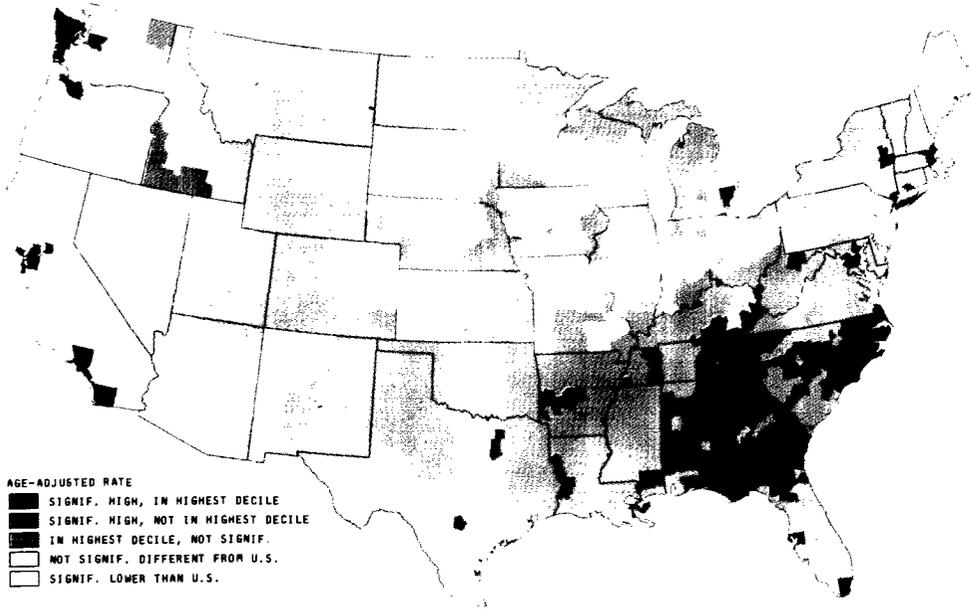
A major indication of the importance of environmental factors lies in the variation in the mortality and incidence of certain cancers over time. Mortality rates for some forms of cancer in the United States have changed greatly over the last 57 years, whereas rates for several other cancers have remained relatively stable (Fig. 9-4).<sup>50</sup> Most striking has been the tenfold increase in lung cancer mortality. The upward trend started earlier among males than among females, for whom the rate of increase accelerated during the 1960s. However, the rates among males have not been rising as rapidly during the 1980s as in previous years. These trends reflect the changing prevalence of smoking habits in the male and female populations.<sup>51</sup> Lung cancer mortality among females has sur-



**FIGURE 9-1.** Average annual mortality rates for intestinal and stomach cancers among U.S.-born whites, migrants from selected countries from 1959 to 1961, and residents of the countries of origin, 1960. Rates standardized for age on the 1950 U.S. population. (Data from Liliensfeld AM, Levin ML, Kessler II. Cancer in the United States. Cambridge, MA: Harvard University Press, 1972)



**FIGURE 9-2.** Mapping of lung cancer mortality rates among white men for United States state economic areas, 1950 to 1969. Rates standardized for age on the 1960 U.S. population. (Adapted from Mason TJ, McKay FW, Hoover R, et al. Atlas of cancer mortality for U.S. counties: 1950-1969. Washington, DC, U.S. Government Printing Office; 1975. U.S. Dept. of Health, Education, and Welfare publication [NIH] 75-780)

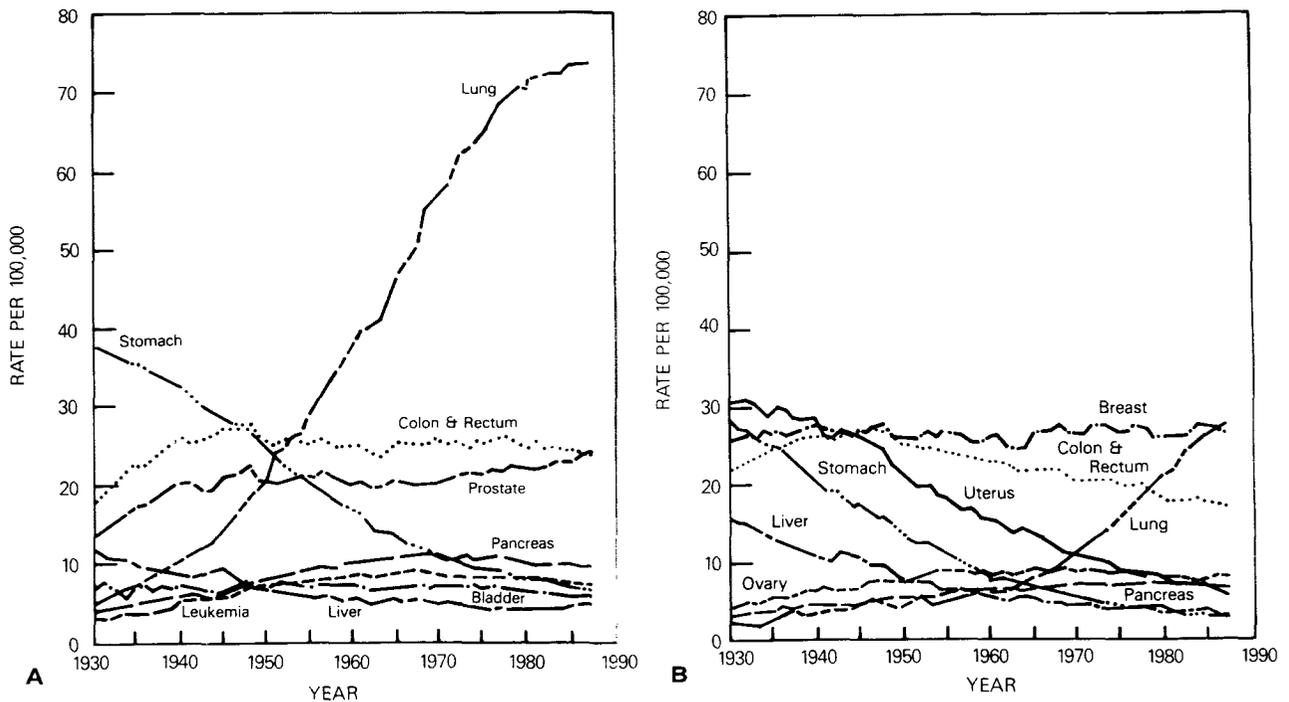


**FIGURE 9-3.** Mapping of oral and pharyngeal cancer mortality rates among white females for United States state economic areas, 1950 to 1969. Rates standardized for age on the 1960 U.S. population. (Adapted from Mason TJ, McKay FW, Hoover R, et al. Atlas of cancer mortality for U.S. counties: 1950-1969. Washington, DC, U.S. Government Printing Office; 1975. U.S. Dept. of Health, Education, and Welfare publication [NIH] 75-780)

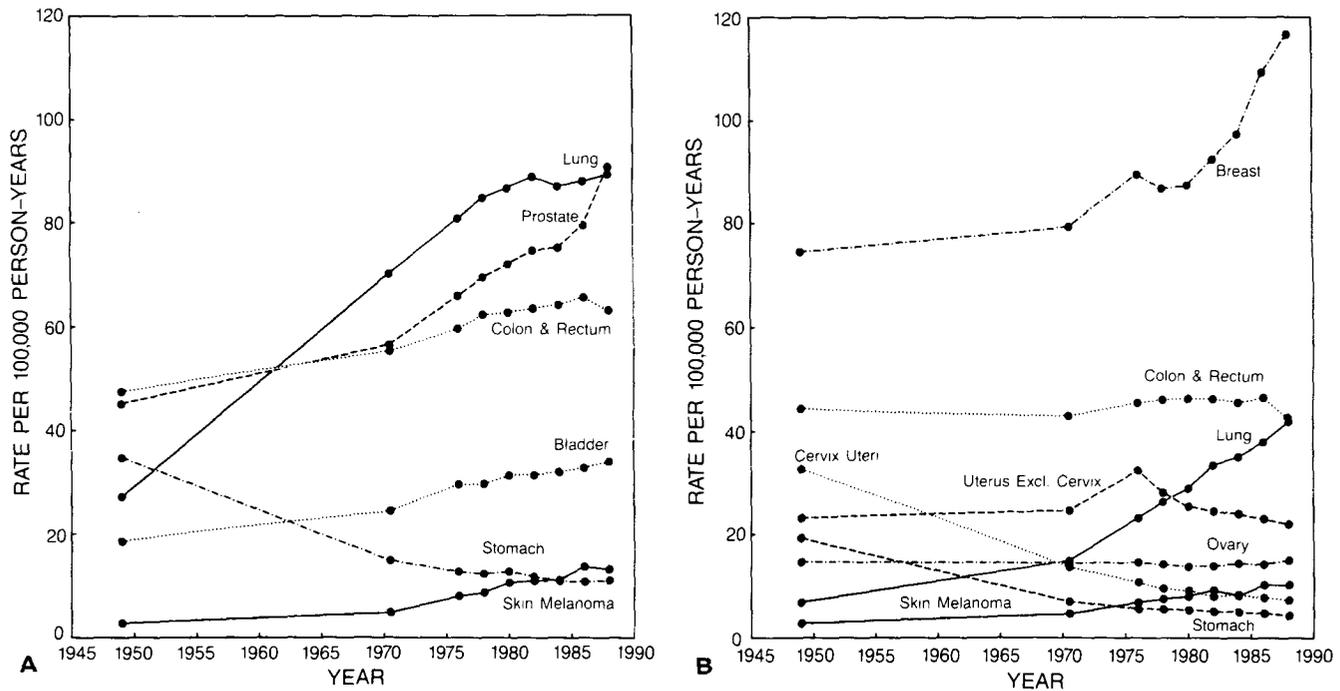
passed that for breast cancer, the rate for which has not changed substantially over the past 50 years. Notable declines are apparent for stomach cancer and uterine cancer (reflecting downward mortality trends for cancers of the cervix and corpus uteri). Colorectal cancer rates increased until the late 1940s in both sexes and have leveled off among males and declined among females. Rates for several forms of cancer (e.g., pancreas) increased during the early years, partly due

to improvements in diagnosis and the accuracy of death certificates. The decreases noted for liver cancer are likely to reflect greater precision in the diagnosis and certification of primary cancer at this site.

Incidence data spanning about 40 years are shown in Figure 9-5 for the white population in five geographic areas of the country.<sup>25</sup> Among males, lung cancer incidence increased almost 3% per year to become the most frequent form of cancer



**FIGURE 9-4.** Cancer mortality trends for selected sites in the U.S. population, 1930 to 1987, among (A) males and (B) females. Rates standardized for age on the 1970 U.S. population. (Data from the National Center for Health Statistics; and Bureau of the Census; and Boring CC, Squires TS, Tong T. Cancer statistics, 1991. CA 1991;41:19)



**FIGURE 9-5.** Cancer incidence trends for selected sites in five geographic areas of the United States, 1947 to 1988, among (A) white males and (B) white females. Rates standardized for age on the 1970 U.S. population. (Data from Devesa SS, Silverman DT, Young JL Jr, et al. Cancer incidence and mortality trends among whites in the United States, 1947-84. *J Natl Cancer Inst* 1987;79:701 and Surveillance, Epidemiology, and End Results program)

until recently; the leveling off in recent years may reflect a decrease in smoking prevalence. Prostatic cancer incidence rose to become the most common cancer among white males, due at least partly to the improved detection of early-stage or latent carcinomas.<sup>52</sup> Some of the increases in bladder cancer among males may be due to changing criteria by cancer registries, notably for papillomas, but trends in smoking must also play a role. Increases of 33% in colorectal cancer and declines of 68% in stomach cancer among males are consistent with a number of dietary hypotheses under active investigation.<sup>53</sup> Melanoma incidence rose nearly fourfold among males, probably due in part to the changing patterns of exposure to sunlight.<sup>54</sup>

Among females, breast cancer incidence rose 56% from the late 1940s to the late 1980s, with most of the increases occurring during the last decade. The striking rise during the early 1970s has been attributed to increased public awareness of breast cancer that precipitated earlier diagnoses, but reasons for the continuing increases, especially among women aged 55 and older, are unclear. Incidence rates have risen most sharply for localized tumors of the breast, and increases in early detection appear to be contributing to the trend.<sup>33,55</sup> In contrast to the prominent upward trend among males, colorectal cancer rates among females have remained relatively stable. Although lung cancer incidence rates are considerably lower among females than males, the proportional increases of almost 6% per year have been greater. The rates for cancer of the body of the uterus appeared stable until the 1970s, when a substantial increase of more than 30% occurred and was followed by decreases of similar magnitude. This pattern follows the upturn and subsequent downturn in the use of

menopausal estrogens that have been implicated in the development of endometrial cancer.<sup>56</sup> Incidence rates for invasive cancer of the cervix uteri declined more than 75% over the 40-year period, or about 4% per year, one of the largest observed for any cancer site in either sex. The decrease is due partly to the increased use of cervical cytology to detect precursor lesions,<sup>57</sup> but the increasing prevalence of women with a hysterectomy has contributed to the trend.<sup>58</sup> Declines of 77% in stomach cancer incidence and increases of almost threefold in melanoma are apparent among females, resembling the trends among males.

#### SURVIVAL TRENDS

Five-year relative survival rates among whites for all cancers combined rose from 39% in the early 1960s to 52% during the 1980s (Table 9-6). Interpretation of the trends should consider that the data come from two sources: the End Results Group for the earliest two periods and the SEER program for the subsequent intervals.<sup>33</sup> The relative survival rate is adjusted to take into account the expected mortality prevailing in the general population. The trend for all sites combined reflects not only improvements in survival for a number of specific cancers but also changes in their relative frequency. Large increases in survival rates have occurred for Hodgkin's disease, skin melanoma, and cancers of the testis, prostate, and bladder. Increases are seen also for leukemia, non-Hodgkin's lymphoma, and several other forms of cancer, due to better methods of treatment and perhaps earlier diagnosis. Melanoma and cancers of the thyroid, testis, and corpus uteri have shown 5-year survival rates of 80% or more in recent

**TABLE 9-6.** Trends in 5-Year Relative Survival Rates for Selected Sites of Cancer Among U.S. Whites, 1960-1987

Type of Cancer	Year of Diagnosis				
	1960-1963* (%)	1970-1973* (%)	1974-1976† (%)	1977-1980† (%)	1981-1987† (%)
All sites	39	43	50	50	52
Oral cavity and pharynx	45	43	55	54	54
Esophagus	4	4	5	6	9
Stomach	11	13	14	16	16
Colon	43	49	50	53	58
Rectum	38	45	48	51	55
Liver	2	3	4	3	5
Pancreas	1	2	3	2	3
Larynx	53	62	66	67	68
Lung and bronchus	8	10	12	13	13
Melanoma of skin	60	68	80	82	82
Breast (females)	63	68	75	75	78
Cervix uteri	58	64	69	68	68
Corpus uteri	73	81	89	86	84
Ovary	32	36	36	38	38
Prostate	50	63	67	72	76
Testis	63	72	78	88	93
Bladder	53	61	74	76	79
Kidney	37	46	52	51	53
Brain and nervous system	18	20	22	24	24
Thyroid	83	86	92	92	94
Hodgkin's disease	40	67	71	73	77
Non-Hodgkin's lymphoma	31	41	47	48	51
Multiple myeloma	12	19	24	25	26
Leukemia	14	22	34	36	36

\* Rates based on data from the End Results Group using a series of hospital registries and one population-based registry.

† Rates based on data from the SEER program with follow-up of patients through 1988. (National Cancer Institute: Cancer Statistics Review 1973-1988. Bethesda, MD, 1991)

years. Survival rates for those with esophageal, stomach, liver, pancreatic, and lung cancers remain poor.

The stage at diagnosis varies substantially by cancer site (Table 9-7). More than 75% of lip and corpus uteri cancers are localized when first detected, as are skin melanomas. At the other extreme are pancreatic and ovarian cancers, more than 50% of which have spread to distant sites. Survival figures for most cancers are greatly affected by the extent of disease at the time of detection. Patients with colon, rectum, bladder, or kidney cancers diagnosed at a localized stage experience 5-year survival rates exceeding 80%, whereas rates are lower than 10% if the cancer has spread to one or more distant sites. The impact of stage at diagnosis is only slightly less striking for melanoma and cancers of the breast and cervix. This suggests that major improvements in overall cancer survival and in mortality rates may be achieved through development and implementation of techniques enabling earlier detection and treatment. Generally less favorable survival rates among blacks than whites are at least partly due to more advanced stages of cancer at the time of diagnosis.<sup>33</sup>

The impact of improved treatment has been remarkable for childhood cancer (Table 9-8).<sup>33</sup> Five-year relative survival rates for all types combined improved from 28% during the early 1960s to 67% in the 1980s. Acute lymphocytic leukemia has been transformed from a virtually fatal cancer with a 4% survival rate to one with a 73% probability of 5-year survival. Children diagnosed with Hodgkin's disease during the early 1960s experienced a 52% survival rate, whereas those diagnosed during the 1980s achieved rates approaching 90%. For Wilms' tumor, survival rates increased from 33% to 84% over the same period. Improvements in therapy and survival have resulted in dramatic declines in childhood cancer mortality in recent years.<sup>59</sup>

#### AGE CURVES

Because of the marked rise in cancer incidence with advancing age, it was suggested that some aspect of the aging process increases susceptibility to cancer, perhaps by impairing immune function. It is now believed that the relation of many

**TABLE 9-7.** Stage Distribution and 5-Year Relative Survival Rates According to Stage at Diagnosis for Selected Sites of Cancer Among U.S. Whites, 1981-1987\*

Type of Cancer	Stage Distribution (%)†			Relative Survival Rates (%)		
	Localized	Regional	Distant	Localized	Regional	Distant
Lip	78	13	1	93	82	‡
Salivary gland	49	34	9	91	52	30
Nasopharynx	19	46	19	75	43	25
Other oral and pharynx	32	47	12	66	40	17
Esophagus	25	21	27	21	6	0
Stomach	16	35	36	57	16	2
Colon	33	41	20	91	60	6
Rectum	41	36	16	83	50	5
Liver	22	21	26	13	5	2
Pancreas	10	21	51	7	4	1
Larynx	51	37	6	84	54	31
Lung and bronchus	18	31	39	41	14	2
Melanoma of skin	81	8	4	90	50	14
Breast (females)	52	38	7	92	72	19
Cervix uteri	48	32	10	89	54	14
Corpus uteri	76	11	9	93	72	29
Ovary	22	21	52	87	39	19
Prostate	61	14	18	89	80	29
Testis	62	23	13	97	96	67
Bladder	74	19	3	91	46	9
Kidney	42	25	28	84	56	8
Brain and nervous system	72	18	1	24	26	26
Thyroid	55	36	6	99	93	50

\* Rates based on data from the SEER program with follow-up of patients through 1988.

† Percentages do not add to 100 due to some cases with unknown stage.

‡ Inadequate numbers to calculate.

(National Cancer Institute: Cancer Statistics Review 1973-1988, Bethesda, MD, 1991, and unpublished SEER data)

**TABLE 9-8.** Trends in 5-Year Relative Survival Rates for Selected Forms of Cancer Among U.S. White Children Under 15 Years of Age, 1960-1987

Type of Cancer	Year of Diagnosis				
	1960-1963* (%)	1970-1973* (%)	1974-1976† (%)	1977-1980† (%)	1981-1987† (%)
All forms	28	45	55	62	67
Acute lymphocytic leukemia	4	34	53	68	73
Acute myeloid leukemia	3	5	16	25	25
Wilms's tumor	33	70	74	80	84
Brain and nervous system	35	45	54	56	58
Neuroblastoma	25	40	49	52	55
Bone	20	30	52	47	56
Hodgkin's disease	52	90	80	88	87
Non-Hodgkin's lymphoma	18	26	43	50	68

\* Rates based on the End Results Group using a series of hospital registries and one population-based registry.

† Rates based on the SEER program with follow-up of patients through 1988.

(National Cancer Institute: Cancer Statistics Review 1973-1988, Bethesda, MD, 1991)

cancers to increasing age mainly reflects the importance of duration of exposure to carcinogens and of long induction periods.<sup>5</sup>

Figure 9-6 shows the age distribution for selected cancers in the white population, with incidence plotted on a semilog scale. Most epithelial cancers are rare under age 30 but then rise progressively with age (e.g., cancers of the colon and rectum, prostate, and bladder), although at the oldest ages a slight downturn in the curve is probably related to underdiagnosis. For cancers of female reproductive sites, the rates appear to reach a plateau or decline at postmenopausal ages, consistent with an influence of endogenous hormones. Only a few non-epithelial cancers rise sharply with age, notably multiple myeloma and chronic lymphocytic leukemia.<sup>5</sup> Deviations from the usual age trends are illustrated by the cancers plotted in Figure 9-6C. Peaks for leukemia and nervous system cancer occur not only at older ages but also in early childhood, suggesting the influence of prenatal factors. The bimodal age curve for Hodgkin's disease has received much attention, and some evidence suggests that the young adult peak may result from an infectious agent.<sup>60</sup> Also intriguing is the pattern of testis cancer, with a peak occurrence among young adult men and a rising incidence over time that remains unexplained.<sup>61</sup> The rates for invasive cervical cancer increase sharply with age among young women, but then level off after age 35.

Table 9-9 shows the incidence rates for the major cancers among white children by age group and sex for the period 1984 to 1988. Except for lymphomas and bone tumors, the highest incidence occurs in children under 5 years. In general, boys have somewhat higher rates than girls in all three age groups, especially for the lymphomas.

ETHNIC VARIATION

The SEER program provides data indicating striking racial and ethnic variations in cancer incidence in the United States (Tables 9-10 and 9-11). For males, the rates for all cancers combined are highest in blacks, followed by whites and Hawaiian Americans, whereas for females the rates are highest for Hawaiian Americans, followed by whites and blacks. The lowest rates in both sexes are in Native Americans. Compared with other groups, whites have especially high rates for melanoma, Hodgkin's disease, non-Hodgkin's lymphoma, leukemia, and cancers of the lip, breast, corpus uteri, ovary, testis, bladder, brain, colon, and rectum. Blacks have elevated rates for multiple myeloma and cancers of the oral cavity, esophagus, colon, pancreas, larynx, lung (males), cervix uteri, and prostate. Hispanic Americans have especially high rates for cervix cancer, and to some extent for cancers of the stomach and biliary tract (especially females), whereas Native Amer-

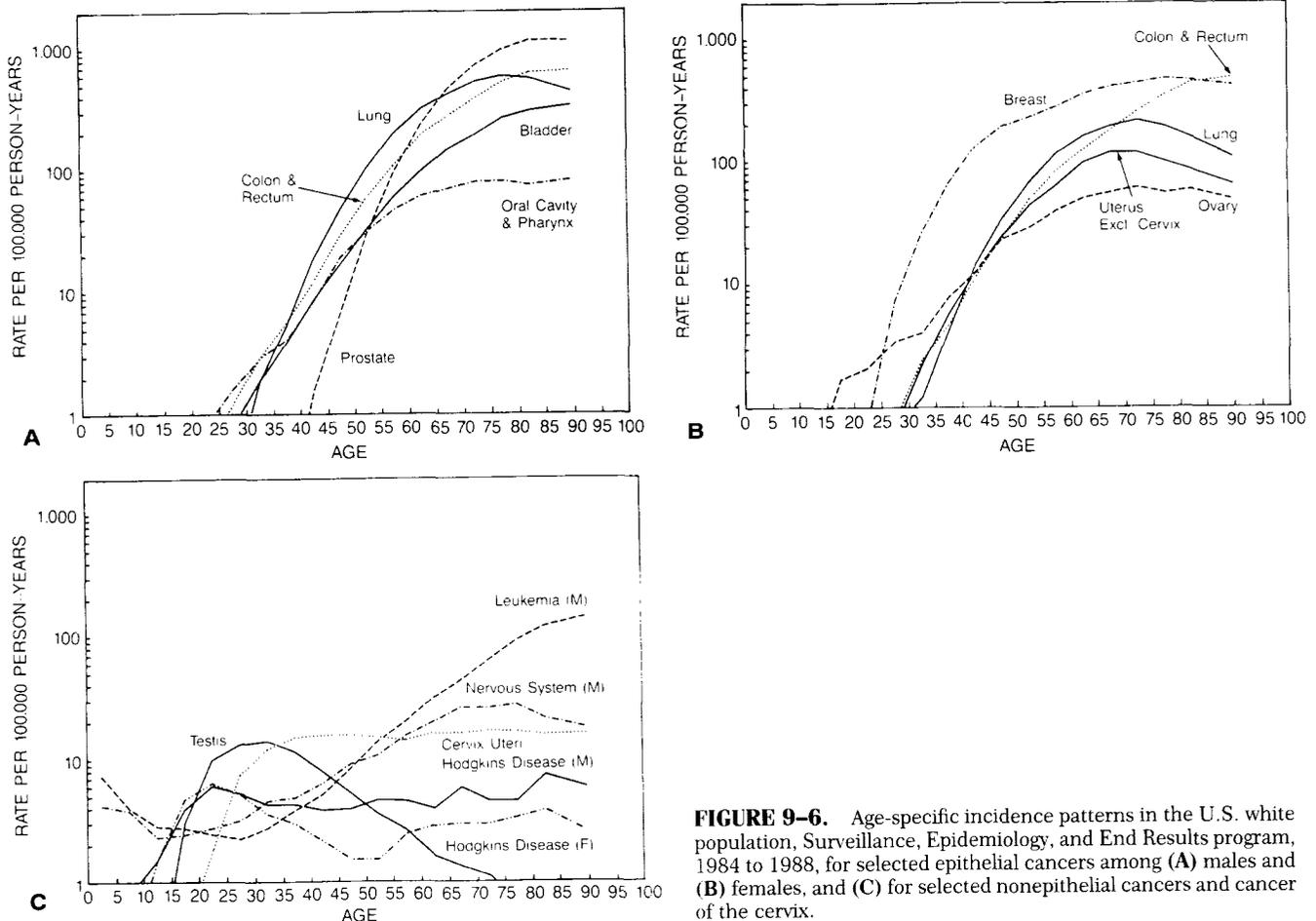


FIGURE 9-6. Age-specific incidence patterns in the U.S. white population, Surveillance, Epidemiology, and End Results program, 1984 to 1988, for selected epithelial cancers among (A) males and (B) females, and (C) for selected nonepithelial cancers and cancer of the cervix.

**TABLE 9-9.** Age-Specific Incidence Rates for Selected Forms of Cancer Among U.S. White Children, 1984-1988\*

Type of Cancer	Boys			Girls		
	0-4†	5-9	10-14	0-4	5-9	10-14
All forms	21.5	13.0	12.8	18.8	9.8	11.9
Leukemia	7.5	4.0	2.8	6.8	2.6	2.6
Brain and central nervous system	4.2	3.8	2.3	3.6	3.2	2.3
Lymphoma	0.8	2.2	3.4	0.4	1.1	2.2
Neuroblastoma	3.6	0.4	0.0	2.8	0.4	0.1
Soft tissue	0.6	0.4	0.5	0.7	0.3	0.7
Wilm tumor	1.6	0.6	0.1	1.9	0.6	0.1
Bone	0.1	0.5	1.6	0.1	0.6	1.4
Retinoblastoma	1.0	0.1	0.0	1.2	0.1	0.0
All others	2.1	1.0	2.1	1.3	0.9	2.5

\* Average annual rates per 100,000 population.

† Age given in years.

(National Cancer Institute: Cancer Statistics Review 1973-1988, Bethesda, MD, 1991, and unpublished SEER data)

**TABLE 9-10.** Average Annual Age-Adjusted Incidence Rates per 100,000 for Selected Cancer Sites by Racial and Ethnic Group, 1975-1985, U.S. Males

Type of Cancer	Whites	Blacks	Hispanics	American Indians	Chinese	Japanese	Filipinos	Hawaiians
All sites	404.1	490.2	265.5	184.5	292.7	303.6	242.0	398.9
Lip	3.7	0.2	3.3	0.0	0.1	0.1	0.0	0.0
Nasopharynx	0.6	1.0	0.9	0.5	13.9	1.4	2.9	1.5
Other oral cavity and pharynx	11.8	20.5	5.2	1.7	6.2	6.0	6.8	10.1
Esophagus	4.9	18.4	2.9	1.9	6.1	5.6	4.9	15.1
Stomach	11.5	20.5	20.8	26.1	14.5	38.6	9.6	40.4
Colon	40.3	40.7	17.9	8.4	33.6	42.1	24.0	25.8
Rectum	20.0	14.9	11.5	5.0	19.3	23.4	16.9	18.7
Liver	2.7	5.2	4.3	4.5	19.5	7.1	10.2	9.8
Gallbladder	0.8	0.8	1.5	8.9	1.2	1.5	1.2	1.4
Other biliary	1.6	1.2	2.2	2.8	2.2	3.9	2.1	2.5
Pancreas	11.2	16.9	12.4	9.0	8.7	9.9	7.9	10.6
Larynx	8.6	12.3	4.2	1.1	2.9	3.9	2.8	6.5
Lung and bronchus	82.1	119.6	32.2	14.2	61.2	48.4	39.9	108.2
Melanoma of skin	9.8	0.8	1.6	2.2	0.4	1.5	1.2	1.6
Prostate	77.3	122.8	71.5	45.5	32.5	45.7	47.4	59.6
Testis	4.2	0.8	3.0	1.8	1.9	1.3	0.5	2.6
Bladder	30.2	15.1	10.9	3.6	13.9	12.5	6.0	10.6
Kidney	10.3	9.6	8.7	9.2	4.9	6.1	4.6	6.9
Brain and other nervous system	7.3	4.3	4.9	3.1	3.0	3.1	3.4	3.1
Thyroid	2.3	1.4	2.9	2.3	4.5	6.2	6.8	7.4
Hodgkin's disease	3.5	2.7	3.3	0.7	0.8	0.8	1.7	1.4
Non-Hodgkin's lymphoma	13.0	8.5	6.9	4.7	10.2	9.2	9.8	10.9
Multiple myeloma	4.6	10.3	2.8	2.7	2.2	1.7	4.6	5.9
Leukemia	13.8	11.1	7.8	5.5	7.7	6.9	8.8	9.5
All others	27.8	30.7	21.8	18.7	21.3	16.6	18.0	28.6

Based on data from the SEER program. Data for Hispanics and American Indians are from New Mexico, whereas those for Chinese, Japanese, and Filipinos are from San Francisco and Hawaii. Rates are age-adjusted based on the 1970 U.S. standard population.

**TABLE 9-11.** Average Annual Age-Adjusted Incidence Rates per 100,000 for Selected Cancer Sites by Racial and Ethnic Group, 1975-1985, U.S. Females

Type of Cancer	Whites	Blacks	Hispanics	American Indians	Chinese	Japanese	Filipinos	Hawaiians
All sites	316.1	296.6	220.4	168.8	242.2	214.0	202.6	344.1
Lip	0.3	0.1	0.4	0.0	0.0	0.1	0.0	0.0
Nasopharynx	0.3	0.5	0.2	0.0	6.7	0.3	1.6	1.1
Other oral cavity and pharynx	5.2	6.2	1.7	0.6	1.3	2.1	5.3	5.3
Esophagus	1.6	5.0	0.8	0.3	1.2	0.8	1.9	2.2
Stomach	5.1	8.5	10.0	12.3	8.7	19.0	7.2	17.9
Colon	32.3	35.0	16.7	8.1	23.7	25.7	14.9	16.3
Rectum	12.8	10.8	7.6	3.2	10.9	10.9	8.1	8.1
Liver	1.1	1.7	1.9	2.6	4.7	2.4	3.2	2.7
Gallbladder	1.6	1.1	7.1	17.1	1.0	1.7	1.8	1.3
Other biliary	1.1	0.8	1.3	4.4	1.9	2.4	0.7	2.6
Pancreas	7.7	11.5	10.8	4.3	7.8	6.0	4.8	9.2
Larynx	1.5	2.2	0.9	0.0	0.2	0.2	0.7	1.6
Lung and bronchus	29.7	31.2	15.6	4.6	27.6	13.2	17.9	45.8
Melanoma of skin	8.2	0.7	2.2	0.7	0.7	1.0	0.9	1.0
Breast	91.5	76.4	50.9	25.6	58.7	57.1	45.6	104.6
Cervix uteri	8.8	19.7	17.1	20.0	10.5	5.8	10.8	14.5
Uterus excluding cervix	27.1	14.8	11.2	5.2	18.2	17.6	11.0	28.0
Ovary	14.1	9.8	11.3	8.9	10.3	8.5	9.7	13.2
Bladder	7.7	5.5	3.3	0.4	4.0	4.4	3.1	6.0
Kidney	4.7	4.6	4.2	6.2	2.5	2.2	2.2	2.8
Brain and other nervous system	5.1	2.9	2.4	1.8	2.7	2.2	1.3	4.2
Thyroid	5.5	3.5	7.9	6.1	6.9	6.6	17.3	13.7
Hodgkin's disease	2.6	1.2	1.3	0.5	0.8	0.3	1.3	0.9
Non-Hodgkin's lymphoma	9.6	5.7	5.5	4.8	6.5	5.9	7.1	6.6
Multiple myeloma	3.1	6.8	2.8	2.2	1.7	1.3	2.6	5.6
Leukemia	8.0	7.0	6.3	4.5	4.7	5.1	6.4	7.0
All others	20.2	23.6	18.8	24.4	18.1	11.1	15.3	22.2

Based on data from the SEER program. Data for Hispanics and American Indians are from New Mexico, whereas those for Chinese, Japanese, and Filipinos are from San Francisco and Hawaii. Rates are age-adjusted based on the 1970 U.S. standard population.

icans have remarkably high rates for cancers of the stomach, biliary tract, cervix, and kidney (females). Chinese Americans experience elevated rates for cancers of the nasopharynx and liver, whereas Japanese Americans have high rates for stomach cancer and (in males) for cancers of the colon, rectum, and thyroid. Filipino Americans have high rates for cancers of the thyroid, whereas Hawaiian Americans show elevated rates for cancers of the lung (notably in females), breast, corpus uteri, stomach, and thyroid. Like migrant populations, the racial and ethnic variations in cancer occurrence within the United States offer special opportunities for studies aimed at clarifying the environmental and host determinants of cancer.

#### SOCIOECONOMIC PATTERNS

Although racial and ethnic variations in rates may reflect genetic influences, many are influenced strongly by environmental factors, some of which may be associated with socioeconomic status. Data from the Third National Cancer

Survey<sup>31</sup> were used to estimate the associations of cancer incidence with median family income and educational achievement as indicated by census tract of residence and to evaluate the impact of adjustment for socioeconomic disparities on the observed black-to-white relative risks.<sup>62</sup> Overall, cancer incidence rates among whites were 20% greater in the lowest income group than in the highest, with a continuous gradient in risk (Table 9-12). This pattern varied by primary site. Cervix cancer was almost four times as frequent among women in the lowest relative to the highest category, for reasons that are not clear. Rates for esophageal cancer among men varied more than twofold, in line with socioeconomic differences in the use of alcohol and tobacco and nutritional status. Striking inverse gradients were also apparent for lung and stomach cancers among males, reflecting smoking and perhaps nutritional patterns. In contrast, positive gradients with income level were apparent for both breast and corpus uteri cancers, which may parallel the distribution of reproductive and menstrual risk factors.

An important question is the extent to which socioeconomic

**TABLE 9-12.** Relative Risks for All Cancers and Selected Sites by Socioeconomic Status (SES) and Race, 1969-1971\*

Site of Cancer	Income Level Among Whites					Black/White Relative Risks	
	Low	2	3	4	High	SES Unadjusted	SES Adjusted†
All sites (males)	1.20	1.09	1.07	1.02	1.00	1.10	1.0
Esophagus (males)	2.13	1.69	1.34	1.20	1.00	3.05	2.3
Stomach (males)	1.39	1.26	1.16	1.02	1.00	1.48	1.2
Lung (males)	1.65	1.44	1.33	1.18	1.00	1.10	0.9
Breast (females)	0.70	0.73	0.80	0.83	1.00	0.85	0.8
Cervix uteri	3.82	2.69	1.95	1.39	1.00	1.74	1.2
Corpus uteri	0.75	0.83	0.88	0.89	1.00	0.70	0.6

\* Data derived from the Third National Cancer Survey, 1969-1971. All relative risks adjusted for age and geographic area.

† Also adjusted for income and education.

factors account for the black-to-white differentials in cancer incidence. When adjusted for racial variations in socioeconomic status, the excess risk among blacks is diminished for cancers of the esophagus, stomach, lung, and cervix. These patterns generally were still apparent in recent years.<sup>63,64</sup> Socioeconomic status may also influence cancer survival and mortality patterns by affecting access to diagnosis and treatment.

## ANALYTIC STUDIES

The major contribution of epidemiology has been to test etiologic hypotheses through analytic studies, usually involving cohort or case-control designs. These studies obtain data on suspected risk factors and disease occurrence at the individual instead of at the aggregate (population) level. By using specific methods to select and compare groups of subjects while controlling for other relevant variables, the risk of disease associated with exposure can be estimated.<sup>4,13,14</sup> In designing these studies, the groups should be sufficiently large and the time intervals between initial exposure and tumor onset sufficiently long to identify the lowest excess risk considered important to detect. Reliable and valid estimates of exposure should be sought, with quantitative measurements to permit dose-response evaluations. Studies must be designed to minimize potential sources of bias (*i.e.*, systematic error) and to permit the detection and control of confounding (*i.e.*, the distortion of exposure-disease associations by extraneous variables).

### COHORT STUDIES

Cohort studies, also referred to as *follow-up studies* or *prospective studies*, identify groups of individuals with and without a particular exposure, follow them over time to determine subsequent health outcomes, and compare their mortality or incidence rates of disease.<sup>4,65</sup> An association is suggested when the rates of disease are different in the exposed than in the unexposed group. These investigations may be based on current exposures and future health outcomes, referred to as *prospective cohort studies*. More often, they use information on exposures collected in the past and are termed *retrospective*

*cohort studies*. Instead of an unexposed comparison group, general population mortality or incidence rates (specific for age, sex, race, geographic area, and calendar time) are often used to estimate an expected number of events. This method assumes that in the absence of the specific exposure of interest the study group would have the same probability of developing the disease as the general population. The cohort approach is used mainly when it is possible to evaluate high exposures in clearly defined subgroups of the population. It has been especially helpful, for example, in assessing the carcinogenic risk from occupational hazards, smoking, or medical exposures such as radiation and certain drugs.

### CASE-CONTROL STUDIES

Case-control studies, also called *case-referent studies* or *retrospective studies*, identify persons with a particular disease (cases) and a group of similar persons without the disease (controls), and then collect information on past exposures by interview or other methods.<sup>4,65</sup> If the proportion of cases with a certain exposure is greater than that of the controls, an association may be indicated. The case-control approach is especially suited for studying uncommon diseases. Although used primarily to test hypotheses, the approach occasionally has taken the form of an exploratory study when a disease is so poorly understood that hypotheses need to be formulated for subsequent investigation. In general, both cases and controls should be selected from the same source, which may be either population-based or hospital-based. Because factors associated with hospitalization may be over-represented among hospital controls, careful consideration should be given to the diagnostic composition of this group. Bias is minimized by selecting hospital controls with a variety of disorders and excluding conditions related to the exposure in question.<sup>66</sup>

### COMPARISON OF METHODS

The case-control and cohort methods have different strengths and weaknesses. Case-control studies provide a more efficient means of studying rare diseases, with fewer individuals needed, a shorter study period, and generally lower costs compared with the cohort approach. In addition, there are

greater opportunities to evaluate more than one risk factor and interactions between them.<sup>67</sup> On the other hand, the case-control approach cannot directly estimate the actual rate associated with a particular exposure and is subject to recall and other biases that affect the comparability of cases and controls and the precision of past exposure measures.<sup>4</sup> Such studies also are usually limited to evaluating one disease at a time.

The advantages of cohort studies are their capacity to measure directly incidence or mortality rates associated with a particular exposure; to reduce subjective biases by obtaining information before the disease develops; to detect associations between a particular exposure and multiple outcomes; and to evaluate temporal relations such as latency period and the duration of an effect. Cohort studies are usually expensive and complex undertakings. They require large numbers of exposed individuals, particularly when uncommon diseases are being investigated, and care in dealing with such problems as persons lost to follow-up or biased estimates of risk, as produced by the healthy worker effect of occupational studies.<sup>4</sup> Moreover, they may not permit as readily an ascertainment of potential confounding factors. To remedy this particular deficiency, case-control studies within defined cohorts, or nested case-control studies, are often initiated.

MEASURES OF ASSOCIATION

For cohort studies, the chief measures of association are based on rates of disease (Table 9-13). The relative risk (RR) is the disease rate in the exposed population,  $I_e$ , divided by the

disease rate in the referent population (usually nonexposed,  $I_0$ ).<sup>4</sup> The relative risk from a cohort study is defined as

$$RR = \frac{I_e}{I_0} = \frac{a/n_e}{c/n_0}$$

This measure gives the relative disease risk between two populations. An RR of 2.0 would indicate that the exposed group has twice the risk of the unexposed group (i.e., a 100% increase in risk). An important aspect of the calculation is the concept of person-time. Usually individuals are followed for different periods owing to variable times of entry to and exit from observation because of either death or loss to follow-up. To accommodate the variable follow-up periods and still preserve the concept of a rate, each person is counted in the denominator only for the interval of time under observation, resulting in measures of person-years or person-months.<sup>4</sup>

An association may also be measured by the risk difference, often referred to as the *attributable risk* ( $A_e$ ). This estimate results from the subtraction of the rate among the unexposed from that among the exposed. The attributable risk is defined as

$$A_e = I_e - I_0 = \frac{a}{n_e} - \frac{c}{n_0}$$

The attributable risk means that if the relation observed is causal, the difference between the rates of exposed and unexposed groups is the amount of disease attributable to that exposure.<sup>4</sup> When expressed as a percentage of the total disease rate in an exposed group, the attributable risk percent ( $A_e\%$ ) is the proportion of the exposed group's total risk that is due to the exposure.<sup>68</sup>

The measures of relative risk and attributable risk have somewhat different uses. The magnitude of the RR indicates the strength of a relation between exposure and disease and the likelihood of causality. The  $A_e$  is influenced not only by the magnitude of the difference between the exposed and unexposed but also by the rate of disease in the absence of exposure.

The amount of disease attributable to a particular exposure can be estimated not only among the exposed but also in the population as a whole.<sup>68</sup> This measure reflects the amount of disease that would be eliminated in a definable population if the exposure were removed and is referred to as the *population attributable risk* ( $A_p$ ). It is calculated by subtracting the rate among the unexposed from the rate that exists in the total population. The population attributable risk is defined as

$$A_p = I_t - I_0 = \frac{a + c}{N} - \frac{c}{n_0}$$

The magnitude of this estimate is influenced by the size of the relative difference in risk between the exposed and unexposed, by the level of the disease among the unexposed, and by the prevalence of the exposure in the population. When this risk is expressed as a proportion of the total disease rate in the population, it is called the *population attributable risk percent* ( $A_p\%$ ) or the etiologic fraction.<sup>69</sup>

These measures are illustrated by a recent cohort study involving 1-year survivors of ovarian cancer from five randomized trials.<sup>70</sup> The incidence rates for acute nonlymphocytic leukemia and preleukemia were evaluated among women treated with no chemotherapy, with cyclophosphamide, and

TABLE 9-13. Measures of Association From a Cohort Study

	Affected Persons (Cases)	Total Persons (or Person-Time)
Exposed	a	$n_e$
Not exposed	c	$n_0$
Total	a + c	N

$$\text{Relative risk (RR)} = \frac{a/n_e}{c/n_0}$$

$$\text{Attributable risk in the exposed (A}_e\text{)} = \frac{a}{n_e} - \frac{c}{n_0}$$

$$\begin{aligned} \text{Attributable risk percent in the exposed (A}_e\text{\%)} &= \frac{(a/n_e) - (c/n_0)}{a/n_e} \\ &= \frac{RR - 1}{RR} \times 100\% \end{aligned}$$

$$\text{Population attributable risk (A}_p\text{)} = \frac{a + c}{N} - \frac{c}{n_0}$$

$$\begin{aligned} \text{Population attributable risk percent (A}_p\text{\%)} &= \frac{(a + c)N - (c/n_0)}{(a + c)N} \\ &= \frac{RR - 1}{RR + 1/P - 1} \times 100\% \end{aligned}$$

where P is the proportion of the population that is exposed, or  $n_e/N$

with melphalan. The corresponding rates were 0.18, 3.21, and 11.46 cases per 1000 women per year. Compared with those receiving no chemotherapy, the RR of leukemic conditions was 18 (3.21/0.18) for women given cyclophosphamide and 64 (11.46/0.18) for those given melphalan. The magnitude of these risks suggests that the drugs are causally related to leukemia. However, the risk differences obtained by subtracting rates among the exposed from the unexposed groups were not great. The  $A_e$  associated with cyclophosphamide is about 3 per 1000 per year, and with melphalan, about 11 per 1000 per year. Given the life-threatening problems posed by ovarian cancer, these risks should not deter physicians from using a therapy whose proven benefit outweighs these risks. Also, when the  $A_e$  is not large, it is possible to see how difficult it is for a clinician or even a large group practice to suspect a leukemia risk related to treatment.

If exposure to all alkylating agents were removed, it would have little impact on the total leukemia rate in the general population because relatively few persons are exposed to these drugs. However, in the clinical populations under study, the overall rate of leukemic conditions was 2.29 per 1000 patients per year. As shown in Table 9-14, subtracting the rate among those not treated with chemotherapy (0.18 per 1000 per year) from the rate for all patients combined yields a population attributable risk of 2.11 cases per 1000 women per year, or an etiologic fraction of 92% in the clinical populations.

For case-control studies, the enumeration of exposed and unexposed populations is not available, as it is in cohort studies, to directly measure rates (or risks). Fortunately, data from

**TABLE 9-14.** Risks of Leukemia and Preleukemia Associated With Chemotherapy

	Cases	Person-Years at Risk	Rate per 1000
Any Chemotherapy	33	4295	7.68
No Chemotherapy	2	10,983	0.18
Total	35	15,278	2.29

$$\text{Relative risk (RR)} = \frac{33/4275}{2/10,983} = \frac{7.68}{0.18} = 42.4$$

$$\text{Attributable risk in the exposed (A}_e\text{)} = 33/4275 - 2/10,983 = 7.50 \text{ per 1000}$$

$$\text{Attributable risk percent in the exposed (A}_e\text{\%)} = \frac{42.4 - 1}{42.4} \times 100\% = 98\%$$

$$\text{Population attributable risk (A}_p\text{)} = \frac{35}{15,278} - \frac{2}{10,983} = 2.11 \text{ per 1000}$$

$$\begin{aligned} \text{Population attributable risk percent (A}_p\text{\%)} \\ = \frac{35/15,278 - 2/10,983}{35/15,278} \times 100\% \\ = 92\% \end{aligned}$$

(Adapted from Greene MH, Harris EL, Gershenson DM, et al. Melphalan may be a more potent leukemogen than cyclophosphamide. *Ann Intern Med* 1986;105:360)

**TABLE 9-15.** Measures of Association From a Case-Control Study

	Cases	Controls
Exposed	a	b
Not exposed	c	d
Total	a + c	b + d

$$\text{Relative odds (R)} = \frac{ad}{bc}$$

$$\text{Attributable risk percent in the exposed (A}_e\text{\%)} = \frac{R - 1}{R} \times 100\%$$

Population attributable risk percent ( $A_p\%$ ) or etiologic fraction

$$\begin{aligned} &= \frac{P_0(R - 1)}{1 + P_0(R - 1)} \times 100\% \\ &= \frac{(R - 1)P_e}{R} \times 100\% \end{aligned}$$

where  $P_0$  is the exposure rate in the controls, or  $\frac{b}{b + d}$  and

$P_e$  is the exposure rate in the cases, or  $\frac{a}{a + c}$

cross-classification tables in a case-control study can be used to calculate reasonable estimates of relative and attributable risks. If the sampling fractions for the cases and the controls are known (i.e., the proportion of all the cases in a defined population that is present in the case series and the proportion of the same population present in the control series), they can be used to estimate the rates among the exposed and unexposed groups and to calculate relative and attributable risks. For most case-control studies, however, sampling fractions are unknown. In this circumstance, the calculation of relative odds, also termed an *odds ratio*, usually gives a good approximation of the relative risk (Table 9-15).<sup>4</sup> The absolute measures of attributable risk cannot be estimated directly, but algebraic properties of cross-classification tables allow estimations of the attributable risk percent and the etiologic fraction (see Table 9-15).<sup>68</sup>

Calculation of these measures is illustrated in Table 9-16, based on a national case-control study of bladder cancer that evaluated the risks associated with smoking.<sup>71</sup> The study estimated a relative risk of 2.2 for cigarette smoking, with 55% of bladder cancer among smokers attributable to their smoking and 43% of bladder cancer in the U.S. population due to smoking. These figures are consistent with the direct estimates of risk from cohort studies.

### INTERVENTION STUDIES

Also referred to as *experimental studies*,<sup>65</sup> controlled intervention trials represent a third strategy of analytic epidemiology. Intervention studies are especially useful for confirming causal relations suggested by cohort or case-control studies and for directly evaluating the effect of possible preventive measures. This method permits control over extraneous variables and biases that may influence results by the random allocation of subjects to study and control groups.

**TABLE 9-16.** Risks of Bladder Cancer Associated With Cigarette Smoking

	Cases	Controls
Smokers	2324	3581
Nonsmokers	657	2198
Total	2981	5779

$$\text{Relative odds (R)} = \frac{(2324)(2198)}{(657)(3581)} = 2.2$$

$$\begin{aligned} \text{Attributable risk percent in the exposed (A}_e\%) &= \frac{2.2 - 1}{2.2} \times 100\% \\ &= 55\% \end{aligned}$$

Population attributable risk percent (A<sub>p</sub>%) or etiologic fraction

$$\begin{aligned} &= \frac{\frac{3581}{5779} (2.2 - 1)}{1 + \frac{3581}{5779} (2.2 - 1)} \times 100\% \\ &= 43\% \end{aligned}$$

$$\text{Alternatively, } \frac{(2.2 - 1)}{2.2} \times \frac{2324}{2981} \times 100\% = 43\%$$

(Adapted from Hartge P, Silverman D, Hoover R, et al. Changing cigarette habits and bladder cancer risk: A case-control study. *JNCI* 1987;78:1119)

There are no clear guidelines as to when evidence is sufficient to conduct intervention trials, yet when there is a reasonable likelihood of benefit resulting from intervention (and any potential for harm), ethical questions may arise. In the field of cancer cause and prevention, opportunities for intervention have been limited for various reasons, including the long latency periods that may be involved before an effect is seen. However, intervention studies are gaining emphasis in the evaluation of diet and nutrition, especially the use of various micronutrient supplements that may inhibit late stages of the carcinogenic process. Also underway are hepatitis B vaccine trials in endemic areas for liver cancer. After intervention, the follow-up and analytic procedures to evaluate outcomes resemble those employed for cohort studies.

## STRENGTHS AND LIMITS OF EPIDEMIOLOGY

### STRENGTHS

In contrast to laboratory studies, epidemiology directly evaluates the experience of human populations and their response to various environmental exposures and host factors (the risk of disease). The consequences of an exposure can be measured as it actually occurs in the population. Questionable extrapolations from other species are also avoided. Although positive findings from animal studies may indicate a potential human risk, epidemiology offers the only means of quantifying the risk. Furthermore, even when the specific causal agent cannot be clearly identified (*e.g.*, the precise carcinogens in cigarette smoke), sufficient information can be obtained for the disease to be prevented.

### LIMITATIONS

Cancer epidemiology has certain limitations. First, epidemiologic studies are mainly observational, relying on natural occurrences in human populations, and the opportunities for experiment are rare and limited to efforts at prevention. Second, epidemiology can seldom indicate a cause with great specificity, particularly when the exposures are multiple or when surrogate measures of exposure are used (*e.g.*, occupation or area of residence), although laboratory techniques may be helpful in such circumstances. Third, study groups chosen on the basis of one characteristic may be distinctive in another, and it may be difficult to disentangle them even with refined analytic methods. Fourth, it is hard to incriminate an agent when there is relative uniformity of exposure in a given population, which may be the case with some dietary factors (*e.g.*, high fat intake). Finally, evidence of an environmental hazard is usually obtained from high or intermediate levels of exposure. As in animal studies, it is difficult to detect causal relations when the exposure level is low or the excess risk is small compared with the baseline incidence rate. In such situations, the numbers of subjects needed to provide definite results may be virtually impossible to assemble for the purposes of a single study.

### BIOCHEMICAL AND MOLECULAR EPIDEMIOLOGY

The power of certain studies may be increased by incorporating laboratory methods into analytic investigations, an approach termed *biochemical or molecular epidemiology*.<sup>72,73</sup> The analysis of biologic samples in the laboratory can permit the study of exposure to oncogenic viruses. It may also be possible to detect past exposures to chemical and physical agents and to clarify early preneoplastic events, various host factors, and mechanisms of action. The approach provides new opportunities to evaluate carcinogenic risks associated with dietary factors and with markers of genetic predisposition. In view of rapid experimental advances, biochemical and molecular epidemiology is a challenging multidisciplinary approach that should help to elucidate further the causes of cancer. Such studies are complex undertakings that require careful planning and teamwork, including the collaboration of clinicians.

### SOURCES OF CLUES

Because an analytic study is designed to evaluate an association between a disease and an antecedent factor, there must be some previous indication or suspicion of such an association. The lead may come from descriptive or correlational studies or from another analytic study. The most fruitful source of etiologic clues has been the alert clinician who has uncovered some of the most striking examples of environmental cancer, starting with Pott's discovery of scrotal cancer among chimney sweeps. Usually the clinician recognizes an excessive number of patients with the same tumor and traces the cluster to a particular cultural, occupational, or iatrogenic exposure.<sup>2</sup> Clinical observations have linked asbestos with mesothelioma, vinyl chloride with hepatic angiosarcoma, furniture-making with nasal adenocarcinoma, radium-dial painting with osteosarcoma, and prenatal exposure to diethylstilbestrol with clear-cell adenocarcinoma of the vagina among offspring. Clinicians

were able to detect these associations because the tumors are rare in the general population and involve exceptionally high risks. In most instances, the associations required epidemiologic study less to confirm them than to quantify them. Clinicians have also identified a wide variety of heritable conditions associated with susceptibility to cancer.<sup>74</sup> Opportunities for the practicing physician to make significant etiologic discoveries were highlighted recently at a symposium entitled "Unusual Occurrences as Clues to Cancer Etiology."<sup>75</sup> On the other hand, epidemiologists can identify causes of cancer that may seem less dramatic in relative risks but are important to public health, such as smoking and asbestos in lung cancer.

Another source of leads has been provided by experimental studies, especially those relating chemicals to tumors in laboratory animals. In the case of mustard gas and 4-aminobiphenyl, for example, carcinogenic risks were found in humans after the substances were shown to induce tumors in animal studies.<sup>2</sup> Whatever the sequence of observations, there is no question that clinical, epidemiologic, and experimental data greatly complement one another in determining the risks and mechanisms involved in carcinogenesis. When all approaches are brought to bear on a particular hypothesis, advances in understanding the carcinogenic process may be extraordinary.

## INTERPRETATION OF EPIDEMIOLOGIC STUDIES

### SAMPLE SIZE AND POWER

A fundamental aspect of planning or evaluating a study is the number of subjects needed to test an etiologic hypothesis.<sup>13</sup> The power of a study is the likelihood of detecting a postulated level of risk. The larger the sample size, the greater the power to detect a specified risk, and the smaller the sample size, the weaker the power.

Issues of sample size and power are of great concern when evaluating negative results of epidemiologic studies.<sup>76</sup> Only large studies may confidently exclude low to moderate levels of risk, whereas negative results of a small study should be viewed with caution because they usually lack adequate power.

### NONCAUSAL ASSOCIATIONS

When interpreting the results of analytic studies, one must ask whether the associations observed between exposure and disease are the result of bias, confounding, chance, or cause-and-effect. Bias or systematic error is usually the result of imperfections in study design or conduct, and often cannot be corrected in the analysis. Many types of bias have been described,<sup>73</sup> but most can be grouped as biases of selection or information.<sup>66</sup> Selection bias involves systematic differences in exposure between those selected and not selected into the study. For example, a case-control study might include only cases referred to a particular institution or only survivors, so that differences observed might reflect factors influencing referral patterns or survival. A similar bias in a cohort study may result from differences in the loss to follow-up between exposed and unexposed groups. Information bias involves differences in measuring the factor in question between groups and is best illustrated by recall bias or interviewer bias, both

of which may affect the outcome of case-control studies. For example, in studies of childhood cancer, parents of cases might provide more reliable or thorough responses than parents of controls because of the soul-searching they have undergone. Also, interviewers might tend to probe more deeply into past events if a subject is known to be a case rather than a control.

*Confounding* refers to the effect of an extraneous variable that may account, entirely or partly, for an apparent association between exposure and disease, or may obscure a real association.<sup>13,66</sup> Confounding can usually be evaluated and accommodated during analysis by adjustment procedures, including the stratification of subjects on the suspected variable. To be a confounder, a variable must be related to the exposure and related causally to the disease. For example, cigarette smoking could contribute to an excess of lung cancer among industrial groups that smoke more heavily than the average. Conversely, a relation between oral contraceptives and invasive cervical cancer became apparent only after adjustment was made for the interval since last Pap smear, because in this study the frequency of screening was found to be related both to pill use and the development of cervical cancer.<sup>78</sup> Whereas analytic methods can control for known confounders, they cannot do this for unknown confounders, which are free to distort observed risk estimates. The advantage of experimental studies is that the randomization process tends to ensure that the prevalence of all potential confounders is similar among the randomized groups.

The role of chance is evaluated in epidemiologic studies by the use of significance testing and confidence limits. If a risk estimate is statistically significant at a specified level (*e.g.*, 0.05, or 1 in 20) or if the 95% confidence limits exclude 1.0, chance can be assumed to be an unlikely explanation. It does not exclude the operation of a chance event, but only indicates that chance would explain a risk estimate of the observed magnitude or greater only 1 out of 20 times. In studies involving multiple comparisons, some significant associations can be anticipated by the play of chance, and each finding should be considered on its own merits.

### DETERMINING CAUSALITY

In interpreting associations found in epidemiologic studies, the investigator is influenced by the magnitude of the risk estimates, their statistical significance (likelihood of being due to chance), and especially the rigor of the study design to avoid methodologic pitfalls. If bias, confounding, and chance are excluded as likely explanations for an association, the issue of causality must be considered through a process of scientific judgment that extends beyond any statement of statistical probability.<sup>13,14,66</sup> During the controversy over cigarette smoking and lung cancer, a set of criteria was formulated to assist the epidemiologist in making causal inferences.<sup>79,80</sup> These criteria provide useful guidelines for determining causality and refer especially to the strength and specificity of an association, the presence of a dose-response gradient, the consistency and reproducibility of results, biologic plausibility and coherence, and an appropriate temporal sequence. It may not be possible to satisfy all the criteria in any particular instance, although evidence that the exposure preceded the disease is obviously crucial.<sup>66</sup> With smaller relative risks, especially when interactions between multiple exposures and

susceptibility states seem important, the term *risk factor* is often used instead of *causal agent*. The finding of small relative risks should not be readily dismissed as due to chance or bias but explored further by examining possible interactions with other risk factors or susceptible subgroups of the population.

Causal inferences from epidemiology usually develop gradually after taking into account all relevant biologic information, including laboratory studies. Although epidemiologic observations can accumulate to the point at which causation is virtually inescapable, strictly speaking it is not possible to prove causality by these means alone. Nevertheless, causation can often be shown to be sufficiently probable to provide a compelling basis for preventive and public health action and certainly so in the case of cigarette smoking and lung cancer.

## CAUSES OF CANCER

This section provides a brief overview of cancer risk factors, based mainly on evidence from analytic epidemiology, including recent observations relevant to the practicing oncologist. The contributions of epidemiology to cancer cause and prevention are presented elsewhere in greater detail.<sup>6,7,81,82</sup> Best known is the success of the epidemiologic approach in discovering or confirming lifestyle and other environmental exposures as causes of cancer (Table 9–17).

### TOBACCO

Among the carcinogenic hazards identified so far, tobacco smoking is the most important in Western countries and increasingly so in developing countries. Smoking has been firmly linked to cancers not only of the lung but also of the larynx, mouth, pharynx, esophagus, bladder, and pancreas.<sup>83</sup> Recent evidence indicates that smokers are also prone to cancers of the kidney parenchyma<sup>84</sup> and pelvis,<sup>85</sup> cervix,<sup>86</sup> nasal passages,<sup>87</sup> stomach<sup>88</sup> and leukemia.<sup>89</sup> The wide variety of neoplasms related to smoking is hardly surprising in view of the large number of chemicals detected in cigarette smoke and delivered to a highly vascular and absorptive organ. In the United States it appears that smoking, especially of cigarettes, accounts for about 40% of all cancer deaths in men and about 20% in women, with lung cancers representing the largest proportion. For smokers of two or more packs per day, the risk of lung cancer is about 20 times that of nonsmokers, and is much greater for squamous and small cell carcinomas than for adenocarcinomas.

Epidemiologic studies have demonstrated the benefits of stopping smoking, with lower risks relative to those of continuing smokers appearing within a few years of quitting.<sup>6,83</sup> This is consistent with evidence that smoking exerts an effect at late and early stages of carcinogenesis. The introduction of lower tar levels in cigarettes and of filter tips has also reduced the risk of lung cancer, although not nearly to the extent seen with cessation of smoking.<sup>90</sup> The risks of cigar and pipe smokers resemble those of cigarette smokers for cancers of the oral cavity, larynx, and esophagus, but are lower for lung cancer.

Smokeless tobacco is also of concern, because oral cancer has been linked with snuff dipping, a common practice in

rural southern parts of the United States.<sup>46</sup> Under suspicion are the high levels of tobacco-specific nitrosamines that have been detected in snuff and in the saliva of snuff users. In parts of Asia, oral cancer is common in people who use tobacco quids often mixed with betel, lime, and other agents.<sup>91</sup> Overall, these findings have prompted recent public health and legislative measures in the United States aimed at discouraging the use of smokeless tobacco, especially among young people.

Passive smoking has been hotly debated as a risk factor for lung cancer. Evidence suggests that nonsmoking women married to smokers have experienced an excess risk on the order of 30%.<sup>92,93</sup> Passive or involuntary smoking is a real concern, because tobacco smoke constituents and metabolites can be detected in the body fluids of exposed nonsmokers. Moreover, a cause-and-effect relation with lung cancer is suggested by the replication of findings in different populations, by a dose-response effect with excess risks of about 70% among heavily exposed nonsmokers, by cell-type patterns resembling those associated with active smoking, and by the similarity in risk estimates between heavy passive smokers and light active smokers.

### ALCOHOL

Consumption of alcoholic beverages has been shown to potentiate the effects of tobacco smoking on cancers of the mouth, pharynx, esophagus, and larynx and has been estimated to account for about 3% of all cancer deaths.<sup>94,95</sup> It has been difficult to study the effects of alcohol alone and the nature of its interaction with smoking because of small numbers in certain categories of exposure (especially drinkers who abstain from smoking). In a large-scale case-control study of oral cancer, the risks shown in Table 9–18 increased with intake of alcohol among nonsmokers, but in combination with smoking the risks multiplied to 35-fold among heavy consumers of both products.<sup>96</sup> Combined exposures were found to account for about 75% of all oral and pharyngeal cancers. The risks were higher with hard liquor or beer than with wine. For esophageal cancer, the highest recorded risks from alcohol are those associated with the consumption of home-brewed apple brandies in the northwest part of France. For larynx cancer, the alcohol effect is more prominent for tumors in the supraglottic segments than for tumors in the intrinsic segments. Because ethanol is not carcinogenic in laboratory animals, the mechanism by which alcohol acts is not clear. It may involve nutritional deficiencies that accompany prolonged heavy drinking, contaminants such as nitrosamines and hydrocarbons, or increased permeability of mucous membranes to other carcinogens. Further evidence for a topical effect comes from a recent analysis suggesting an excess risk of oral cancer associated with the use of mouthwash high in alcohol content.<sup>97</sup>

Alcohol is an important cause of hepatic cirrhosis, which is sometimes complicated by hepatocellular carcinoma, although alcohol may also have an independent effect on the risk of this cancer. The role of alcohol in other cancers remains uncertain. Rectal cancer in men has shown positive geographic correlations with beer consumption, but the findings from analytic studies have been inconsistent. For example, cohort studies of brewery workers (who receive a free

**TABLE 9-17.** Environmental Causes of Human Cancer

<i>Agent</i>	<i>Type of Exposure</i>	<i>Site of Cancer</i>
Aflatoxin	Contaminated foodstuffs	Liver
Alcoholic beverages	Drinking	Mouth, pharynx, esophagus, larynx, liver
Alkylating agents (melphalan, cyclophosphamide, chlorambucil, semustine)	Medication	Leukemia
Androgen-anabolic steroids	Medication	Liver
Aromatic amines (benzidine, 2-naphthylamine, 4-aminobiphenyl)	Manufacturing of dyes and other chemicals	Bladder
Arsenic (inorganic)	Mining and smelting of certain ores, pesticide manufacturing and use, medication, drinking water	Lung, skin, liver (angiosarcoma)
Asbestos	Manufacturing and use	Lung, pleura, peritoneum
Benzene	Leather, petroleum, and other industries	Leukemia
Bis(chloromethyl)ether	Manufacturing	Lung (small cell)
Chlornaphazine	Medication	Bladder
Chromium compounds	Manufacturing	Lung
Estrogens	Medication	
Synthetic (diethylstilbestrol)		Vagina, cervix (adenocarcinoma)
Conjugated (Premarin)		Endometrium
Steroid contraceptives		Liver, cervix
Immunosuppressants (azathioprine, cyclosporine)	Medication	Non-Hodgkin's lymphoma, skin (squamous carcinoma and melanoma), soft-tissue tumors (including Kaposi's sarcoma)
Ionizing radiation	Atomic bomb explosions, treatment and diagnosis, radium dial painting, uranium and metal mining	Most sites
Isopropyl alcohol production	Manufacturing by strong acid process	Nasal sinuses
Leather industry	Manufacturing and repair (boot and shoe)	Nasal sinuses, bladder
Mustard gas	Manufacturing	Lung, larynx, nasal sinuses
Nickel dust	Refining	Lung, nasal sinuses
Parasites	Infection	
<i>Schistosoma haematobium</i>		Bladder (squamous carcinoma)
<i>Clonorchis sinensis</i>		Liver (cholangiocarcinoma)
Pesticides	Application	Non-Hodgkin's lymphoma, lung
Phenacetin-containing analgesics	Medication	Renal pelvis
Polycyclic hydrocarbons	Coal carbonization products and some mineral oils	Lung, skin (squamous carcinoma)
Tobacco chews, including betel nut	Snuff dipping and chewing of tobacco, betel, lime	Mouth
Tobacco smoke	Smoking, especially cigarettes	Lung, larynx, mouth, pharynx, esophagus, bladder, pancreas, kidney
Ultraviolet radiation	Sunlight	Skin (including melanoma), lip
Viruses	Infection	
Epstein-Barr virus		Burkitt's lymphoma, nasopharyngeal carcinoma
Hepatitis B and C virus		Hepatocellular carcinoma
Human immunodeficiency virus		Kaposi's sarcoma, non-Hodgkin's lymphoma
Human papillomavirus		Cervix, other anogenital tumors
Human T-lymphotropic virus type I		T-cell leukemia/lymphoma
Vinyl chloride	Manufacturing of polyvinyl chloride	Liver (angiosarcoma)
Wood dusts	Furniture manufacturing (hardwood)	Nasal sinuses (adenocarcinoma)

**TABLE 9-18.** Relative Risks For Oral and Pharyngeal Cancer Associated With Smoking and Drinking

Smoking Status*	Number of Alcoholic Drinks Per Week				
	<1	1-4	5-14	15-29	30+
Nonsmoker	1.0	1.3	1.6	1.4	5.8
Former smoker	0.7	2.2	1.4	3.2	6.4
Light smoker	1.7	1.5	2.7	5.4	7.9
Moderate smoker	1.9	2.4	4.4	7.2	23.8
Heavy smoker	7.4	0.7	4.4	20.2	37.7

\* Light, moderate, and heavy smokers. 1-19, 20-39, and 40+ cigarettes per day for 20+ years, respectively.

(Adapted from Blot WJ, McLaughlin JK, Winn DM, et al. Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Res* 1988;48:3282)

beer allocation) have revealed an excess risk of rectal cancer in Dublin but not in Copenhagen.<sup>98</sup> Recent interest has centered on the possible relation of alcohol with breast cancer, with a series of prospective studies showing an excess risk and dose-response gradient.<sup>99,100</sup> Further investigation is needed to determine if this relation is causal, or if indirect, how it is mediated, especially because the elevated risk in some studies is associated with consumption levels as low as 1 to 2 drinks per day.

#### OCCUPATIONAL HAZARDS

The study of occupational groups has identified more carcinogens than any other branch of cancer epidemiology and has led to cancer prevention by reducing or eliminating hazardous exposures in the workplace.<sup>101,102</sup> Occupational exposures appear to account for about 5% of all cancer deaths, although the proportion is higher in certain areas for particular cancers, such as those of the bladder and lung. Most carcinogenic exposures in the workplace were first detected by clinicians, whereas others were noticed initially by epidemiologists as in the case of asbestos (lung cancer), inorganic arsenic (lung cancer), and the leather industry (nasal cancer) or by experimentalists, as in the case of 4-aminobiphenyl.<sup>2</sup> All compounds shown to be carcinogenic in humans have been positive in long-term animal testing, except for arsenic and alcohol. This argues for the importance of bioassay programs, but the exceptions remind us that it is not prudent to rely solely on laboratory work.

Asbestos represents the major occupational carcinogen in many countries due to its induction of lung cancers rather than mesotheliomas. This is true even though the relative risk for lung cancer is little more than twofold and that for mesothelioma is well over 100-fold, because lung cancer is much more common than mesothelioma in people unexposed to asbestos. A multiplicative relation exists between asbestos exposure and smoking in the development of lung cancer.<sup>103</sup> American shipyard workers (whose exposure to asbestos was heavy during World War II) have experienced a high incidence, but the far greater excess among smokers than nonsmokers indicates a synergism between the risk factors (Fig. 9-7).<sup>44</sup> The risks also vary according to the type of asbestos

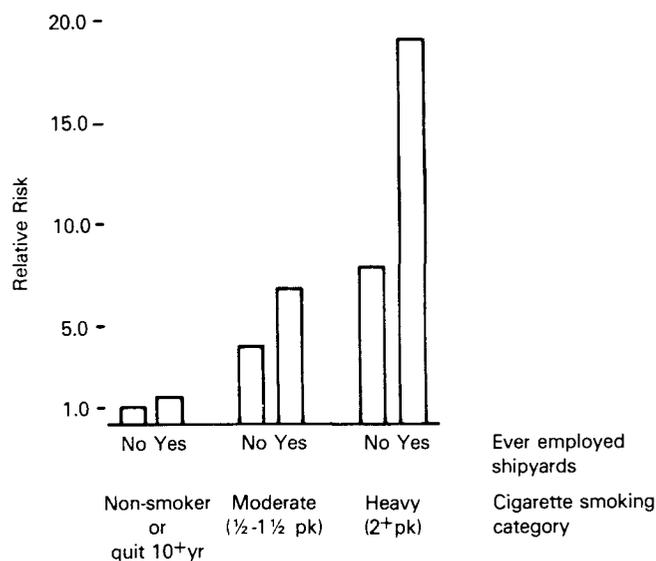
fiber and are highest for crocidolite, which is banned in many countries. Much research is in progress on man-made mineral fibers, but there is no clear evidence of a carcinogenic risk to humans.<sup>102</sup>

Many of the occupational cancers listed in Table 9-17 are characterized by high relative risks and rarity in the general population. A challenge facing epidemiologists is to detect hazards with smaller relative risks that may have a greater impact on the public health when the exposure is widespread and the tumor in question is common. This problem is particularly acute for lung cancer because variations in the prevalence and duration of smoking may inhibit the detection of occupational risks. Recent studies have implicated various occupational exposures including phenoxyacetic acid herbicides with non-Hodgkin's lymphoma,<sup>47</sup> motor exhausts with lung and bladder cancers,<sup>104,105</sup> and formaldehyde with nasal and nasopharyngeal cancers.<sup>106</sup> Such findings illustrate that the discovery of occupational hazards may have implications beyond the workplace, because they point to potential risks experienced at a lower level by the general public.

#### ENVIRONMENTAL POLLUTION

Pollutants in the urban air have long been suspected in the cause of lung cancer. Fossil fuel combustion products, especially polycyclic hydrocarbons, are of special concern. The subject has been difficult to study, primarily due to the overpowering effects of smoking, which first became popular in urban areas. Nevertheless, there is suggestive evidence that atmospheric pollution plays a limited role in the causation of lung cancer.<sup>6</sup>

Asbestos bodies and calcified pleural plaques are common in urban populations, but the risks of cancer after nonoccupational exposures are uncertain. There are many case reports suggesting that mesotheliomas may result from neighborhood



**FIGURE 9-7.** Relative risk of lung cancer according to usual cigarette-smoking category and employment in shipyards during World War II. (Blot WJ, Harrington JM, Toledo A, et al. Lung cancer after employment in shipyards during World War II. *N Engl J Med* 1978;299:620)

exposures to asbestos industries and from household contact with asbestos dust, perhaps through the laundering of work clothing.<sup>107</sup> A striking example of an environmental carcinogen is the naturally occurring zeolite fiber in parts of Turkey that causes a high mortality from pleural mesothelioma.<sup>108</sup> Another hazard may result from airborne arsenic, because increased mortality rates for lung cancer have been reported in both sexes in the neighborhood of arsenic-emitting smelters and cannot be explained by smoking and occupational exposures.<sup>109</sup>

There is much interest in the role of indoor air pollution by radon gas and tobacco smoke in the cause of lung cancer. In China, the high rates of lung cancer among nonsmoking women have been related to cooking oil vapors generated by wok cooking<sup>110</sup> and to effluents from coal-heating stoves.<sup>111</sup> Also under investigation are contaminants in drinking water, especially because several halogenated organic compounds produced during chlorination are carcinogenic and mutagenic in laboratory tests. A large case-control study of bladder cancer has found a modest excess risk associated with prolonged use of chlorinated surface water,<sup>112</sup> and studies are underway to see if this risk can be confirmed and whether it extends to other cancers. In Taiwan, high levels of inorganic arsenic in drinking water have been linked to skin cancer and possibly other cancers.<sup>113</sup> It has been estimated that only about 2% of cancer deaths are due to environmental pollution,<sup>6</sup> but this estimate is based on limited data and may be modified by the results of future research.

#### IONIZING RADIATION

Along with tobacco smoking, more is known about the carcinogenic effects of ionizing radiation than about any other human carcinogen.<sup>114-116</sup> This dates from early observations on radiologists to the comprehensive studies among survivors of the atomic bombs in Japan and among patients receiving radiotherapy for cervical cancer and ankylosing spondylitis. It is difficult to measure directly the effects of low doses of ionizing radiation such as x-rays or  $\gamma$  rays, and extrapolations have to be made from populations exposed to high and moderate doses for medical, occupational, or military reasons. Although much has been learned about the carcinogenic risks of radiation therapy for different conditions, there are little firm data about risks from the lower doses of diagnostic radiation, except for a 50% increase in leukemia and other childhood cancers associated with prenatal exposures.

About 5% of all cancer deaths may be attributed to radiation,<sup>116</sup> but the upper limit might be somewhat higher if certain estimates are confirmed about the risk of lung cancer associated with indoor levels of radon emanating mainly from soils containing uranium deposits. Studies of underground miners exposed to relatively high doses of  $\alpha$ -radiation have shown excess lung cancer risks, even at levels that might be attained through long-term residential exposure in some parts of the United States.<sup>117</sup> More reliable data should come from ongoing case-control studies of lung cancer that involve careful measurements of indoor radon.

Nearly all sites of the body appear vulnerable to the carcinogenic effects of radiation, with the most radiosensitive tissues being the bone marrow, breast, and thyroid.<sup>118</sup> The patterns of risk provide insights into mechanisms of carci-

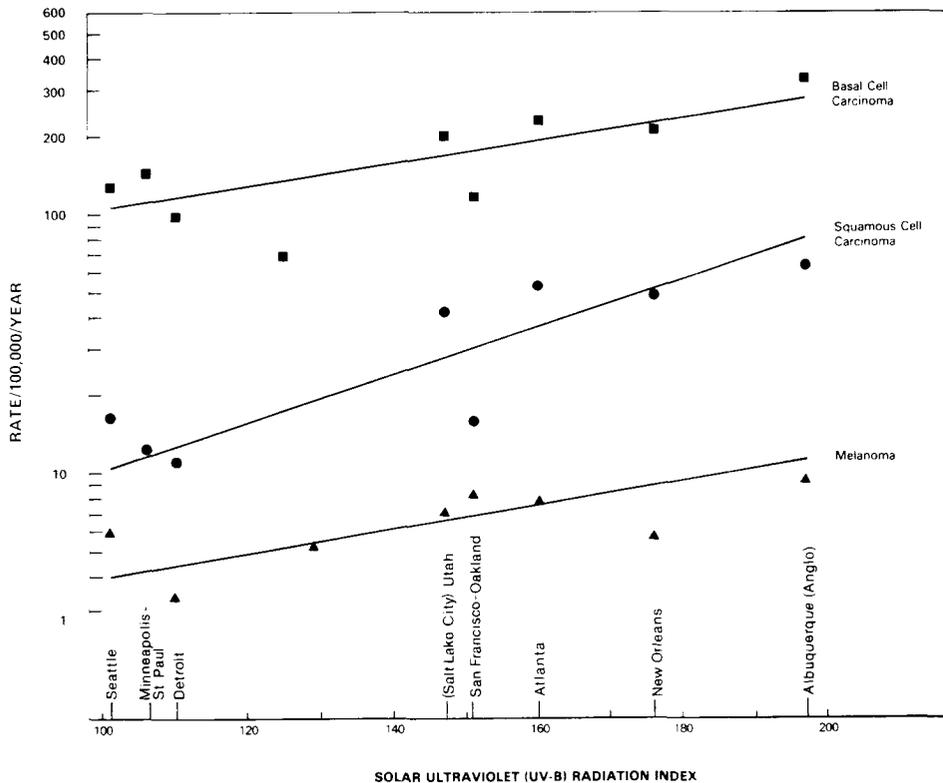
nogenesis and guidelines for radiation protection. For example, radiogenic leukemia shows a distinctive wave-like pattern with the excess risk starting 2 to 4 years after exposure, peaking at 6 to 8 years, and declining to normal within 25 years. In contrast, radiogenic carcinomas have a minimal latent period of 5 to 10 years and a temporal distribution that resembles the natural age-specific incidence curve, suggesting the influence of other factors acting at a later stage of carcinogenesis. The advent of large-scale mammography has renewed interest in the breast cancer experience of atomic bomb survivors and women exposed to medical x-rays. Despite a reasonably linear dose-response curve for breast cancer, the radiation effect is most pronounced among young women and is not evident among those who were exposed after age 40. This finding is reassuring for women in midlife who are most likely to undergo periodic screening with mammography.

Recent reports of increases in childhood leukemia among families living near nuclear facilities in the United Kingdom were not confirmed in France or the United States.<sup>119</sup> Persons living in areas of high natural background radiation in China,<sup>120</sup> and patients given radioactive iodine in Sweden<sup>121</sup> were not found to be at increased cancer risk. These data suggest that radiation given gradually over time may cause less cancers overall than if the same radiation dose were given over a brief interval.

#### SOLAR RADIATION

Ultraviolet (UV) radiation from sunlight is the major risk factor for skin cancer, both squamous and basal cell carcinomas and melanoma.<sup>122</sup> The evidence includes the tendency of tumors to arise on sun-exposed sites, the high incidence associated with outdoor activities, and the predisposition of fair-complexioned people who sunburn easily. Exceptionally high risks of skin cancer occur among persons with genetic diseases exacerbated by sunlight (xeroderma pigmentosum and albinism). Furthermore, in experimental animals, repeated doses of UV radiation, particularly in the UV-B spectral range (290 to 320 nm), can induce skin cancer. In addition, about one half of the melanomas appear to arise from dysplastic nevi, a precursor state that should greatly expand opportunities for early detection and treatment.<sup>123</sup>

Because incidence data for nonmelanoma skin cancer are not collected routinely by most population-based cancer registries, special surveys in the United States were conducted in the 1970s as an adjunct to the SEER program together with measures of UV-B radiation at ground level.<sup>124</sup> The gradient with UV-B levels was steepest for squamous cell carcinoma followed by basal cell carcinoma, and was least apparent for melanoma (Fig. 9-8). These differences are consistent with analytic studies suggesting that intermittent (recreational) exposures associated with sunburning are important in melanoma,<sup>54</sup> whereas cumulative (occupational) exposures appear more closely related to nonmelanoma skin cancer. The steady rise in the incidence and mortality rates for melanoma may be related to short-term intense sun exposures that have accompanied changes in leisure-time activities and clothing habits. Increases in squamous cell carcinoma of the skin have also been documented.<sup>125</sup> There is no evidence so far that ground-level measures of UV-B have increased,<sup>126</sup> but recent reports of stratospheric ozone depletion have prompted con-



**FIGURE 9-8.** Annual age-adjusted incidence rates for basal and squamous cell carcinomas and melanoma among white females, according to annual UV-B measurements at selected areas of the United States. (Scotto J, Fraumeni JF Jr. Skin [other than melanoma]. In: Schottenfeld D, Fraumeni JF Jr, eds. *Cancer epidemiology and prevention*. Philadelphia; WB Saunders, 1982:996. Melanoma data are from the Surveillance, Epidemiology, and End Results program [1973-1976] and nonmelanoma data from a special survey [1977-1978]. Regression lines are based on exponential model.)

cerns about future trends in skin cancer that would presumably result from increases in UV-B reaching the earth's surface. International efforts are under way to phase out chlorofluorocarbons (used in aerosol propellants and air conditioners) that may reduce the protective ozone layer.

#### MEDICATIONS

Several of the carcinogens listed in Table 9-17 have been detected by studies of patients exposed to medicinal agents that may account for as much as 2% of all cancers. Some drugs have been withdrawn from clinical practice, whereas others are retained because their benefits are judged to outweigh their side effects. A major discovery was that synthetic estrogens given during pregnancy produced adenocarcinomas of the vagina and cervix several years later in daughters exposed in utero.<sup>127</sup> This was the first demonstration of transplacental carcinogenesis in humans. Endometrial cancer can result from conjugated estrogens taken for menopausal symptoms, and some studies have suggested an excess of breast cancer in long-term users.<sup>128</sup> Oral contraceptives are still under evaluation, with some studies suggesting an elevated risk of breast cancer when there is early and prolonged use or when there exist predisposing conditions such as familial occurrence or benign breast disease.<sup>129</sup> Also, a relation of pill use to invasive cervical cancer is suggested by recent studies that have made careful attempts to control for confounding variables such as sexual activity and screening history.<sup>78</sup> A reduced risk of endometrial and ovarian cancers has been reported with the combined oral contraceptives, especially after long-term use. The effects of exogenous hormones, along

with the relation of female cancers to reproductive and menstrual variables, indicate the importance of investigating endogenous hormones as risk factors.<sup>130</sup>

An excess risk of acute nonlymphocytic leukemia has been noted among patients receiving alkylating agents, especially melphalan, cyclophosphamide, and chlorambucil.<sup>70</sup> The monitoring of carcinogenic risks should be part of randomized therapy trials. For example, when semustine (methylcyclohexylchloroethyl nitrosurea [MeCCNU]) was evaluated as adjuvant therapy for gastrointestinal cancer, the risks of leukemia and preleukemia were found to be elevated, with a clear dose-response relation (Table 9-19).<sup>131,132</sup> This finding demonstrates the importance of carefully weighing risks and benefits in designing treatment regimens that involve alkylating agents, especially for those cancer patients with a low risk of relapse or for patients with nonmalignant diseases.

Immunosuppressive agents, particularly azathioprine, have been assessed mainly by studies of renal transplant recipients. The risk of non-Hodgkin's lymphoma is high within a few months of transplantation and remains at about the same level.<sup>133,134</sup> This rapid onset is in marked contrast to the usual behavior of chemical carcinogens and suggests activation of a latent oncogenic virus by immunologic mechanisms. Contrary to the prediction of the so-called *immunosurveillance hypothesis* as first proposed, the increase of other cancers is not generalized but is confined to particular types such as squamous carcinoma of the skin, melanoma, Kaposi's sarcoma, liver cancer, and cervical cancer (Table 9-20). Although the risk of posttransplant lymphoma might be influenced by antigenic stimulation by the graft, patients treated with azathioprine for other conditions have shown a tenfold

**TABLE 9-19.** Risk of Leukemic Disorders According to Dose of Semustine

	Cumulative Dosage (mg/m <sup>2</sup> )				
	0	1-	500-	750-	1000+
Number of leukemic disorders	1	3	3	7	5
Number of patients	1,566	714	442	633	278
Relative risk*	1.0	8.7	10.5	18.7	36.9
5-year cumulative risk (%)†	0.1	0.8	1.2	1.1	2.5

\* The referent category was those who did not receive semustine. Maximum likelihood estimates of relative risk were adjusted for survival times.

† Cumulative probabilities were estimated by the Kaplan-Meier technique (Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457) (Boice JD Jr, Greene MH, Killen JY Jr, et al. Leukemia after adjuvant chemotherapy with semustine [methyl-CCNU]—Evidence of a dose-response effect. *N Engl J Med* 1986;314:119)

excess of lymphoma.<sup>134</sup> A predominance of lymphomas has been seen with primary immunodeficiency disorders such as ataxia-telangiectasia, Wiskott-Aldrich syndrome, and the X-linked lymphoproliferative syndrome.<sup>135</sup> For lymphomas in the latter group and in transplant patients, there is evidence of causation by the Epstein-Barr virus.<sup>136</sup> This finding is consistent with animal experiments, indicating that immunosurveillance primarily operates against viral-induced neoplasms.

Recent studies have suggested that nonsteroidal antiinflammatory drugs such as aspirin may protect against large bowel cancer, perhaps through its effect on prostaglandin metabolism.<sup>137</sup>

## VIRUSES

The laboratory discovery of many different oncogenic viruses in animals has long suggested that some human cancers have similar causes, but convincing evidence in humans was slow to emerge until recently.<sup>138</sup> The proportion of viral-related cancer in the United States has been roughly estimated at 5%,<sup>6</sup> but one can only speculate about upper bounds as rapid advances in molecular virology are made. However, the estimate must surpass 5% in certain developing countries. Fur-

thermore, other infectious agents are receiving increasing attention, notably the relation between *Helicobacter pylori* infection and the risk of gastric cancer.<sup>139</sup>

The Epstein-Barr virus (EBV) is widely considered the necessary cause of endemic Burkitt lymphoma and probably also of nasopharyngeal cancer.<sup>140</sup> In Burkitt's lymphoma, holoendemic malaria appears to enhance the oncogenic effect of EBV and produce uneven distribution and occasional clustering of the lymphoma in Africa. EBV appears involved also in the lymphomas that occur in certain immunodeficiency disorders, perhaps by interacting with immunologic and genetic mechanisms. The relation of EBV to nasopharyngeal cancer has been suggested by the higher antibody levels seen in patients than in controls and the presence of viral genome in epithelial cells from the tumor. The high rates of this cancer in southern China cannot be attributed to EBV infection alone, and other risk factors such as consumption of salted fish or histocompatibility antigens appear to be involved.

Hepatitis B virus (HBV) infection is an important cause of hepatocellular carcinoma, especially in endemic regions of Asia and Africa. The most convincing evidence comes from a cohort study of 22,707 men in Taiwan in which the risk of liver carcinoma was more than 200 times greater among carriers of hepatitis B surface antigen than among noncarriers

**TABLE 9-20.** Relative Risk of Certain Cancers in Renal Transplant Recipients in Two Major Studies (With Observed Cancers in Parentheses)

Types of Cancer	United Kingdom-Australasian Study	American College of Surgeons Study*
All types†	2.8 (86)	2.8 (136)
Non-Hodgkin's lymphoma	45.9 (42)	26.9 (53)
Primary liver cancer	37.5 (3)	20.0 (4)
Skin melanoma	8.7 (2)	2.5 (5)
Other cancer‡	1.3 (39)	1.7 (74)

\* Based on unpublished data from Hoover RN and Fraumeni JF Jr, 1989.

† Excludes cervix cancer in situ and nonmelanoma skin cancer, although increases in squamous carcinoma of skin have been reported.

‡ Includes excesses of mesenchymal tumors, notably Kaposi's sarcoma.

(Adapted from Kinlen LJ. Immunosuppressive therapy and cancer. *Cancer Surv* 1, 1982;1:565)

(Table 9–21).<sup>141</sup> The oncogenic effects of hepatitis B may be enhanced by early-life infection and dietary exposures to aflatoxin. Infection with hepatitis C virus may also increase the risk of liver cancer.<sup>142</sup>

The high incidence of adult T-cell leukemia in some areas of Japan and the Caribbean has been linked to infection with the human T-lymphotropic virus type I (HTLV-I), the first retrovirus to be detected in humans.<sup>143</sup> In endemic areas, the virus appears to be transmitted early in life and may also be spread by sexual activity, parenteral drug use, and blood transfusions.

Another human retrovirus, the human immunodeficiency virus (HIV), has been shown to cause the acquired immunodeficiency syndrome (AIDS).<sup>144</sup> Recognized since 1981, AIDS in the United States affects mainly homosexual men, hemophiliacs, and intravenous drug users and predisposes patients to Kaposi's sarcoma and non-Hodgkin's lymphoma. The much higher incidence of Kaposi's sarcoma among male homosexuals than other high-risk groups with AIDS suggests that an oncogenic agent is superimposed on HIV infection and is also sexually transmitted. The classic or endemic form of Kaposi's sarcoma in Africa and Mediterranean areas has been associated with cytomegalovirus infection in some studies, but the findings in AIDS patients suggest that it is a passenger virus.

The relation of cervical cancer to multiple sexual partners has long suggested the venereal transmission of an infectious agent. Although herpes simplex virus type 2 was a candidate agent for some time, the chief suspect is the human papillomavirus (HPV). DNA sequences from certain HPV types, notably HPV-16 and HPV-18, have been found in a high percentage of biopsies from invasive cervical cancer.<sup>145</sup> HPV has been isolated also from many vulvar, penile, and anal cancers and from squamous cell skin cancers associated with the genetic syndrome of epidermodysplasia verruciformis.

Investigations of clusters of leukemia or lymphoma in the community have provided no solid clues to cause, and particularly for childhood leukemia, statistical studies have not detected any general tendency for space-time clustering of these malignancies. However, space-time clustering would not be expected if a disease is a rare response to some underlying infective agent. The mixing of previously separated groups of people, especially in rural areas, has been associated with increases in childhood leukemia consistent with an infective

basis.<sup>146</sup> A viral origin for Hodgkin's disease in young adults has been suggested by its association with certain childhood environments, such as small family size, that would tend to reduce or delay early-life exposures to infections, such as in paralytic poliomyelitis.<sup>60</sup> EBV has been suspected, because an increased risk of Hodgkin's disease has been reported among persons with infectious mononucleosis and among those with elevated levels of antibodies to EBV antigens.<sup>147</sup> Recent molecular viral studies have suggested that in some cases the relation between EBV and Hodgkin's disease may be causal.<sup>148</sup> Despite mounting evidence of oncogenic viruses in humans, there is little indication that any form of cancer is contagious.

## DIET AND NUTRITION

When viewed in the light of experimental work showing how dietary manipulation can influence the yield of tumors in laboratory animals, the recent growth of interest in dietary causes of human cancer seems not merely logical but overdue. International correlations and migrant studies also suggest that certain aspects of the affluent Western diet contribute to a sizable but uncertain proportion of all cancers. Various hypotheses about causative and protective factors are under intensive study, but the specific dietary components are elusive and the mechanisms of action appear complex. Problems stem from the inherent limitations of nutritional methods such as dietary recall, but progress may come from cohort studies in which specimens have been stored for subsequent biochemical assay, from molecular markers of intermediate endpoints, and from intervention studies to determine whether certain dietary modifications and nutrient supplements exert a protective effect against cancer.

Dietary fat has been suggested as a risk factor for certain cancers, especially of the breast and large bowel, by the strongly positive correlations that exist between age-adjusted rates in different countries and per capita consumption of fat.<sup>149</sup> Although the results of case-control and cohort studies have not provided strong support for the fat hypothesis in breast cancer,<sup>53,150</sup> recent studies have suggested a relation of colon cancer to dietary sources of animal fat.<sup>151,152</sup> It is not known whether this association operates through fat or one of its correlates (*e.g.*, protein, cooking-derived carcinogens). Furthermore, no positive relation has been found between the levels of serum cholesterol, which are influenced by fat intake, and subsequent risk of breast or large bowel cancers. The issue is complicated by methodologic difficulties in estimating or measuring intake of fat and different types of fat, the limited variation in fat consumption within many countries, problems in evaluating dietary habits in early life (which may be especially important for breast cancer), and difficulties in differentiating fat per se from calories (because fat is more calorogenic than other macronutrients). Calories may influence the risk of breast and other reproductive cancers by increasing body weight or size, for obesity is an established risk factor for certain cancers in women, especially cancer of the endometrium.<sup>56</sup> It is possible that obesity elevates the risk of endometrial and breast cancers by increasing the serum levels of circulating estrogens through a conversion from androstenedione in adipose tissue and perhaps also by a lowering of the sex-hormone binding globulin.<sup>130</sup> Caloric intake is also related to physical activity, which lowers the risk of colon cancer<sup>151</sup> and perhaps other tumors.

**TABLE 9–21.** Deaths From Liver Disease According to Hepatitis B Surface Antigen (HBsAg) Status on Recruitment Into Study

HBsAg Status	Cause of Death		Population at Risk	Mortality From Liver Cancer*
	Liver Cancer	Cirrhosis		
Positive	40	17	3,454	1.158
Negative	<u>1</u>	<u>2</u>	<u>19,253</u>	<u>5</u>
Total	41	19	22,707	181

\* Mortality from primary hepatocellular carcinoma per 100,000 during study period.

(Adapted from Beasley RP, Hwang L-Y, Lin C-C, et al. Hepatocellular carcinoma and hepatitis-B virus. *Lancet*, 1981;2:1129)

A low intake of certain food groups may predispose persons to cancer, and a lower consumption of vegetables and fruit has been one of the more consistent findings in dietary studies of cancer.<sup>153</sup> A protective action for fiber was proposed by Burkitt, who was impressed by the low rates of colon cancer in parts of Africa where fiber intake and stool bulk were high. Correlational studies have indicated that fiber intake, especially when measured as nonstarch polysaccharides, tends to be lower in high-incidence regions.<sup>154</sup> Although the results are less consistent, there is some support from case-control studies that fiber protects against colon cancer.<sup>155</sup> The subject is complicated by the relatively crude characterization of fiber and by difficulty in separating the effects of micronutrients found in fiber sources such as fruits and vegetables.

Micronutrients may be responsible for the inverse gradients in risk associated with the intake of fruits and vegetables. Several epithelial cancers, especially of the lung, show this negative relation both in case-control studies and some cohort studies employing serologic tests; the effect has been attributed by some workers to beta-carotene,<sup>53,156</sup> although other carotenoids deserve attention.<sup>153</sup> More limited evidence suggests that vitamin C may protect against gastric and certain other cancers, perhaps by blocking the endogenous formation of nitrosamines. However, other components of fruits and vegetables have been suggested as protective factors in experimental and epidemiologic studies. For example, indole compounds in cruciferous vegetables may decrease the risk of colon cancer,<sup>157</sup> and allyl sulfide in garlic and onions may lower the risk of gastric cancer.<sup>88</sup> Vitamin D and calcium have been suggested as protective factors for colon and breast cancers.<sup>158,159</sup> The effects of vitamin E, selenium, and folic acid are also under study. Mixed or multiple deficiencies in the diet may be involved in some tumors, especially among populations with high risks of esophageal cancer.<sup>160</sup> Intervention studies are ideally suited to test the micronutrient hypotheses after sufficient information is obtained from analytic studies and laboratory animals, and the results of several ongoing trials are awaited with interest.

Other dietary factors, including additives and contaminants, have attracted attention. The consumption of aflatoxin, a carcinogenic metabolite of the fungus *Aspergillus flavus*, has been linked to liver cancer by correlation studies, followed by a case-control study,<sup>161</sup> and recently by characteristic p53 mu-

tations in tumors associated with high aflatoxin intake.<sup>162</sup> A relation between salted foods and stomach cancer has been claimed in some studies,<sup>88</sup> but this has not been consistently observed. The consumption of salted fish containing high concentrations of nitrosamines has been linked to the high rates of nasopharyngeal cancer in Hong Kong and southern China.<sup>163</sup> Coffee intake has been associated with bladder and pancreatic cancers, but this has not been confirmed in many other studies and there is no evidence for a causal relation. The artificial sweeteners saccharin and cyclamate cause bladder cancer in laboratory animals, but a large case-control study of bladder cancer indicated that the risk in humans at past levels of consumption is small if present at all.<sup>164</sup> Cooking practices may generate polycyclic hydrocarbons, heterocyclic aromatic amines, or other carcinogens in the food at high temperatures, but relevant epidemiologic data are scarce.<sup>165</sup>

#### GENETIC SUSCEPTIBILITY

Although the geographic and ethnic differentials for most cancers appear largely determined by environmental influences, genetic factors may contribute to some high rates (*e.g.*, nasopharyngeal cancer among Chinese and gallbladder cancer among Native Americans) and some low rates (*e.g.*, testicular cancer and Ewing's sarcoma among blacks in Africa and the United States). Genetic susceptibility is most evident for skin cancer, with geographic and ethnic variations corresponding to the degree of protective skin pigmentation. The apparently limited evidence for genetic factors based on these patterns does not exclude even large variations in individual susceptibility. Furthermore, the relatively small differences in risk between close relatives of patients with various cancers and other people are in fact consistent with large differences in genetic predisposition. The truth of this perhaps surprising statement can be demonstrated mathematically.<sup>166</sup> Only with advances in biochemical and molecular methods will it be possible to further define the impact of genetic factors or genetic-environmental interactions in causing cancer. For example, the phenotype associated with the rapid metabolic oxidation of certain drugs appears to influence the risk of smoking-related lung cancer,<sup>167</sup> supporting the long-held suspicion that certain persons have a higher risk of smoking-induced lung cancer than others because of genetic consti-

**TABLE 9-22.** Hereditary Neoplasms

	<i>Inheritance Features</i>	
Retinoblastoma	AD	Susceptibility to second primary tumors, including osteosarcoma of leg and radiogenic sarcoma of orbit; chromosome deletion (13q14) in some cases
Nevoid basal cell carcinoma	AD	Basal cell cancers of skin increased by UV and ionizing radiation; medulloblastoma, ovarian fibromas, and developmental defects in some cases
Multiple endocrine neoplasia I	AD	Adenomas of anterior pituitary, parathyroid, pancreatic islet cells, thyroid, and adrenal cortex; carcinoid tumors of intestine and bronchus in some cases
Multiple endocrine neoplasia II	AD	Pheochromocytoma and medullary thyroid carcinoma; parathyroid tumors and neurofibromas in some cases
Polyposis coli	AD	Multiple adenomatous polyps and adenocarcinomas of large bowel; some families exhibit osteomas, fibromas, lipomas, and epidermal cysts (Gardner's syndrome)
Dysplastic nevus syndrome	AD	Hereditary melanomas derived from nevi, especially after sun exposure

AD, autosomal dominant.

tution. The claim is sometimes made that the proportion of people who are susceptible to cancer is limited, with variations only in the specific sites affected (Cramer's hypothesis). This notion has been shown to be false<sup>5</sup> and has given way to mutation models and genetic hypotheses<sup>168</sup> that are stimulating further research into the nature of cancer susceptibility genes.

Although only a small fraction of cancer is inherited in a mendelian fashion, over 200 single-gene disorders have been linked to neoplasia.<sup>169</sup> This does not include several constitutional cytogenetic disorders that predispose persons to cancer, such as Down's syndrome with leukemia, Klinefelter's syndrome with mediastinal teratoma, gonadal dysgenesis with gonadoblastoma, and aniridia with Wilms' tumor.<sup>74,166</sup> Table 9-22 lists some cancers that occur as an inherited trait (hereditary neoplasms) and Table 9-23 presents those arising as a complication of inherited precursor lesions (preneoplastic states). In several of the listed syndromes, sunlight contributes to multiple skin cancers, including the dysplastic nevus syndrome predisposing to melanoma, and xeroderma pigmentosum predisposing to various skin cancers. Genetically de-

termined neoplasms tend to occur earlier in life than other cancers of the same anatomic type and often have a multifocal origin. In a growing number of syndromes, alterations in tumor suppressor genes and oncogenes are being recognized. In some conditions, such as familial adenomatous polyposis, the cascade of mutations are defining key events involved in the multistage mechanisms of carcinogenesis.<sup>170</sup> In addition, common neoplasms such as breast and colon cancers show small familial risks on the order of twofold to threefold, but among subgroups on patients with onset at young ages and bilateral or multifocal origin, the risks may be as high as 20- to 30-fold.<sup>171</sup> Some families show remarkable aggregations of site-specific cancer that appear consistent with autosomal dominant inheritance. Recent linkage analysis of families prone to early-onset breast cancer has pointed to a susceptibility gene located on chromosome 17q21.<sup>172</sup>

Because cancer is so common, it is sometimes difficult to know whether familial clusters are simply due to chance, especially if different types of cancer are involved.<sup>173</sup> In this circumstance, it can be useful to consider the possibility of a

**TABLE 9-23.** Hereditary Preneoplastic Syndromes

	<i>Inheritance</i>	<i>Neoplasms</i>
<b>Phacomatoses</b>		
Neurofibromatosis	AD	Sarcomatous change in the neurofibromas of 10% of cases; gliomas of brain and optic nerve, acoustic neuromas, meningiomas, and acute leukemia
Tuberous sclerosis	AD	Hamartomatous growths in several organs; brain tumors, chiefly giant-cell astrocytoma, in 1-3% of patients
von Hippel-Lindau syndrome	AD	Angiomatosis of retina and cerebellum; renal adenocarcinoma, pheochromocytoma, and ependymoma in some cases
Peutz-Jeghers syndrome	AD	Rare malignant change in hamartomatous polyps of gastrointestinal tract; ovarian neoplasms in 5% of female patients
Cowden's multiple hamartoma syndrome	AD	Oral papillomas, cystic mastopathy and breast cancer, thyroid and colonic neoplasms
<b>Genodermatoses</b>		
Xeroderma pigmentosum	AR	Various skin cancers in all patients exposed to sunlight
Albinism	AR	Skin cancers, chiefly squamous, in sun-exposed areas
Epidermodysplasia verruciformis	AR	Skin cancers, chiefly squamous, in multiple warts induced by papillomavirus
Werner's syndrome (adult progeria)	AR	Soft tissue sarcoma, other tumors
<b>Chromosome Instability</b>		
Bloom's syndrome	AR	Acute leukemia, non-Hodgkin's lymphoma, other cancers
Fanconi's anemia	AR	Acute myelomonocytic leukemia and squamous carcinoma of mucous membranes; hepatoma reported after androgen-anabolic steroids
<b>Immunodeficiency</b>		
Ataxia-telangiectasia	AR	Non-Hodgkin's lymphoma, acute lymphocytic leukemia, stomach cancer, other tumors; heterozygous carriers prone to cancer, especially of the breast
Common variable immunodeficiency	?AR	Non-Hodgkin's lymphoma, stomach cancer
Wiskott-Aldrich syndrome	XR	Non-Hodgkin's lymphoma, acute leukemia
X-linked (Bruton's) agammaglobulinemia	XR	Non-Hodgkin's lymphoma, acute leukemia
X-linked lymphoproliferative syndrome	XR	Non-Hodgkin's lymphoma, plasmacytoma

AD, autosomal dominant; AR, autosomal recessive; XR, X-linked recessive.

familial multiple-cancer syndrome. A distinct pattern is seen, for example, with a familial aggregation involving several childhood and adult cancers, including soft-tissue and bone sarcomas, breast carcinoma, brain tumors, leukemia, and adrenocortical neoplasms (Li-Fraumeni syndrome).<sup>174,175</sup> Family members with this syndrome are prone to multiple primary cancers, including radiogenic sarcomas. Recently, molecular studies of these cancer-prone families have identified germline mutations of p53, a tumor suppressor gene on chromosome 17p13 that often occurs as somatic mutations in a number of human cancers.<sup>176</sup> By delineating genetic and familial syndromes of cancer, clinicians have been instrumental not only in helping to identify and protect high-risk individuals but also in pointing experimentalists to new research opportunities. A multidisciplinary approach to genetic susceptibility ranging from clinical observations and epidemiology to molecular biology shows promise in identifying carcinogenic mechanisms and may have consequences in cancer prevention that are at least as important as the detection of environmental carcinogens.

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