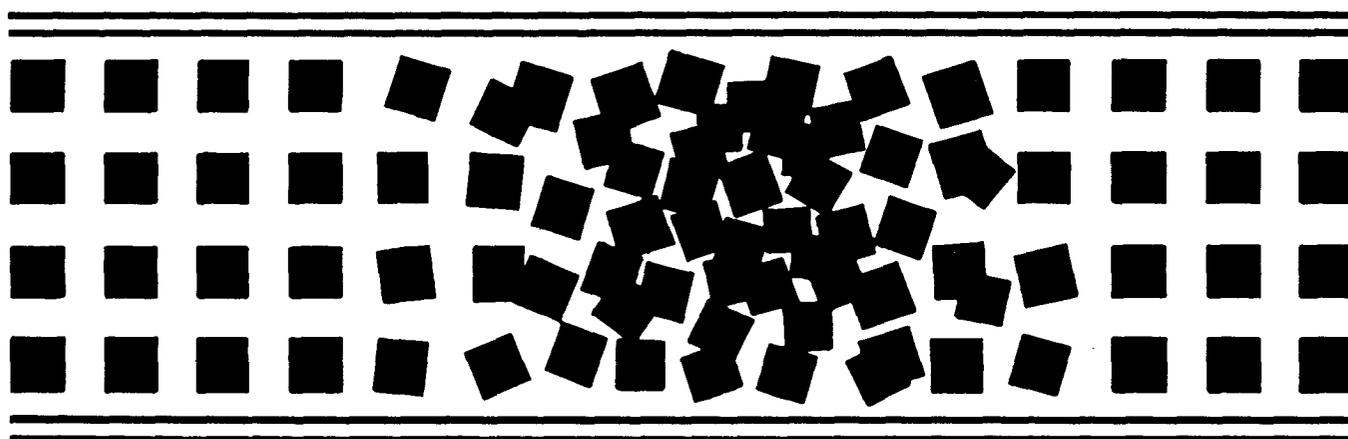


# ***CANCER***

*Principles & Practice  
of Oncology*



*3rd Edition*

Joseph F. Fraumeni, Jr.

Robert N. Hoover

Susan S. Devesa

Leo J. Kinlen

---

## CHAPTER 13 *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 with 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, thereby avoiding the selection factors that can determine the experience of individual clinicians.

Following 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 etiology 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, collaborate in epidemiologic studies, and make clinical observations relevant to etiology. In view of the large volume of current research into the origins of cancer and its prevention, it is 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 noted 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 epidemiologic study of cancer, in any modern sense, 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 noted in the 19th century: lung cancer (though 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,<sup>2,3</sup> illustrate the importance of clinical observations as a source of new discoveries in cancer etiology. They also include an early indication of the long latent interval in human carcinogenesis, for Pott noted that some of the men with scrotal cancer had not worked as chimney sweeps since

boyhood. Furthermore, they show how some causes can be detected (and diseases prevented) before specific agents and mechanisms are elucidated by laboratory investigators. Indeed, many decades elapsed before evidence was available to indicate that polycyclic hydrocarbons, radioactive substances, and aromatic amines explained some of the early findings described above.

### AIMS OF EPIDEMIOLOGY

It is convenient to stress several key words in the definition of epidemiology, which is the study of the distribution and determinants of disease frequency in human populations.<sup>4</sup> The word "humans" distinguishes the approach from those 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 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. Finally, 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, while analytical 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, thus providing the basis for instituting preventive measures. Epidemiologic data support the concept that carcinogenesis is a lengthy multi-stage 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, there is some evidence that the process is retarded by dietary factors, such as certain micronutrients that appear to diminish the risk of various cancer sites including smoking-related lung cancer.

Thus, 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. While 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. Indeed, 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 etiology. 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 individuals 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 labelled as rates, such as case-fatality rates. Sample calculations of these measures are derived from numbers given in Table 13-1.

The incidence rate provides a direct measure of the probability of developing cancer, and 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 mid-year population serving as the denominator. The rates are usually expressed per 100,000 or per million persons. For example, from the data in Table 13-1, the annual occurrence of Hodgkin's disease per 100,000 residents in Connecticut is calculated using the equation on the next page:

TABLE 13-1. 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 315:1394, 1986.

† 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.

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

Incidence rates may be crude (all ages), as in this example, or age-specific. Because of the great dependence of cancer incidence on age, it is much more informative to use age-specific rates. 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 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 13-1, the mortality rate for Hodgkin's 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 very 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>

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 13-1, 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 below.

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 data in Table 13-1, the prevalence of Hodgkin's disease on January 1, 1982 is calculated as follows:

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

Table 13-2 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 or deaths are unknown. This may occur in surveys of hospital patients or death certificates, where 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> However, since the denominator refers to total deaths rather than the population at risk, the magnitude of the ratio for a particular cancer may be misleading since it also fluctuates according to the number of deaths from other causes. Thus, 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 ecological) approach, in which the rates of disease in populations are compared with the geographic or temporal distribution of

TABLE 13-2. Measures of Frequency for Hodgkin's Disease and Pancreatic Cancer, Connecticut, 1982\*

Measure	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, calculated from data in Table 13-1.

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 relationships. 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 they 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, since other factors such as air pollution and improvements in diagnosis showed a similar pattern. It required analytical studies that pursued these leads to establish the cause-and-effect relationship between smoking and lung cancer. Correlational studies also may provide supporting evidence in evaluating relationships detected by analytical 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> Nevertheless, while correlational data may provide clues to etiology, one must be careful not to draw a premature or inappropriate conclusion, sometimes referred to as an ecological 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 etiology 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 a number of demographic 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 1959–1960 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 continu-

ing through 1955.<sup>15</sup> Geographic variations in cancer mortality at the state level were evaluated for the years 1950–1967.<sup>16</sup> Analyses at the county level for 1950–1969<sup>17</sup> formed the basis for computer-generated color atlases portraying geographic patterns on a small-area scale for whites and nonwhites.<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</sup> Computer graphics have also been used to display national trends by age, race, and sex for 1950–1977.<sup>22</sup> Long-term trends in U.S. cancer mortality and incidence were examined for 1935–1974<sup>23</sup> and more recently for 1947–1984.<sup>24</sup> The geographic and temporal variations of cancer mortality have also been analysed on an international scale.<sup>25</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>26</sup> However, changes in diagnostic and certification practices as well as 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. It is important, however, that the death certificates of the study group 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>27</sup> Several other registries covering states or cities have been in existence for varying time periods.

The NCI has coordinated several periodic surveys of cancer incidence in selected areas of the country. The first survey was in 1937–1939 and the second in 1947–1948,<sup>28</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>29</sup> The Third National Cancer Survey included cases diagnosed during 1969–1971 in two states and seven cities.<sup>30</sup> Since 1973, the SEER program has included several population-based cancer registries that continuously gather information on cancer incidence, mortality, and survival.<sup>10,31</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>23,24</sup> In other countries a number of cancer reporting systems have been in existence for varying lengths of time, 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*. 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>32,33</sup> However, since the advent of the SEER program in 1973, it has been possible to continuously monitor population-based survival statistics.<sup>34,35</sup>

### 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>36</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 cancer etiology.

## 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>37</sup> Among women aged 35 to 74, it is the leading cause of death. Almost one million newly diagnosed cases of cancer and nearly 500,000 deaths due to cancer are predicted for the United States during 1988 (Table 13-3). 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. Next most common are cancers of the breast and prostate, so that these four cancers account for 54% and 55% of the total cancer cases and deaths, respectively. The 11 sites shown in Table 13-3 comprise 79% of all cancer cases and 75% of cancer deaths.

Table 13-4 presents the age-adjusted incidence and mortality rates for 44 forms of cancer among white males and females in the United States for the period 1981-1985. Among males the incidence and mortality rates are highest for lung cancer, followed by prostate and colon cancers, whereas among females the rates are highest for breast cancer, followed by cancers of the lung and colon. However, the differential between incidence and mortality is much less for lung cancer than for the other leading cancers, re-

TABLE 13-3. Estimated New Cases and Deaths in the United States for Major Forms of Cancer—1988

	Number of Cases	Number of Deaths
All sites	985,000	494,000
Lung	152,000	139,000
Colon and rectum	147,000	61,500
Breast	135,900*	42,300
Prostate	99,000	28,000
Urinary tract	68,900	20,000
Uterus	46,900*	10,000
Oral cavity and pharynx	30,200	9,050
Skin	27,300†	7,800‡
Pancreas	27,000	24,500
Leukemia	26,900	18,100
Ovary	19,000	12,000
All other sites	204,900	121,750

From Silverberg E, Lubera JA: *Cancer Statistics, 1988*. CA 38:5. 1988. Based on incidence data from National Cancer Institute SEER program 1982-1984 and mortality data from the National Center for Health Statistics. All figures are rounded.

\* Invasive cancers only; more than 5,000 carcinomas in situ of the breast and 50,000 carcinomas in situ of the cervix are estimated.

† Melanoma only; more than 500,000 nonmelanoma skin cancers are estimated.

‡ Melanoma 5,800; other skin cancers 2,000.

flecting well-known survival differences. 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. It is convenient to regard the lowest risk as the baseline level for "spontaneous" tumors that in theory cannot be prevented.

Table 13-5 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>38</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 factors may play some role, as in melanoma, which tends to affect fair-skinned populations, the available evidence suggests that the international differences are mainly due to environmental factors. The patterns observed in Table 13-5 are in fact likely to underestimate the true global variation, since some regions with exceptionally high rates of certain cancers are not covered by registries, such as 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.

TABLE 13-4. Average Annual Age-Adjusted Incidence and Mortality Rates per 100,000 Among U.S. Whites by Primary Cancer Site, 1981-1985\*

	Incidence (SEER)		Mortality (U.S.)	
	Males	Females	Males	Females
All sites	412.1	322.2	211.3	136.2
Lip	3.3	0.3	0.1	0.0
Salivary gland	1.1	0.7	0.3	0.2
Nasopharynx	0.6	0.2	0.4	0.1
Other oral cavity and pharynx	11.9	5.3	4.0	1.4
Esophagus	4.8	1.6	4.6	1.2
Stomach	11.0	4.9	7.1	3.3
Small intestine	1.1	0.8	0.4	0.3
Colon	41.6	32.3	21.2	15.4
Rectum	19.7	12.7	4.1	2.5
Liver	2.8	1.1	2.8	1.3
Gallbladder	0.8	1.6	0.6	1.1
Other biliary	1.6	1.1	1.2	0.9
Pancreas	10.9	8.1	10.1	6.9
Larynx	8.5	1.6	2.5	0.4
Lung and bronchus	82.7	33.8	71.4	24.4
Pleura	1.3	0.2	0.3	0.1
Nasal cavity and sinuses	0.8	0.5	0.3	0.1
Bones and joints	1.0	0.7	0.6	0.3
Soft tissue	2.5	1.7	1.2	1.0
Melanoma of skin	10.7	8.6	3.0	1.7
Other nonepithelial skin	2.5	0.7	1.2	0.3
Breast	0.8	95.7	0.2	27.1
Cervix uteri	—	7.9	—	2.9
Uterus excluding cervix	—	24.2	—	3.7
Ovary	—	14.1	—	8.0
Vagina	—	0.7	—	0.2
Vulva	—	1.6	—	0.3
Prostate	81.3	—	21.4	—
Testis	4.4	—	0.4	—
Penis	0.8	—	0.2	—
Bladder	30.5	7.8	6.4	1.8
Kidney	11.0	4.9	4.7	2.1
Ureter	1.0	0.3	0.2	0.1
Eye and orbit	0.9	0.7	0.1	0.1
Brain and other nervous system	7.5	5.2	5.0	3.5
Thyroid	2.3	5.6	0.3	0.4
Hodgkin's disease	3.5	2.6	1.0	0.6
Non-Hodgkin's lymphoma	14.2	10.2	6.8	4.7
Multiple myeloma	4.5	3.1	3.1	2.1
Acute lymphocytic leukemia	1.6	1.3	0.8	0.5
Chronic lymphocytic leukemia	4.1	2.0	1.7	0.7
Acute myeloid leukemia	3.3	2.2	2.5	1.7
Chronic myeloid leukemia	1.6	0.9	1.0	0.6
Other leukemias	2.6	1.3	2.7	1.6
Miscellaneous	14.8	11.4	15.7	10.8

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

## 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>39</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 continue for generations. In contrast to general environmental exposures, lifestyle practices may change slowly among migrants, depending upon 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>40</sup> Figure 13-1 shows the age-adjusted mortality rates for colorectal and stomach cancers.<sup>41</sup> Stomach cancer rates among migrants are generally lower than in the country of

TABLE 13-5. International Variation in Cancer Incidence\*

	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

From C. Muir and M. Parkin, 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.

\*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.

origin, but higher than among U.S.-born whites. 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 for U.S. native-born whites. Analytical 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 1950–1969 revealed a variety of high-risk areas<sup>18,19</sup> that have led to the investigation of environmental exposures. For example, as shown in Figure 13-2, 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.<sup>42</sup> Similarly, a clustering of high-risk areas in Louisiana was traced in part to heavy smoking by the Cajun population.<sup>43</sup> Furthermore, studies of the elevated rates for oral cancer among women in the rural south, shown in Figure 13-3, have pointed to the hazards associated with the practice of snuff dipping.<sup>44</sup> A recent update of the cancer maps through the period 1970–1980 has revealed patterns resembling those in the earlier atlas, but with a tendency toward greater uniformity of rates around the country.<sup>21</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>45</sup> The U.S. cancer maps were soon followed by similar atlases from other countries, the total reaching 15 at last count. Most remarkable are the maps from China that have disclosed dramatic variations in mortality and have stimulated a number of analytical studies in areas with exceptionally high rates.<sup>46</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.

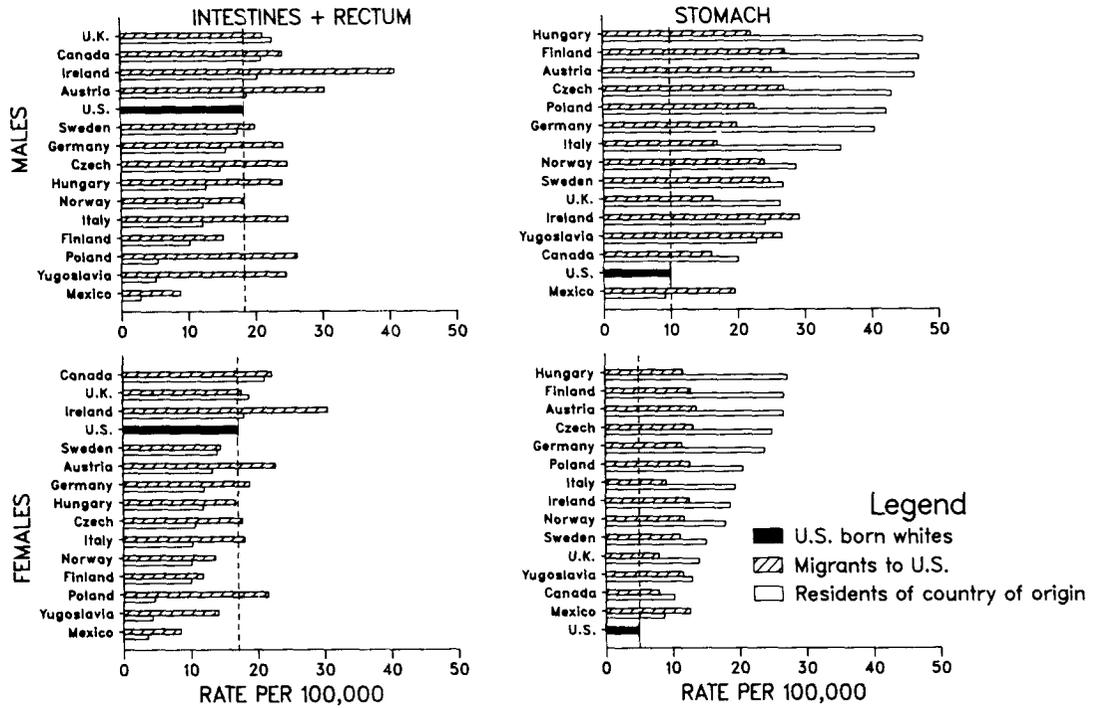
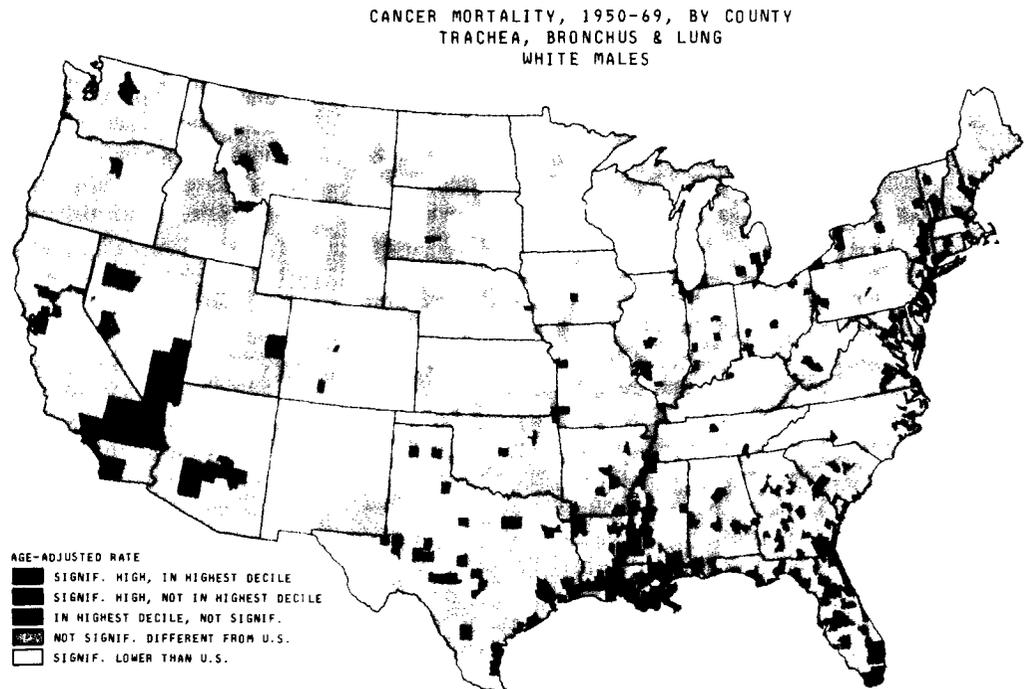


FIG. 13-1. Average annual mortality rates for intestinal and stomach cancers among U.S.-born whites, migrants from selected countries from 1959 to 1961, and residents of the countries of origin, 1960. Rates standardized for age on the 1950 U.S. population. (Data from Lilienfeld AM, Levin ML, Kessler II: Cancer in the United States. Cambridge, MA, Harvard University Press, 1972)

FIG. 13-2. Mapping of lung cancer mortality rates among white males for United States counties. 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. DHEW Publication No. [NIH] 75-780. Washington, DC, US Government Printing Office, 1975)



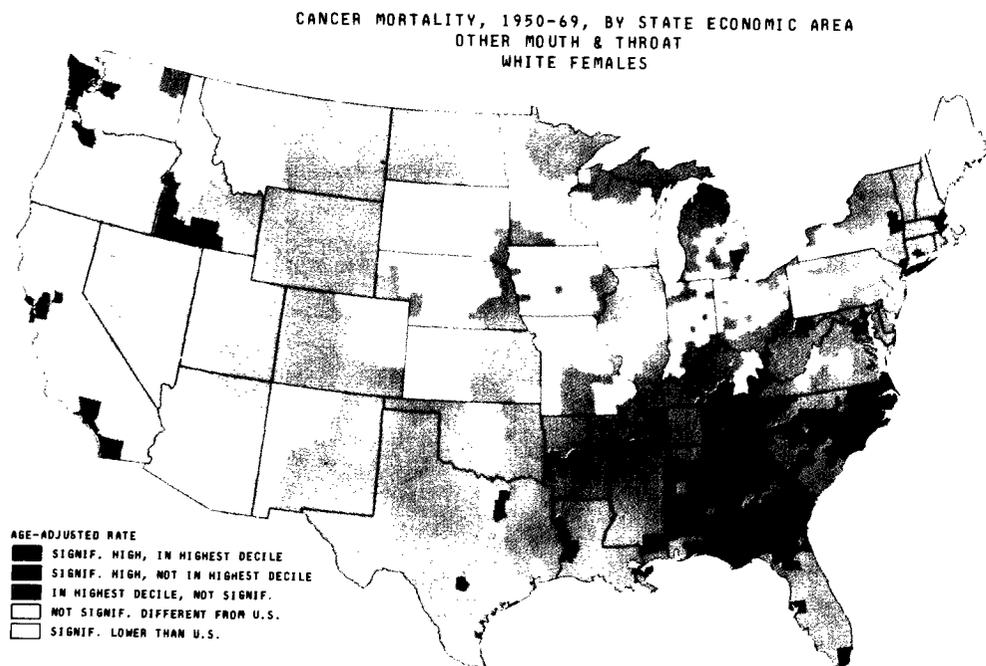


FIG. 13-3. Mapping of oral and pharyngeal cancer mortality rates among white females for United States counties, 1950 to 1969. Rates standardized for age on the 1960 U.S. population. (Adapted from Mason TJ, McKay FW, Hoover R, et al: Atlas of Cancer Mortality for U.S. Counties: 1950-1969. DHEW Publication No. [NIH] 75-780. Washington, DC, US Government Printing Office, 1975)

### 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. As shown in Figure 13-4, mortality rates for some forms of cancer in the United States have changed greatly over the last 55 years, whereas rates for several other cancers have remained relatively stable.<sup>37</sup> Most striking has been the 10-fold 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 prior years. These trends reflect the changing prevalence of smoking habits in the male and female populations.<sup>47</sup> Lung cancer mortality among females in some areas is on the verge of surpassing the rates for breast cancer, which have 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 then 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 a 35-year time period are shown in Figure 13-5 for the white population in five geographic areas of the country.<sup>24</sup> Among males lung cancer incidence

increased almost 3% per year to become the most frequent form of cancer, but the decline in the most recent years may reflect a decrease in smoking prevalence. Prostatic cancer incidence increased substantially, particularly since 1970, which must be due at least partly to the improved detection of early-stage or latent carcinomas. 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 60% in colorectal cancer and declines of 69% in stomach cancer among males are consistent with a number of dietary hypotheses under active investigation.<sup>48</sup> Melanoma incidence rose nearly four-fold among males, probably due in part to the changing patterns of exposure to sunlight.<sup>49</sup>

Among females, breast cancer incidence increased 31% from the late 1940s to the mid-1980s. 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 are unclear. In contrast to the prominent upward trend among males, colorectal cancer among females increased only about 10%, primarily during the 1970s. 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, 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>50</sup> Incidence rates for invasive cancer of the cervix uteri declined

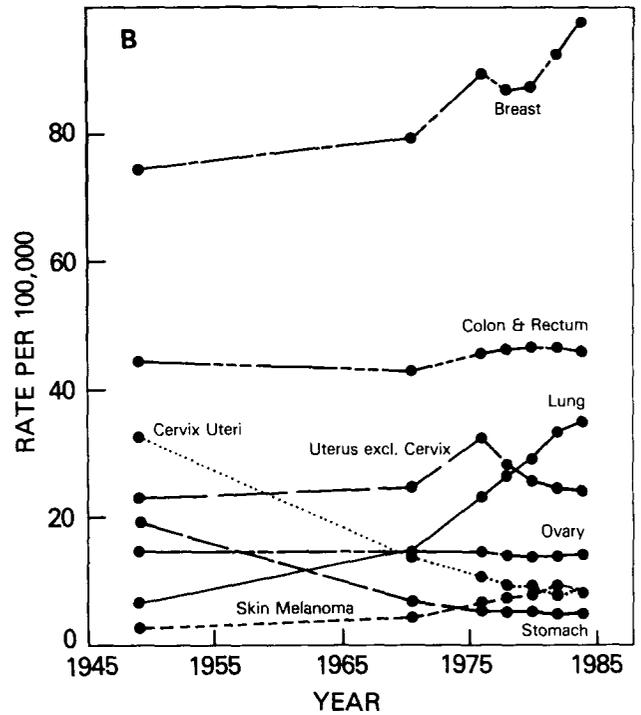
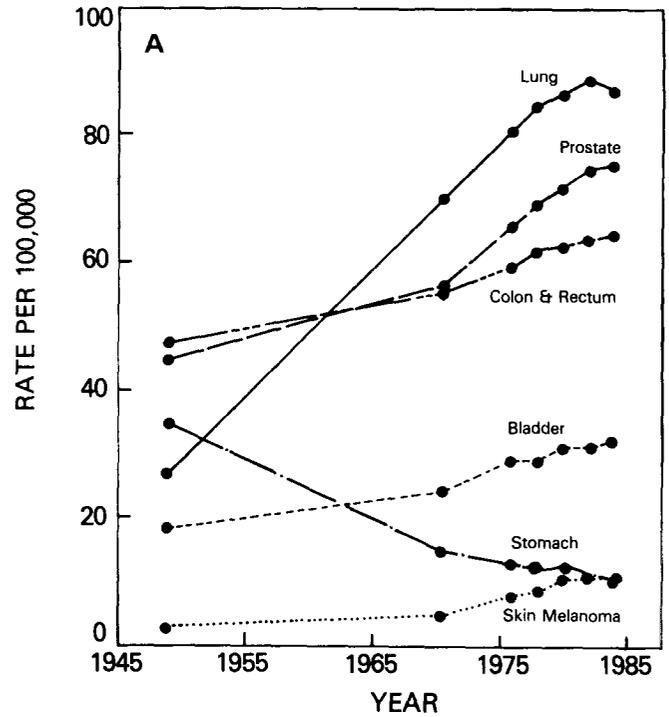
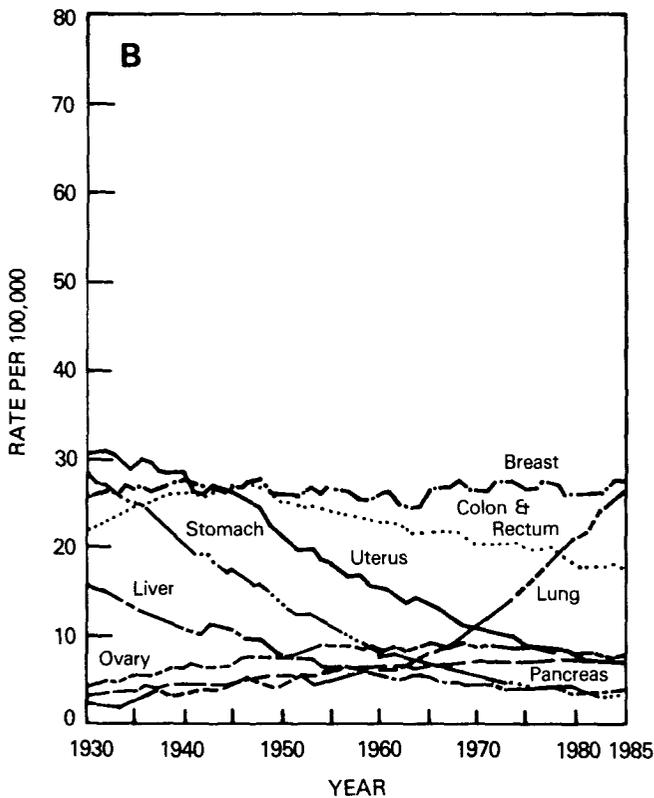
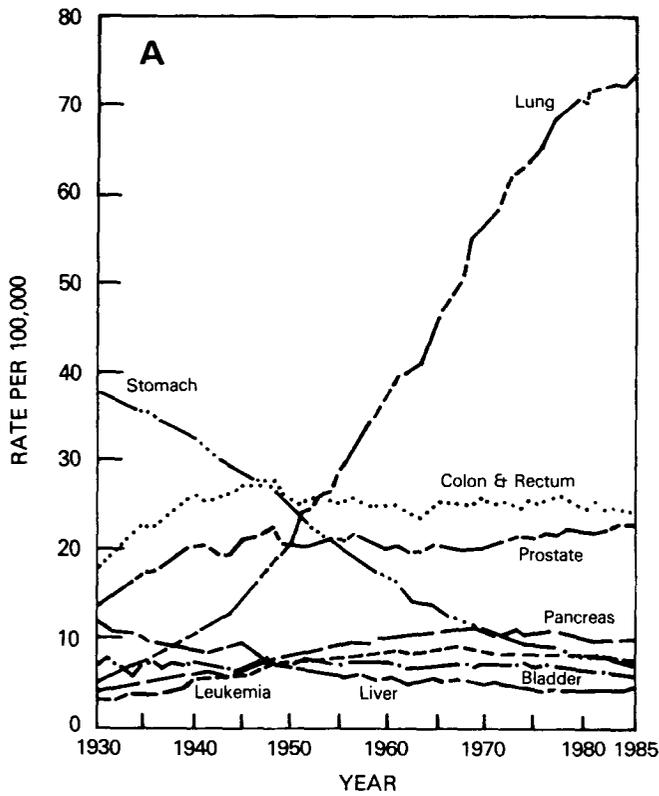


FIG. 13-4. Cancer mortality trends for selected sites in the United States population, 1930 to 1985, among males (A) and females (B). Rates standardized for age on the 1970 U.S. population. (Data from the National Center for Health Statistics and Bureau of the Census. Modified from Silverberg E, Lubera JA: Cancer Statistics, 1988. CA 38:5, 1988)

FIG. 13-5. Cancer incidence trends for selected sites in five geographic areas of the United States, 1947 to 1984, among white males (A) and white females (B). Rates standardized for age on the 1970 U.S. population. (Adapted from Devesa SS, Silverman DT, Young JL Jr, et al: Cancer incidence and mortality trends among whites in the United States, 1947-84. JNCI 79:701, 1987)

75% over the 35-year period, or about 4% per year, 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>51</sup> but the increasing prevalence of women with a hysterectomy<sup>52</sup> has contributed to the trend. Declines of 74% 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 50% during the early 1980s (Table 13-6). 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. 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 years. Survival rates for those with esophageal, stomach, liver, pancreatic, and lung cancers remain poor.

Survival figures for most cancers are greatly affected by the extent of disease at the time of detection (Table 13-7). 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 thus mortality may be achieved through development and implementation of techniques enabling earlier detection and treatment. The 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.

The impact of improved treatment has been remarkable for childhood cancer (Table 13-8). Five-year relative survival rates for all types combined improved from 28% during the early 1960s to 63% in the early 1980s. Acute lymphocytic leukemia has been transformed from a virtually fatal cancer with a 4% survival rate to one with a 65% 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 early 1980s achieved

TABLE 13-6. Trends in 5-Year Relative Survival Rates for Selected Sites of Cancer Among U.S. Whites, 1960-1984

	Year of Diagnosis				
	1960-1963* (%)	1970-1973* (%)	1974-1976† (%)	1977-1978† (%)	1979-1984† (%)
All sites	39	43	50	50	50
Oral cavity and pharynx	45	43	54	53	53
Esophagus	4	4	5	6	7
Stomach	11	13	14	15	16
Colon	43	49	50	52	54
Rectum	38	45	48	50	52
Liver	2	3	4	3	3
Pancreas	1	2	3	2	3
Larynx	53	62	66	69	66
Lung and bronchus	8	10	12	13	13
Melanoma of skin	60	68	78	80	80
Breast (females)	63	68	74	75	75
Cervix uteri	58	64	70	69	67
Corpus uteri	73	81	88	87	83
Ovary	32	36	36	37	37
Prostate	50	63	67	70	73
Testis	63	72	78	86	91
Bladder	53	61	73	75	77
Kidney	37	46	51	50	51
Brain and nervous system	18	20	22	23	23
Thyroid	83	86	92	92	92
Hodgkin's disease	40	67	71	73	74
Non-Hodgkin's lymphoma	31	41	47	48	49
Multiple myeloma	12	19	24	24	24
Leukemia	14	22	34	37	32

From National Cancer Institute: Annual Cancer Statistics Review Including Cancer Trends 1950-1985. Bethesda, MD, 1988.

\* 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 1985.

TABLE 13-7. Five-Year Relative Survival Rates Among U.S. Whites for Selected Sites of Cancer According to Stage at Diagnosis, 1979-1984\*

	Localized (%)	Regional (%)	Distant (%)
Oral cavity and pharynx	77	42	17
Esophagus	15	5	1
Stomach	57	15	2
Colon	87	58	6
Rectum	81	46	3
Pancreas	6	4	1
Larynx	81	53	24
Lung and bronchus	35	14	1
Melanoma of skin	90	52	12
Breast (females)	90	69	18
Cervix uteri	88	52	15
Corpus uteri	91	71	25
Ovary	84	45	20
Prostate	85	74	31
Testis	97	94	61
Bladder	89	45	8
Kidney	83	53	7
Thyroid	99	91	49

From National Cancer Institute: Annual Cancer Statistics Review Including Cancer Trends 1950-1985. Bethesda, MD 1988.

\* Rates based on data from the SEER program, with follow-up of patients through 1985.

rates exceeding 90%. For Wilms' tumor, survival rates increased from 33% to 82% over the same period. The improvements in therapy and survival have resulted in dramatic declines in childhood cancer mortality in recent years.<sup>53</sup>

AGE CURVES

The marked rise in cancer incidence with advancing age has suggested in the past that some aspect of the aging process increases susceptibility to cancer, perhaps by impairing im-

mune function. It is now considered, however, that the relationship of many cancers with increasing age mainly reflects the importance of duration of exposure to carcinogens and of long induction periods.<sup>5</sup> The age-specific incidence rates for cancers of individual sites are reproduced in Appendix Tables 13-1 to 13-4. The rates cover the years 1981 to 1985 for the SEER program of the NCI, and are given by sex and race (whites and blacks).

Figure 13-6 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 nonepithelial cancers rise sharply with age, notably multiple myeloma and chronic lymphocytic leukemia.<sup>5</sup> Deviations from the usual age trend are illustrated by the cancers plotted in Figure 13-6C. 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 there is some evidence suggesting that the young adult peak may result from an infectious agent.<sup>54</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>55</sup> The rates for invasive cervical cancer increase sharply with age among young women, but then level off after age 35.

Table 13-9 shows the incidence rates for the major cancers among white children by age group and sex for the period 1981 to 1985. Except for lymphomas and bone tumors, the highest incidence occurs in children under 5 years of age. In general, boys have somewhat higher rates than girls in all three age groups, especially for the lymphomas.

TABLE 13-8. Trends in 5-Year Relative Survival Rates for Selected Forms of Cancer Among U.S. White Children Under 15 Years of Age, 1960-1984

	Year of Diagnosis				
	1960-1963* (%)	1970-1973* (%)	1974-1976† (%)	1977-1978† (%)	1979-1984† (%)
All forms	28	45	55	62	63
Acute lymphocytic leukemia	4	34	53	73	65
Acute myeloid leukemia	3	5	16	27	25
Wilms' tumor	33	70	74	80	82
Brain and nervous system	35	45	54	55	56
Neuroblastoma	25	40	48	46	56
Bone	20	30	52	53	48
Hodgkin's disease	52	90	80	82	91
Non-Hodgkin's lymphoma	18	26	43	44	60

From National Cancer Institute: Annual Cancer Statistics Review Including Cancer Trends 1950-1985. Bethesda, MD, 1988.

\* 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 1985.

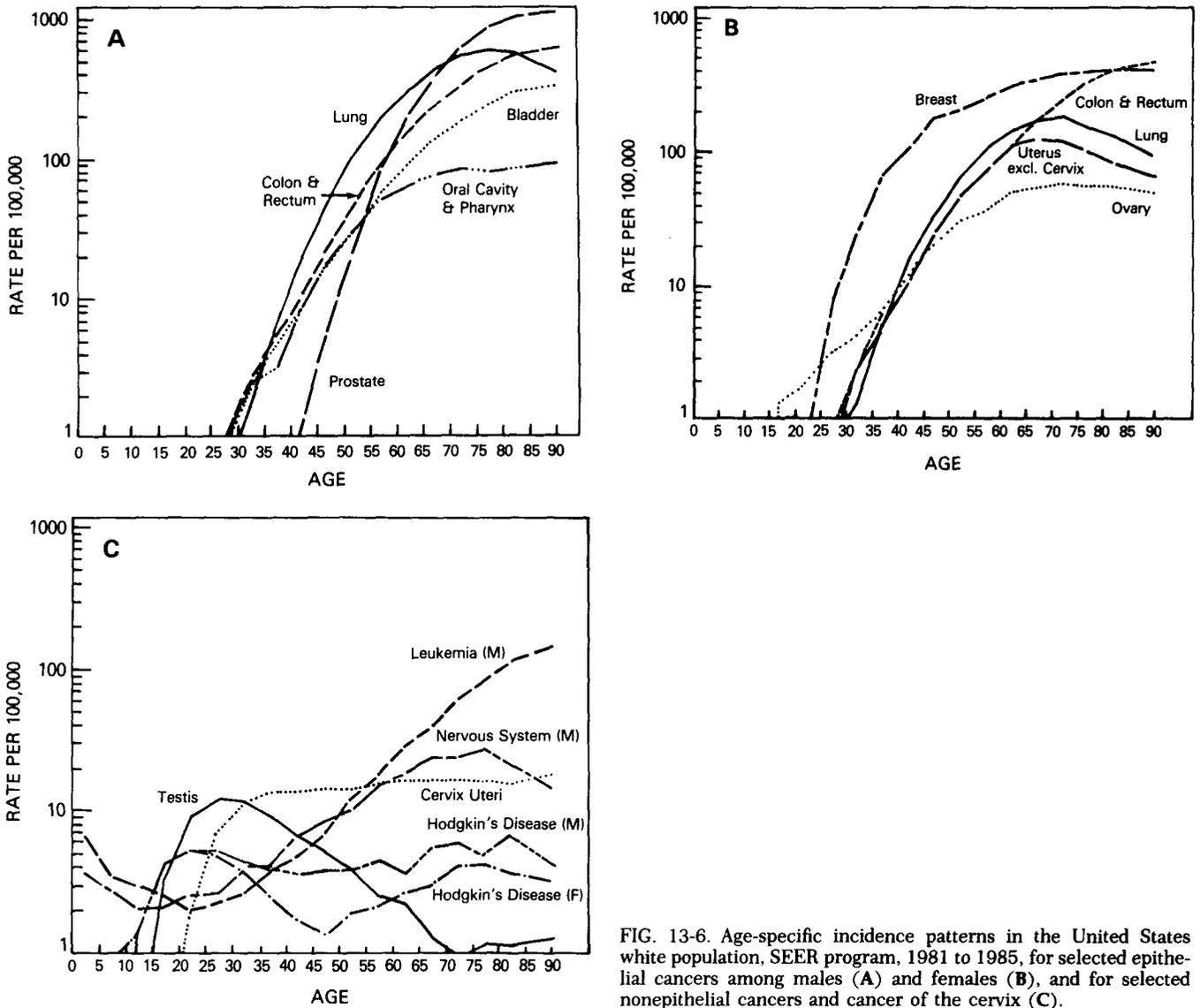


FIG. 13-6. Age-specific incidence patterns in the United States white population, SEER program, 1981 to 1985, for selected epithelial cancers among males (A) and females (B), and for selected non-epithelial cancers and cancer of the cervix (C).

TABLE 13-9. Age-Specific Incidence Rates for Selected Forms of Cancer Among U.S. White Children, 1981-1985\*

	Boys			Girls		
	0-4	5-9	10-14	0-4	5-9	10-14
All forms	19.9	11.7	11.8	17.4	9.6	10.7
Leukemia	6.8	3.4	3.0	6.1	3.2	2.3
Brain and central nervous system	3.8	2.8	2.2	2.9	2.6	1.7
Lymphoma	0.8	2.5	3.2	0.3	0.4	1.8
Neuroblastoma	3.3	0.3	0.1	3.0	0.4	0.1
Soft tissue	0.8	0.5	0.6	0.8	0.2	0.6
Wilms' tumor	1.9	0.6	0.2	1.8	0.7	0.1
Bone	0.1	0.7	1.3	0.2	0.7	1.2
Retinoblastoma	1.0	0.1	0.0	1.1	0.1	0.0
All others	2.1	0.9	1.2	2.0	1.4	2.9

\* Average annual rates per 100,000 population, based on data from the SEER program.

ETHNIC VARIATION

The SEER program provides data indicating striking racial and ethnic variations in cancer incidence in the United States (Table 13-10). For males, the rates for all cancers combined are highest in blacks, followed by whites and Hawaiians, whereas for females the rates are highest for Hawaiians, followed by whites and blacks. The lowest rates in both sexes are in American Indians. Compared to 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. Hispanics have especially high rates for cervix cancer, and to some extent for cancers of the stomach and biliary tract (females), whereas American Indians have remarkably high rates for cancers of the stomach, biliary tract, cervix, and kidney (females). Chinese experience elevated rates for cancers of the nasopharynx and liver, while Japanese have high rates for stomach cancer and (in males) for cancers of the colon, rectum, and thyroid. Filipinos have high rates for cancers of the thyroid, while Hawaiians 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

Whereas part of the racial and ethnic variations in rates may reflect genetic influences, many appear strongly influenced by environmental factors, some of which may be associated with socioeconomic status. Data from the Third National Cancer Survey<sup>30</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/white relative risks.<sup>56</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 13-11). This pattern varied by primary site, however. Cervix cancer was almost four times as frequent among women in the lowest relative to the highest category, for reasons that are not entirely clear. Rates for esophageal cancer among men varied more than twofold, in line with socioeconomic differences in the use of alcohol and tobacco as well as 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 factors account for the black/white differentials in cancer incidence. When adjusted for racial variations in socioeconomic status, the excess risk among blacks is dimin-

TABLE 13-10A. Average Annual Age-Adjusted Incidence Rates per 100,000 for Selected Cancer Sites by Racial and Ethnic Group, 1975-1985, U.S. Males\*

	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 age-adjusted based on the 1970 U.S. standard population.

TABLE 13-10B. Average Annual Age-Adjusted Incidence Rates per 100,000 for Selected Cancer Sites by Racial and Ethnic Group 1975-1985, U.S. Females\*

	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 age-adjusted based on the 1970 U.S. standard population.

ished for cancers of the esophagus, stomach, lung, and cervix. Socioeconomic status may also influence cancer survival and mortality patterns by affecting access to diagnosis and treatment.

## ANALYTICAL STUDIES

The major contribution of epidemiology has been to test etiologic hypotheses through analytical 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

TABLE 13-11. Relative Risks (RR) for All Cancers and Selected Sites by Socioeconomic Status (SES) and Race, 1969-1971\*

	Income Level Among Whites					Black/White RR	
	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.

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>4,57</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 a prospective cohort study; but more often they use information on exposures collected in the past, termed a retrospective cohort study. 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>4,57</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 well-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, it is desirable that both cases and controls are selected from the same source, which may be either population-based or hospital-based. However, since 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>58</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 as compared with the cohort approach. In addition,

there are greater opportunities to evaluate more than one risk factor and interactions between them.<sup>59</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 relationships such as latency period and the duration of an effect. However, 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 with biased estimates of risk, as produced for example by the healthy worker effect of occupational studies.<sup>4</sup> Moreover, they may not permit as ready 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. The relative risk (RR) or risk ratio is the disease rate in the exposed,  $I_e$ , divided by the disease rate in the referent (usually nonexposed,  $I_o$ ) population.<sup>4</sup> As illustrated by Table 13-12, the relative risk from a cohort study is defined as

$$RR = I_e I_o = \frac{a}{n_e} \frac{c}{n_o}$$

This measure gives the relative disease risk between two populations. Thus, 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. In order 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. From Table 13-12, the attributable risk is defined as

$$A_e = I_e - I_o = \frac{a}{n_e} - \frac{c}{n_o}$$

The attributable risk means that if the relationship observed is causal, the difference between the rates of exposed

TABLE 13-12. Measures of Association from a Cohort Study

	Affected Persons (Cases)	Total Persons (Person-Time)
Exposed	a	$n_e$
Not Exposed	c	$n_o$
Total	a + c	N
Relative risk (RR)	$= \frac{a/n_e}{c/n_o}$	
Attributable risk in the exposed ( $A_e$ )	$= \frac{a}{n_e} - \frac{c}{n_o}$	
Attributable risk percent in the exposed ( $A_e\%$ )	$= \frac{(a/n_e) - (c/n_o)}{a/n_e} = \frac{RR-1}{RR} \times 100\%$	
Population attributable risk ( $A_p$ )	$= \frac{a+c}{N} - \frac{c}{n_o}$	
Population attributable risk percent ( $A_p\%$ )	$= \frac{(a+c)/N - (c/n_o)}{(a+c)/N} = \frac{RR-1}{RR + 1/P-1} \times 100\%$	
where P is the proportion of the population that is exposed, or $n_e/N$		

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>60</sup>

The measures of relative risk and attributable risk have somewhat different uses. The magnitude of the RR indicates the strength of a relationship 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>60</sup> This measure would thus reflect 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. Again, from Table 13-12, the population attributable risk is defined as

$$A_p = I_t - I_o = \frac{a+c}{N} - \frac{c}{n_o}$$

Thus, 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 the attributable risk is expressed as a proportion of the total disease rate in population, it is called the population attributable risk percent ( $A_p\%$ ) or the etiologic fraction.<sup>61</sup>

These measures are illustrated by a recent cohort study involving 1-year survivors of ovarian cancer from five randomized trials.<sup>62</sup> The incidence rates for acute nonlymphocytic leukemia and preleukemia were evaluated among women treated with no chemotherapy, with cyclophosphamide, and with melphalan. The corresponding rates were 0.18, 3.21, and 11.46 cases per 1000 women per year. Com-

pared to 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 very 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 therapy whose proven benefit outweighs these risks. Also, when the  $A_e$  is not large, one can see how difficult it is for an individual 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 very little impact on the total leukemia rate in the general population, for 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 13-13, subtracting the rate among those not treated with chemotherapy (.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 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), these can be used to estimate the rates among the exposed and unexposed groups and thus to calculate relative and attributable risks. For most case-control studies, however, sampling fractions are unknown. In this circumstance,

TABLE 13-13. Risks of Leukemia and Preleukemia Associated with Chemotherapy

	Cases	Person-Years at Risk	Rate per 1,000
Any Chemotherapy	33	4,295	7.68
No Chemotherapy	2	10,983	0.18
Total	35	15,278	2.29

Relative risk (RR) =  $\frac{33/4,279}{2/10,983} = \frac{7.68}{0.18} = 42.4$

Attributable risk in the exposed ( $A_e$ ) =  $33/4,279 - 2/10,983 = 7.40$  per 1,000

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

Population attributable risk ( $A_p$ ) =  $\frac{35}{15,278} - \frac{2}{10,983} = 2.11$  per 1,000

Population attributable risk percent ( $A_p\%$ ) =  $\frac{35/15,278-2/10,983}{35/15,278} \times 100\% = 92\%$

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

as shown in Table 13-14, the calculation of relative odds, also termed an odds ratio, usually gives a good approximation of the relative risk.<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<sup>60</sup> as shown in Table 13-14.

Calculation of these measures is illustrated in Table 13-15, based on a national case-control study of bladder cancer that evaluated the risks associated with smoking.<sup>63</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>57</sup> controlled intervention trials represent a third strategy of analytical epidemiology that is especially useful for confirming causal relationships 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. 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 (as well as any potential for harm), ethical questions may arise. In the field of cancer etiology and prevention, opportunities for inter-

TABLE 13-14. Measures of Association from a Case-Control Study

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

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

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

Population attributable risk percent ( $A_p\%$ ) or etiologic fraction =  $\frac{P_o(R-1)}{1 + P_o(R-1)} \times 100\%$   
 $= \frac{(R-1)P_e}{R} \times 100\%$

where  $P_o$  is the exposure rate in the controls, or  $\frac{b}{b+d}$  and  $P_e$  is the exposure rate in the cases, or  $\frac{a}{a+c}$

TABLE 13-15. Risks of Bladder Cancer Associated with Cigarette Smoking

	Cases	Controls
Smokers	2324	3581
Nonsmokers	657	2198
Total	2981	5779

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

Attributable risk percent in the exposed ( $A_e\%$ ) =  $\frac{2.2-1}{2.2} \times 100\% = 55\%$

Population attributable risk percent ( $A_p\%$ ) or etiologic fraction =  $\frac{\frac{3581}{5779}(2.2-1)}{1 + \frac{3581}{5779}(2.2-1)} \times 100\%$   
= 43%

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 78:1119, 1987.

vention have been limited for various reasons, including the long latency periods that may be involved before an effect is seen. However, intervention studies are now 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 analytical 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). Thus, 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

However, cancer epidemiology has certain limitations. First, 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), though 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 analytical 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 relationships when the exposure level is low or the excess risk is small compared to 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 EPIDEMIOLOGY

The power of certain studies may be increased by incorporating laboratory methods into analytical investigations, so-called biochemical or molecular epidemiology.<sup>64,65</sup> The analysis of biological samples in the laboratory can obviously 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. At present the approach is providing new opportunities to evaluate carcinogenic risks associated with dietary factors and with markers of genetic predisposition. In view of rapid experimental advances, biochemical epidemiology represents 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

Since an analytical study is designed to evaluate an association between a disease and an antecedent factor, there must be some prior indication or suspicion of such an association. The lead may come from descriptive or correlational studies or from another analytical study. However, 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> Thus, 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 the offspring. It was possible for clinicians to detect these associations because they involved tumors that are rare in the general population and they also involved exceptionally high risks. In most instances the associations hardly required epidemiologic study for their confirmation, but only to quantify them. Clinicians have also identified a wide variety of heritable conditions associated with susceptibility to cancer.<sup>66</sup> Opportunities for the practicing physician to make significant etiologic discoveries were highlighted recently at a symposium sponsored by the Princess Takamatsu Cancer fund, entitled "Rare Events as Clues to Cancer Etiology."<sup>67</sup> On the other hand, epidemiologists can identify causes of cancer that may seem less dramatic in relative risks but are very 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 conversely, the smaller the sample size, the weaker the power.

The issues of sample size and power are of great concern when evaluating negative results of epidemiologic studies.<sup>68</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 analytical 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>69</sup> but most can be grouped as biases of selection or information.<sup>58</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 had 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>13,58</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 some industrial groups if they smoke more heavily than the average. Conversely, a relationship between oral contraceptives and invasive cervical cancer became apparent only after adjustment was made for 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>70</sup> Whereas analytical methods can control for known confounders, it cannot do this for unknown confounders, which are free to distort observed risk estimates. The advantage of experimental studies, of course, 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 of course 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, one 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>13,14,58</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>71,72</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, biological 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>58</sup> With smaller relative risks, especially when interactions between multiple exposures and susceptibility states seem important, the term risk factors is often used instead of causal agents. 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 biological information, including laboratory studies. Although epidemiologic observations can accumulate to the point at which causation is virtually inescapable, strictly speaking it is not possible by these means alone to prove causality. 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 is intended to provide a brief overview of cancer risk factors, based mainly on evidence from analytical epidemiology, including recent observations relevant to the practicing oncologist. The contributions of epidemiology to cancer etiology and prevention are presented elsewhere in greater detail.<sup>6,7,73,74</sup> Best known is the success of the epidemiologic approach in discovering or confirming a number of lifestyle and other environmental exposures as causes of cancer (Table 13-16).

#### 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>75</sup> Recent evidence indicates that smokers are also prone to cancers of the kidney parenchyma<sup>76</sup> and pelvis,<sup>77</sup> cervix,<sup>78</sup> nasal passages,<sup>79</sup> and perhaps stomach cancer<sup>80</sup> and leukemia.<sup>81</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>6,75</sup> This is consistent with evidence that smoking exerts an effect at late as well as 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>82</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, since oral cancer has been linked with snuff dipping, a common practice in rural southern parts of the United States.<sup>44</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>83</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. A review of the available evidence suggests that nonsmoking women married to smokers have experienced an excess risk of the order of 30%.<sup>84</sup> There is little question that passive or involuntary smoking is real, since tobacco smoke constituents and metabolites can be detected in the body fluids of exposed nonsmokers. Moreover, a cause-and-effect relationship 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 very 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>85,86</sup> It has been difficult to study the effects of alcohol alone and the

TABLE 13-16. Environmental Causes of Human Cancer

<i>Agent</i>	<i>Type of Exposure</i>	<i>Site of Cancer</i>
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	Cervix, vagina (adenocarcinoma)
Synthetic (DES)		Endometrium
Conjugated (Premarin)		Liver (benign)
Steroid contraceptives		
Immunosuppressants (azathoprine, cyclosporin)	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	
Schistosoma haematobium		Bladder (squamous carcinoma)
Clonorchis sinensis		Liver (cholangiocarcinoma)
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 virus		Hepatocellular carcinoma
Human T-lymphotrophic virus, type I		T-cell leukemia/lymphoma
Vinyl chloride	Manufacturing of polyvinyl chloride	Liver (angiosarcoma)
Wood dusts	Furniture manufacturing (hardwood)	Nasal sinuses (adenocarcinoma)

nature of the 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 13-17 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>87</sup> Combined exposures were found to account for about three fourths of all oral and pharyngeal cancers. The risks were not uniform for all forms of alcohol, being 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 occurring in the supraglottic than in the intrinsic segments. Since ethanol is not carcinogenic in laboratory animals, the mechanism by which alcohol acts is not clear, but it may involve nutritional deficiencies that accompany drinking, contaminants such as nitrosamines and hydrocarbons, or increased permeability of mucous membranes to other carcinogens.

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 analytical studies have been inconsistent. For example, cohort studies of brewery workers (who receive a free beer allocation) have revealed an excess risk of rectal cancer in Dublin but not in Copenhagen.<sup>88</sup> Recent interest has centered around the possible relationship of alcohol with breast cancer, with a series of prospective studies showing an excess risk and dose-response gradient.<sup>89,90</sup> Further investigation is needed to determine if this relationship is causal, or if indirect, how it is mediated.

#### 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>91,92</sup> Occupational exposures

may account for about 5% of all cancer deaths, while 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, while others were noted 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> It is noteworthy that 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 may not be 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 despite the fact that the relative risk for lung cancer is little more than twofold, whereas that for mesotheliomas is well over 100-fold, the reason being that lung cancer is much more common than mesothelioma in people unexposed to asbestos. A multiplicative relationship exists between asbestos exposure and smoking in the development of lung cancer.<sup>93</sup> As shown in Figure 13-7, 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.<sup>42</sup> The risks also vary according to the type of asbestos fiber and are highest for crocidolite, which is now banned in many countries. Much research is in progress on man-made mineral fibers, but as yet there is no clear evidence of a carcinogenic risk to humans.<sup>92</sup>

Many of the occupational cancers listed in Table 13-16 are characterized by high relative risks and specificity of cell type. 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 mask the detection of occupational risks. The discovery of occupational hazards may also have implications beyond the workplace, since they may point to potential risks experienced at a lower level by the general public.

TABLE 13-17. Relative Risks for Oral and Pharyngeal Cancer Associated with Smoking and Drinking

Smoking Status	Number of Alcohol Drinks Per Week				
	<1	1-4	5-14	15-24	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

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

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

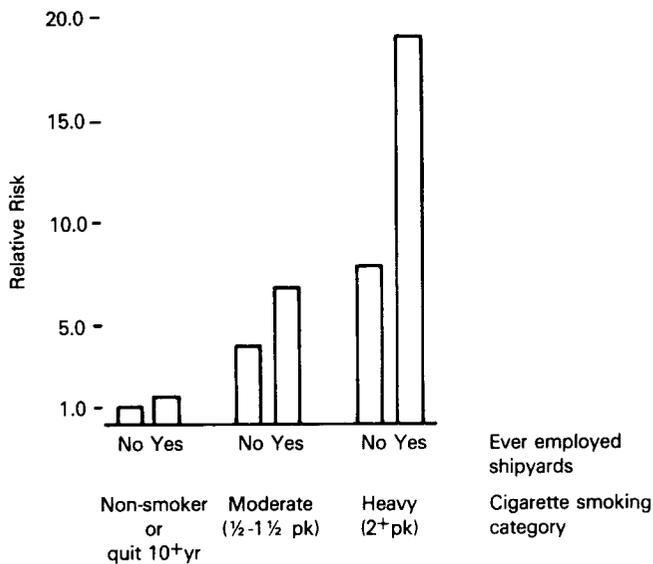


FIG. 13-7. Relative risk of lung cancer according to usual cigarette-smoking category and employment in shipyards during World War II. (Blot WJ, Harrington JM, Toledo A, et al: Lung cancer after employment in shipyards during World War II. *N Engl J Med* 299:620, 1978)

#### ENVIRONMENTAL POLLUTION

Pollutants in the urban air have long been suspected in the etiology of lung cancer, with fossil fuel combustion products, especially polycyclic hydrocarbons, being 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 following non-occupational exposures are uncertain. There are many case reports suggesting that mesotheliomas may result from neighborhood exposures to asbestos industries and from household contact with asbestos dust, perhaps through the laundering of work clothing.<sup>94</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>95</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 that cannot be explained by smoking and occupational exposures.<sup>96</sup>

There is much current interest in the role of indoor air pollution by radon gas and tobacco smoke in lung cancer etiology. In China, the high rates of lung cancer among nonsmoking women have been related to cooking oil vapors generated by wok cooking<sup>97</sup> and to effluents from coal-heating stoves.<sup>98</sup> Also under investigation are contaminants in drinking water, especially since 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>99</sup> and studies are underway to see if this risk can be confirmed and whether it extends to other cancers. 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>100</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 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 a great deal has been learned about the carcinogenic risks of radiation therapy used for many conditions, there is little firm data about risks from the lower doses of diagnostic radiation, except for a 50% increase of leukemia and other childhood cancers associated with prenatal exposures.

It has been estimated that approximately 3% of all cancer deaths may be attributed to radiation,<sup>101</sup> but the upper limit might be twice as high if certain estimates are confirmed about the risks 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>102</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>103</sup> The patterns of risk provide insights into mechanisms of carcinogenesis 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.

SOLAR RADIATION

Ultraviolet (UV) radiation from sunlight is the major risk factor for skin cancer, both squamous and basal cell carcinomas and melanoma.<sup>104</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 fairly recently described precursor state that should greatly expand opportunities for early detection and treatment.<sup>105</sup>

Since 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>106</sup> The gradient with UV-B levels was steepest for squamous cell carcinoma followed by basal cell carcinoma, and was least apparent for melanoma (Figure 13-8). These differences are consistent

with analytical studies suggesting that intermittent (recreational) exposures associated with sunburning are important in melanoma,<sup>49</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. There is no evidence so far that ground-level measures of UV-B have increased,<sup>107</sup> but recent reports of stratospheric ozone depletion have prompted concerns about future trends in skin cancer that would presumably result from increases of UV-B reaching the earth's surface. International efforts are under way to lower the production of chlorofluorocarbons (used in aerosol propellants, air conditioners, etc.) that may reduce the protective ozone layer.

MEDICATIONS

Several carcinogens included in Table 13-16 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

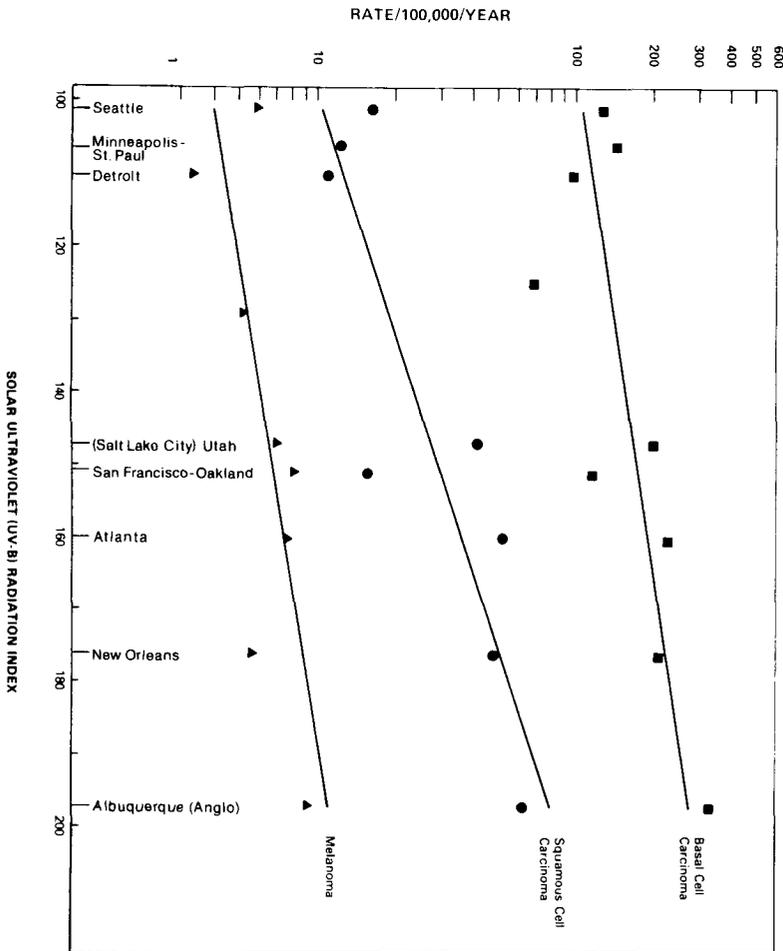


FIG. 13-8. Annual age-adjusted incidence rates for basal and squamous cell carcinomas and melanoma among white females, according to annual UV-B measurements at selected areas of the United States. (Scotto J, Fraumeni JF Jr: Skin (other than melanoma). In Schottenfeld D, Fraumeni JF Jr [eds]: Cancer Epidemiology and Prevention, p 996. Philadelphia, WB Saunders, 1982. Melanoma data are from the SEER program [1973-1976] and nonmelanoma data from a special survey [1977-1978]. Regression lines are based on exponential model.)

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>108</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>109</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>110-112</sup> Also, a relationship of pill use to invasive cervical cancer is suggested by recent studies that have controlled carefully for confounding variables such as sexual activity and screening history.<sup>70</sup> It is noteworthy that a reduced risk of endometrial and ovarian cancers has been reported with the combined oral contraceptives, especially following 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>112,113</sup>

An excess risk of acute nonlymphocytic leukemia has been noted among patients receiving alkylating agents, especially melphalan, cyclophosphamide, and chlorambucil.<sup>62</sup> Thus, the monitoring of carcinogenic risks should be part of randomized therapy trials. For example, when semustine (methyl-CCNU) was evaluated as adjuvant therapy for gastrointestinal cancer, the risks of leukemia and preleukemia were found to be elevated, with a clear dose-response relationship (Table 13-18).<sup>114,115</sup> This finding demonstrates the importance of carefully weighing risks and benefits in designing treatment regimens involving 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 very high within a few months of transplantation and remains at about the same level.<sup>116,117</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 "immunosurveil-

lance 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, and liver cancer (Table 13-19). Although the risk of post-transplant lymphoma might be influenced by antigenic stimulation by the graft, patients treated with azathioprine for other conditions have shown an approximately 10-fold excess of lymphoma.<sup>117</sup> A predominance of lymphomas has been seen also with primary immunodeficiency disorders such as ataxia-telangiectasia, Wiskott-Aldrich syndrome, and the X-linked lymphoproliferative syndrome.<sup>118</sup> For lymphomas in the latter group as well as in transplant patients, there is evidence of causation by the Epstein-Barr virus (EBV).<sup>119</sup> This finding is consistent with animal experiments, indicating that immunosurveillance primarily operates against viral-induced neoplasms.

## VIRUSES

The laboratory discovery of many different oncogenic viruses in animals has long suggested that some human cancers have a similar etiology, but convincing evidence in humans was slow to emerge until recently.<sup>120</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.

EBV is widely considered the necessary cause of endemic Burkitt's lymphoma and perhaps also nasopharyngeal cancer.<sup>121</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.

TABLE 13-18. 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
Five-year cumulative risk (%)†	0.1	0.8	1.2	1.1	2.5

Adapted from 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* 314:119, 1986.

\* 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* 53:457, 1958).

TABLE 13-19. Relative Risk of Certain Cancers in Renal Transplant Recipients in Two Major Studies (with Observed Cancers in Parentheses)

<i>Types of Cancer</i>	<i>United Kingdom-Australasian Study</i>	<i>American College of Surgeons Study*</i>
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)

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

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

† 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.

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 13-20).<sup>122</sup> It is possible that the oncogenic effects of hepatitis-B are enhanced by early-life infection and dietary exposures to aflatoxin.

The high incidence of adult T-cell leukemia in certain areas, such as Japan and the Caribbean, has been linked to infection with the human T-lymphotrophic virus type I (HTLV-I), the first retrovirus to be detected in humans.<sup>123</sup> In endemic areas the virus appears to be transmitted early in life and may also be spread by sexual activity, drug abuse, and blood transfusions.

Another human retrovirus, now called the human immunodeficiency virus (HIV), has been shown to cause the acquired immunodeficiency syndrome (AIDS).<sup>124</sup> Recognized since 1981, AIDS in the United States affects mainly homosexual men, hemophiliacs, and intravenous drug abusers, and predisposes 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 Mediterra-

nean areas has been associated with cytomegalovirus infection in some studies, but the findings in AIDS patients suggest that it is a passenger virus.

The relationship of cervical cancer to multiple sexual partners has long suggested the venereal transmission of an infectious agent. Although herpes simplex virus type 2 has been a candidate agent for some time, the chief suspect at present 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>125</sup> HPV has been isolated also from many vulvar, penile, and anal cancers, as well as 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 etiology, and statistical studies have not detected any general tendency for space-time clustering of these tumors. 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>54</sup> EBV has been suspected, since antibody levels tend to be higher in cases than controls and an increased risk of Hodgkin's disease has been reported among persons with infectious mononucleosis. However, molecular viral studies have not been supportive and the relationship with EBV may

TABLE 13-20. Deaths from Liver Disease According to Hepatitis-B Surface Antigen (HBsAg) Status on Recruitment into Study

<i>HBsAg Status</i>	<i>Cause of Death</i>		<i>Population at Risk</i>	<i>Mortality from Liver Cancer*</i>
	<i>Liver Cancer</i>	<i>Cirrhosis</i>		
Positive	40	17	3,454	1158
Negative	1	2	19,253	5
Total	41	19	22,707	181

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

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

be indirect. Despite mounting evidence for oncogenic viruses in humans, there is no 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 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>126</sup> However, the results of case-control and cohort studies have not provided strong support for the fat hypothesis.<sup>48,127,128</sup> Furthermore, no positive relationship 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 methodological difficulties in estimating 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 distinguishing fat per se from calories (since fat is more calorogenic than other nutrients). 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>50</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>112,113</sup>

Evidence is accumulating that a low intake of certain food groups may predispose to cancer, and indeed a lower consumption of green vegetables and fresh fruit has been one of the more consistent findings in dietary studies of cancer. 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>129</sup> Although the results are less consistent, there is some support from case-control studies that fiber protects against colon cancer.<sup>130</sup> However, 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 risks associated with the intake of fruits and vegetables. Several epithelial cancers, especially of the lung, show this negative relationship both in case-control studies and some cohort studies employing serologic tests; the effect has been attributed by some workers to beta-carotene.<sup>48,131</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 epidemiological studies, for example, indole compounds in cruciferous vegetables that may decrease the risk of colon cancer,<sup>132</sup> and allyl sulfide in garlic and onions that may lower the risk of gastric cancer.<sup>80</sup> The effects of vitamin E, selenium, and calcium are also under study. Furthermore, mixed or multiple deficiencies in the diet may be involved in some tumors, especially among populations with high risks of esophageal cancer.<sup>133</sup> Intervention studies are ideally suited to test the micronutrient hypotheses, and the results of several ongoing trials are awaited with interest.

A variety of 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 and more recently by a case-control study.<sup>134</sup> A relationship between salted foods and stomach cancer has been claimed in some studies,<sup>80</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>135</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 relationship. 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 very small if present at all.<sup>136</sup> Cooking practices may generate hydrocarbons or other carcinogens in the food at high temperatures, but no relevant epidemiologic data are available.

## 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 American Indians) as well as 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, however, does not exclude even large variations in individual susceptibility. Furthermore, the relatively small differences in risk between close relatives of patients with cancer and other people for childhood tumors

other than retinoblastoma are in fact consistent with large differences in genetic predisposition. The truth of this perhaps surprising statement can be demonstrated mathematically.<sup>137</sup> Only with advances in biochemical and molecular methods, however, does it seem possible to further define the impact of genetic factors or genetic-environmental interactions in cancer etiology.<sup>138</sup> For example, the phenotype associated with the rapid metabolic oxidation of certain drugs appears to influence the risk of smoking-related lung cancer,<sup>139</sup> supporting the long-held suspicion that certain persons have a higher risk of smoking-induced lung cancer than others because of genetic constitution. 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>140</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>141</sup> This does not include several constitutional cytogenetic disorders that predispose 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>66</sup> Table 13-21 lists some cancers that occur as an inherited trait (hereditary neoplasms) and Table 13-22 presents those arising as a complication of inherited precursor lesions (preneoplastic states). Included are several syndromes in which sunlight contributes to multiple skin cancers, including the dysplastic nevus syndrome predisposing to melanoma and xeroderma pigmentosum predisposing to a variety of skin cancers. Genetically determined neo-

plasms tend to occur earlier in life than other cancers of the same anatomic type and often have a multifocal origin. In addition, several common neoplasms such as breast and colon cancers show small familial risks of the order of two-fold to threefold, but among subgroups of patients with onset at young ages and bilateral or multifocal origin, the risks may be as high as 20- to 30-fold.<sup>142</sup> Some families show remarkable aggregations of site-specific cancer that appear consistent with autosomal dominant inheritance. However, 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>143</sup> In this circumstance it can be useful to consider the possibility of a 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 (the Li-Fraumeni cancer family syndrome).<sup>144,145</sup> Family members with this syndrome are prone to multiple primary cancers, including radiogenic sarcomas. Currently, molecular studies including DNA probes are attempting to understand the genetic events and biological mechanisms that may be shared by a variety of neoplasms, including breast cancer.<sup>146,147</sup> Thus, 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 thus may have consequences in cancer prevention that are at least as important as the detection of environmental carcinogens.

Table 13-21. Hereditary Neoplasms

	<i>Inheritance*</i>	<i>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.

TABLE 13-22. Hereditary Preneoplastic Syndromes

	<i>Inheritance*</i>	<i>Neoplasms</i>
<i>Phacomatoses</i>		
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	Angiomas 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
<i>Genodermatoses</i>		
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
<i>Chromosome instability</i>		
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
<i>Immune deficiency</i>		
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.

## REFERENCES

- Shimkin MB: Contrary to Nature. National Institutes of Health (NIH) Report 76-720. Washington, DC, US Government Printing Office, 1977
- Doll R: Pott and the prospects for prevention. *Br J Cancer* 32:263, 1975
- Doll R: The epidemiology of cancer. *Cancer* 45:2475, 1980
- MacMahon B, Pugh TF: *Epidemiology: Principles and Methods*. Boston, Little, Brown, 1970
- Doll R: An epidemiologic perspective of the biology of cancer. *Cancer Res* 38:3573, 1978
- Doll R, Peto R: The causes of cancer. *JNCI* 66:1191, 1981
- Schottenfeld D, Fraumeni JF Jr (eds): *Cancer Epidemiology and Prevention*. Philadelphia, WB Saunders, 1982
- Muir CS, Malhotra A: Changing patterns of cancer incidence in five continents. *Gann Monogr Cancer Res* 33:3, 1987
- Hill AB: *Principles of Medical Statistics*. New York, Oxford University Press, 1966
- Young JL Jr, Percy CL, Asire AJ (eds): *Surveillance, Epidemiology, and End Results: Incidence and Mortality Data, 1973-77*. Natl Cancer Inst Monogr 57, 1981
- Feldman AR, Kessler L, Myers MH, et al: The prevalence of cancer: Estimates based on the Connecticut Tumor Registry. *N Engl J Med* 315:1394, 1986
- Decouffe P, Thomas TL, Pickle LW: Comparison of the proportionate mortality ratio and standardized mortality ratio risk measures. *Am J Epidemiol* 111:263, 1980
- Kelsey JL, Thompson WD, Evans AS: *Methods in Observational Epidemiology*. New York, Oxford University Press, 1986
- Lilienfeld A, Pederson E, Dowd JE: *Cancer Epidemiology: Methods of Study*. Baltimore, Johns Hopkins Press, 1967

15. Gordon T, Crittenden M, Haenszel W: Cancer mortality trends in the United States, 1930-1955. *Natl Cancer Inst Monr* 6:133, 1961
16. Burbank F: Patterns in Cancer Mortality in the United States: 1950-1967. *Natl Cancer Inst Monr* 33, 1971
17. Mason TJ, McKay FW: US Cancer Mortality by County: 1950-1969. DHEW Publication No. (NIH)74-615. Washington, DC, US Government Printing Office, 1974
18. Mason TJ, McKay FW, Hoover R, et al: Atlas of Cancer Mortality for US Counties: 1950-1969. DHEW Publication No. (NIH)75-780. Washington, DC, US Government Printing Office, 1975
19. Mason TJ, McKay FW, Hoover R, et al: Atlas of Cancer Mortality among US Non-whites: 1950-1969. DHEW Publication No. (NIH)76-1204. Washington, DC, US Government Printing Office, 1976
20. Riggan WB, Van Bruggen J, Acquavella JF, et al: US Cancer Mortality Rates and Trends, 1950-1979, Vols 1-3. Publication No. EPA-600/1-83-015a. Washington, DC, US Government Printing Office, 1983
21. Pickle LW, Mason TJ, Howard N, et al: Atlas of US Cancer Mortality Rates and Trends among Whites, 1950-1980. DHHS Publication No. (NIH)87-2900. Washington, DC, US Government Printing Office, 1987
22. McKay FW, Hanson MR, Miller RW: Cancer Mortality in the United States: 1950-1977. *Natl Cancer Inst Monr* 59, 1982
23. Devesa SS, Silverman DT: Cancer incidence and mortality trends in the United States: 1935-74. *J Natl Cancer Inst* 60:545, 1978
24. Devesa SS, Silverman DT, Young JL Jr, et al: Cancer incidence and mortality trends among whites in the United States, 1947-84. *JNCI* 79:701, 1987
25. Segi M, Aoki K, Kurihara M: World cancer mortality. *Gann Monogr Cancer Res* 26:121, 1981
26. Percy C, Stanek E III, Gloeckler L: Accuracy of cancer death certificates and its effect on cancer mortality statistics. *Am J Public Health* 71:242, 1981
27. Heston JF, Kelly JB, Meigs JW, et al (eds): Forty-five Years of Cancer Incidence in Connecticut: 1935-79. *Natl Cancer Inst Monr* 70, 1986
28. Dorn HF, Cutler SJ: Morbidity from Cancer in the United States: Parts I and II. *Public Health Monogr* 56, 1959
29. Haenszel W, Marcus SC, Zimmerer EG: Cancer Morbidity in Urban and Rural Iowa. *Public Health Monogr* 37, 1956
30. Cutler SJ, Young JL Jr (eds): Third National Cancer Survey: Incidence Data. *Natl Cancer Inst Monr* 41, 1975
31. Horn JW, Asire AJ, Young JL Jr, et al (eds): SEER Program. Cancer Incidence and Mortality in the United States, 1973-81. DHHS Publication No. (NIH)85-1837. Bethesda, MD, National Institutes of Health, 1984
32. Axtell LM, Asire AJ, Myers MH: Cancer Patient Survival. Report No. 5. DHEW Publication No. (NIH)77-992. Bethesda, MD, National Institutes of Health, 1976
33. Myers MH, Hankey BF: Cancer Patient Survival Experience. NIH Publication No. (NIH)80-2148. Bethesda, MD, National Institutes of Health, 1980
34. Ries LG, Pollack ES, Young JL Jr: Cancer patient survival: Surveillance, epidemiology, and end results program, 1973-79. *JNCI* 70:693, 1983
35. Young JL Jr, Ries LG, Pollack ES: Cancer patient survival among ethnic groups in the United States. *JNCI* 73:341, 1984
36. Newell GR: Hospital- and population-based tumor registries. *Cancer Bull* 35:283, 1983
37. Silverberg E, Lubera JA: Cancer statistics, 1988. *CA* 38:5, 1988
38. Muir C, Waterhouse J, Mack T, et al: Cancer Incidence in Five Continents, Vol V. Lyon, International Agency for Research on Cancer, 1987
39. Haenszel W: Migrant studies. In Schottenfeld D, Fraumeni JF Jr (eds): *Cancer Epidemiology and Prevention*, p 194. Philadelphia, WB Saunders, 1982
40. Lilienfeld AM, Levin ML, Kessler II: *Cancer in the United States*. Cambridge, MA, Harvard University Press, 1972
41. Ziegler RG, Devesa SS, Fraumeni JF Jr: Epidemiologic patterns of colorectal cancer. In DeVita VT Jr, Hellman S, Rosenberg SA (eds): *Important Advances in Oncology* 1986, p 209. Philadelphia, JB Lippincott, 1986
42. Blot WJ, Harrington JM, Toledo A, et al: Lung cancer after employment in shipyards during World War II. *N Engl J Med* 299:620, 1978
43. Pickle LW, Correa P, Fontham E: Recent case-control studies of lung cancer in the United States. In Mizell M, Correa P (eds): *Lung Cancer: Causes and Prevention*, p 101. Deerfield Beach, FL, Verlag-Chemie International, 1984
44. Winn D, Blot WJ, Shy CM, et al: Snuff dipping and oral cancer among women in the southern United States. *N Engl J Med* 304:745, 1981
45. Hoar SK, Blair A, Holmes FF, et al: Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. *JAMA* 256:1141, 1986
46. Liu JY, Liu BQ, Li GY, et al: Atlas of cancer mortality in the People's Republic of China: An aid for cancer control and research. *Int J Epidemiol* 10:127, 1981
47. National Center for Health Statistics: *Health: United States, 1985*. DHHS Publication No. (PHS)86-1232. Washington, DC, US Government Printing Office, 1985
48. Willett WC, MacMahon B: Diet and cancer—an overview. *N Engl J Med* 310:633, 697, 1984
49. Elwood JM, Hislop TG: Solar radiation in the etiology of cutaneous malignant melanoma in Caucasians. *Natl Cancer Inst Monr* 62:167, 1982
50. Weiss NS: Epidemiology of carcinoma of the endometrium. In Lilienfeld AM (ed): *Reviews in Cancer Epidemiology*, vol 2, p 46. New York, Elsevier, 1983
51. Cramer DW: Uterine cervix. In Schottenfeld D, Fraumeni JF Jr (eds): *Cancer Epidemiology and Prevention*, p 881. Philadelphia, WB Saunders, 1982
52. Pokras R, Hufnagel VG: Hysterectomies in the United States, 1965-84. *Vital and Health Statistics. Series 13, No. 92*. DHHS Publication No. (PHS)88-1753. Washington, DC, US Government Printing Office, 1987
53. Miller RW, McKay FW: Decline in US childhood cancer mortality. *JAMA* 251:1567, 1984
54. Gutensohn N, Cole P: Epidemiology of Hodgkin's disease. *Semin Oncol* 7:92, 1980
55. Brown LM, Pottern LM, Hoover RN, et al: Testicular cancer in the United States: Trends in incidence and mortality. *Int J Epidemiol* 15:164, 1986
56. Devesa SS, Diamond EL: Association of breast cancer and cervical cancer incidences with income and education among whites and blacks. *JNCI* 65:515, 1980
57. Hutchison GB: The epidemiologic method. In Schottenfeld D, Fraumeni JF Jr (eds): *Cancer Epidemiology and Prevention*, p 3. Philadelphia, WB Saunders, 1982
58. Rothman KJ: *Modern Epidemiology*. Boston, Little, Brown, 1986
59. Cole P: The evolving case-control study. *J Chronic Dis* 32:15, 1979
60. Cole P, MacMahon B: Attributable risk percent in case-control studies. *Br J Prev Soc Med* 25:242, 1971
61. Miettinen OS: Proportion of disease caused or prevented by a given exposure, trait or intervention. *Am J Epidemiol* 99:325, 1974
62. Greene MH, Harris EL, Gershenson DM, et al: Melphalan may be a more potent leukemogen than cyclophosphamide. *Ann Intern Med* 105:360, 1986
63. Hartege P, Silverman D, Hoover R, et al: Changing cigarette habits and bladder cancer risk: A case-control study. *JNCI* 78:1119, 1987
64. Harris CC (ed): *Biochemical and Molecular Epidemiology of Cancer*. New York, Alan R. Liss, 1986
65. Perera FP, Weinstein IB: Molecular epidemiology and carcinogen-DNA adduct detection: New approaches to studies of human cancer causation. *J Chronic Dis* 35:581, 1982
66. Miller RW: Genes, syndromes, and cancer. *Pediatr Rev* 8:153, 1986
67. Miller RW: Meeting report—Rare events as clues to cancer etiology. *Cancer Res* 48:3544, 1988
68. Wald NJ, Doll R (eds): *Interpretation of Negative Epidemiological Evidence for Carcinogenicity*. IARC Scientific Publication No. 65. Lyon, International Agency for Research on Cancer, 1985
69. Sackett DL: Bias in analytic research. *J Chronic Dis* 32:51, 1979
70. Brinton LA, Huggins GR, Lehman HF, et al: Long-term use of oral contraceptives and risk of invasive cervical cancer. *Int J Cancer* 38:339, 1986
71. Hill AB: The environment and disease: Association or causation? *Proc R Soc Med* 58:295, 1965
72. Smoking and Health: Report of the Advisory Committee to the Surgeon General. Public Health Service Publication No. 1103. Washington, DC, US Government Printing Office, 1964
73. Vessey MP, Gray M (eds): *Cancer Risks and Prevention*. Oxford, Oxford University Press, 1985
74. MacClure KM, MacMahon B: An epidemiologic perspective of environmental carcinogenesis. *Epidemiol Rev* 2:19, 1980
75. International Agency for Research on Cancer: Tobacco Smoking. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol 38. Lyon, International Agency for Research on Cancer, 1986
76. McLaughlin JK, Mandel JS, Blot WJ, et al: A population-based case-control study of renal cell carcinoma. *JNCI* 72:275, 1984
77. McLaughlin JK, Blot WJ, Mandel JS, et al: Etiology of cancer of the renal pelvis. *JNCI* 71:287, 1983
78. Brinton LA, Schairer C, Haenszel W, et al: Cigarette smoking and invasive cervical cancer. *JAMA* 255:3265, 1986
79. Brinton LA, Blot WJ, Becker JA, et al: A case-control study of cancers of the nasal cavity and paranasal sinuses. *Am J Epidemiol* 119:896, 1984
80. You WC, Blot WJ, Chang YS, et al: Diet and the high risk of stomach cancer in Shandong, China. *Cancer Res* 48:3518, 1988
81. Kinlen LJ, Rogot E: Leukemia and smoking habits. *Br Med J* (in press)
82. Lubin JH, Blot WJ, Berino F, et al: Patterns of lung cancer risk according to type of cigarette smoked. *Int J Cancer* 33:569, 1984
83. International Agency for Research on Cancer: Tobacco Habits Other Than Smoking: Betel-Quid and Areca-Nut Chewing, and Some Related Nitrosamines. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol 37. Lyon, International Agency for Research on Cancer, 1985
84. Blot WJ, Fraumeni JF Jr: Passive smoking and lung cancer. *JNCI* 77:993, 1986
85. Tuyns AJ: Alcohol. In Schottenfeld D, Fraumeni JF Jr (eds): *Cancer Epidemiology and Prevention*, p 293. Philadelphia, WB Saunders, 1982
86. Rothman KJ: The proportion of cancer attributable to alcohol consumption. *Prev Med* 9:174, 1980
87. Blot WJ, McLaughlin JK, Winn DM, et al: Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Res* 48:3282, 1988
88. Jensen OM: Cancer morbidity and causes of death among Danish brewery workers. *Int J Cancer* 23:454, 1979
89. Schatzkin A, Jones DY, Hoover RN: Alcohol consumption and breast cancer in the epidemiologic follow-up study of the first National Health and Nutrition Examination Survey. *N Engl J Med* 316:1169, 1987
90. Willett WC, Stampfer MJ, Colditz GA, et al: Moderate alcohol consumption and the risk of breast cancer. *N Engl J Med* 316:1174, 1987
91. Decoufle P: Occupation. In Schottenfeld D, Fraumeni JF Jr (eds): *Cancer Epidemiology and Prevention*, p 318. Philadelphia, WB Saunders, 1982

92. Saracci R: Occupation. In Vessey MP, Gray M (eds): *Cancer Risks and Prevention*, p 99. Oxford, Oxford University Press, 1985
93. Saracci R: Asbestosis and lung cancer: An analysis of the epidemiological evidence on the asbestos-smoking interaction. *Int J Cancer* 20:323, 1977
94. Tagnon I, Blot WJ, Stroube RB, et al: Mesothelioma associated with the shipbuilding industry in coastal Virginia. *Cancer Res* 40:3875, 1980
95. Arvinli M, Baris YI: Malignant mesotheliomas in a small village in the Anatolian region of Turkey: An epidemiologic study. *JNCI* 63:17, 1979
96. Brown LM, Pottern LM, Blot WJ: Lung cancer in relation to environmental pollutants emitted from industrial sources. *Environ Res* 34:250, 1984
97. Gao YT, Blot WJ, Zheng W, et al: Lung cancer among Chinese women. *Int J Cancer* 40:604, 1987
98. Mumford JL, He XZ, Chapman RS, et al: Lung cancer and indoor air pollution in Xuan Wei, China. *Science* 235:217, 1987
99. Cantor KP, Hoover R, Hartge P, et al: Bladder cancer, drinking water source, and tap water consumption: A case-control study. *JNCI* 79:1269, 1987
100. Boice JD Jr, Fraumeni JF Jr (eds): *Radiation Carcinogenesis: Epidemiology and Biological Significance*. Progress in Cancer Research and Therapy, Vol 26. New York, Raven Press, 1984
101. Jablon S, Bailar JC III: The contribution of ionizing radiation to cancer mortality in the United States. *Prev Med* 9:219, 1980
102. National Research Council, Committee on the Biological Effects of Ionizing Radiations (BEIR) IV: *Health Risks of Radon and Other Internally Deposited Alpha-Emitters*. Washington, DC, National Academy Press, 1988
103. Boice JD Jr, Land CE: Ionizing radiation. In Schottenfeld D, Fraumeni JF Jr (eds): *Cancer Epidemiology and Prevention*, p 231. Philadelphia, WB Saunders, 1982
104. Scotto J, Fears TR, Fraumeni JF Jr: Solar radiation. In Schottenfeld D, Fraumeni JF Jr (eds): *Cancer Epidemiology and Prevention*, p 254. Philadelphia, WB Saunders, 1982
105. Greene MH, Clark WH, Tucker MA, et al: Acquired precursors of cutaneous malignant melanoma: The familial dysplastic nevus syndrome. *N Engl J Med* 312:91, 1985
106. Scotto J, Fraumeni JF Jr: Skin (other than melanoma). In Schottenfeld D, Fraumeni JF Jr (eds): *Cancer Epidemiology and Prevention*, p 996. Philadelphia, WB Saunders, 1982
107. Scotto J, Cotton G, Urbach F, et al: Biologically effective ultraviolet radiation: Surface measurements in the United States, 1974 to 1985. *Science* 239:762, 1988
108. Herbst AL, Cole P, Colton T, et al: Age incidence and risk of diethylstilbestrol-related clear cell carcinoma of the vagina and cervix. *Am J Obstet Gynecol* 128:43, 1977
109. Brinton LA, Hoover R, Fraumeni JF Jr: Menopausal oestrogens and breast cancer risk: An expanded case-control study. *Br J Cancer* 54:825, 1986
110. Key TJA, Pike MC: The role of oestrogens and progestogens in the epidemiology and prevention of breast cancer. *Eur J Cancer Clin Oncol* 24:29, 1988
111. Vessey MP: Exogenous hormones. In Vessey MP, Gray M (eds): *Cancer Risks and Prevention*, p 166. Oxford, Oxford University Press, 1985
112. Henderson BE, Ross R, Bernstein L: Estrogens as a cause of human cancer. *Cancer Res* 48:246, 1988
113. Pike MC: Endogenous hormones. In Vessey MP, Gray M (eds): *Cancer Risks and Prevention*, p 195. Oxford, Oxford University Press, 1985
114. Boice JD Jr, Greene MH, Killen JY Jr, et al: Leukemia and preleukemia after adjuvant treatment of gastrointestinal cancer with semustine (methyl-CCNU). *N Engl J Med* 309:1079, 1983
115. 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* 314:119, 1986
116. Hoover R, Fraumeni JF Jr: Risk of cancer in renal-transplant recipients. *Lancet* 2:55, 1973
117. Kinlen LJ: Immunosuppressive therapy and cancer. *Cancer Surv* 1:565, 1982
118. Filipovich AH, Spector BD, Kersey J: Immunodeficiency in humans as a risk factor in the development of malignancy. *Prev Med* 9:252, 1980
119. List AF, Greco FA, Vogler LB: Lymphoproliferative diseases in immunocompromised hosts: The role of the Epstein-Barr virus. *J Clin Oncol* 5:1673, 1987
120. Evans AS: Viruses. In Schottenfeld D, Fraumeni JF Jr (eds): *Cancer Epidemiology and Prevention*, p 364. Philadelphia, WB Saunders, 1982
121. Levine PH, Ablashi DV, Nonoyama M, et al (eds): *Epstein-Barr Virus and Human Disease*. Clifton, NJ, Humana Press, 1987
122. Beasley RP, Hwang LY, Lin CC, et al: Hepatocellular carcinoma and hepatitis B virus: A prospective study of 22,707 men in Taiwan. *Lancet* 2:1129, 1981
123. Blattner WA: Human retroviruses. In Feigin RD, Cherry JD (eds): *Textbook of Pediatric Infectious Diseases*, 2nd ed, p 1795. Philadelphia, WB Saunders, 1987
124. Goedert JJ, Blattner WA: The epidemiology and natural history of human immunodeficiency virus. In DeVita VT Jr, Hellman S, Rosenberg SA (eds): *AIDS: Etiology, Diagnosis, Treatment and Prevention*, 2nd ed. Philadelphia, JB Lippincott, 1988
125. zur Hausen H: Papillomaviruses in human cancer. *Cancer* 59:1692, 1987
126. Armstrong BK, McMichael AJ, MacLennan R: Diet. In Schottenfeld D, Fraumeni JF Jr (eds): *Cancer Epidemiology and Prevention*, p 419. Philadelphia, WB Saunders, 1982
127. Graham S: Toward a dietary prevention of cancer. *Epidemiol Rev* 5:38, 1983
128. Kinlen LJ: Fat and breast cancer. *Cancer Surv* 6:585, 1987
129. Bingham SA, Williams DRR, Cummings JH: Dietary fibre consumption in Britain: New estimates and their relation to large bowel cancer mortality. *Br J Cancer* 52:399, 1985
130. Greenwald P, Lanza E: Role of dietary fiber in the prevention of cancer. In DeVita VT Jr, Hellman S, Rosenberg SA (eds): *Important Advances in Oncology*, 1986, p 37. Philadelphia, JB Lippincott, 1986
131. Ziegler RG, Mason TJ, Stemhagen A, et al: Carotene intake, vegetables, and the risk of lung cancer among white men in New Jersey. *Am J Epidemiol* 123:1080, 1986
132. Graham S, Dayal H, Swanson M, et al: Diet in the epidemiology of cancer of the colon and rectum. *J Natl Cancer Inst* 61:709, 1978
133. Kinlen LJ: Meat and fat consumption and cancer mortality: A study of strict religious orders in Britain. *Lancet* 1:946, 1982
134. Bulatao-Jayme J, Almero EM, Castro MCA, et al: A case-control dietary study of primary liver cancer risk from aflatoxin exposure. *Int J Epidemiol* 11:112, 1982
135. Yu MC, Ho JHC, Lai SH, et al: Cantonese-style salted fish as a cause of nasopharyngeal carcinoma: Report of a case-control study in Hong Kong. *Cancer Res* 46:956, 1986
136. Hoover RN, Strasser PH: Artificial sweeteners and human bladder cancer. *Lancet* 1:837, 1980
137. Peto J: Genetic predisposition to cancer. *Banbury Report* 4:203, 1980
138. Chaganti RSK, German JL (eds): *Genetics in Clinical Oncology*. New York, Oxford University Press, 1985
139. Ayesh R, Idle JR, Ritchie JC, et al: Metabolic oxidation phenotypes as markers for susceptibility to lung cancer. *Nature* 312:169, 1984
140. Knudson AG: Hereditary cancer, oncogenes, and antioncogenes. *Cancer Res* 45:1437, 1985
141. Mulvihill JJ: Clinical genetics of pediatric cancer. In Pizzo P, Poplack DP (eds): *Principles and Practice of Pediatric Oncology*, pp 19–38. Philadelphia, JB Lippincott, 1989
142. Anderson DE: Familial predisposition. In Schottenfeld D, Fraumeni JF Jr (eds): *Cancer Epidemiology and Prevention*, p 483. Philadelphia, WB Saunders, 1982
143. Mulvihill JJ: Clinical ecogenetics: Cancer in families. *N Engl J Med* 312:1569, 1985
144. Li FP, Fraumeni JF Jr: Soft-tissue sarcomas, breast cancer, and other neoplasms: A familial syndrome? *Ann Intern Med* 71:747, 1969
145. Li FP, Fraumeni JF Jr, Mulvihill JJ, et al: A cancer family syndrome in 24 kindreds. *Cancer Res* (in press)
146. Chang EH, Pirolo KF, Zou ZQ, et al: Oncogenes in radioresistant, noncancerous skin fibroblasts from a cancer-prone family. *Science* 237:1036, 1987
147. Hansen MF, Cavenee WK: Genetics of cancer predisposition. *Cancer Res* 47:5518, 1987

APPENDIX TABLE 13-1. Average Annual Age-Specific Cancer Incidence Rates per 100,000 Population by Site, SEER Program, 1981-1985: White Males

	<5	5-9	10-14	15-19	20-24	25-29	30-34	35-39
All sites	19.9	11.7	11.8	21.2	32.3	43.0	61.9	86.3
Oral cavity and pharynx	—	0.0	0.2	0.2	0.6	0.9	2.5	3.2
Digestive system	1.2	0.2	0.1	0.4	1.1	2.1	4.8	10.0
Esophagus	—	—	—	—	—	0.0	0.1	0.2
Stomach	—	—	0.0	0.1	0.1	0.3	0.5	1.3
Small intestine	0.0	0.0	—	—	—	0.1	0.2	0.2
Colon	—	—	0.0	0.3	0.5	0.8	2.1	4.3
Rectum	—	—	—	—	0.1	0.3	0.8	1.6
Anus and anal canal	—	—	—	—	0.0	0.0	0.2	0.3
Liver	0.6	0.0	—	0.0	0.1	0.1	0.2	0.4
Gallbladder	—	—	—	—	0.0	—	0.0	0.1
Other biliary	0.0	—	—	—	0.0	0.1	0.1	0.1
Pancreas	—	—	—	0.0	0.0	0.1	0.4	1.2
Retroperitoneum	0.6	0.2	—	0.0	0.1	0.1	0.2	0.2
Respiratory system	0.4	0.1	—	0.3	0.6	0.6	2.3	8.0
Nasal cavity, sinuses, ear	0.0	0.0	—	0.0	0.0	0.0	0.1	0.3
Larynx	—	—	—	—	0.0	0.1	0.2	0.9
Lung and bronchus	—	—	—	0.2	0.2	0.4	1.8	6.3
Pleura	—	—	—	—	—	—	0.1	0.2
Bones and joints	0.1	0.7	1.3	2.1	1.0	0.7	0.7	0.5
Soft tissue	1.4	0.5	0.6	0.8	1.1	1.4	1.5	2.0
Melanoma of skin	0.1	0.0	0.1	0.9	2.4	4.6	7.9	11.6
Breast	—	—	—	—	—	0.0	0.1	0.1
Male genital system	0.6	0.2	0.2	3.4	9.5	12.6	12.1	9.9
Prostate gland	0.1	—	—	0.0	0.0	—	0.0	0.1
Testis	0.5	0.1	0.2	3.3	9.3	12.5	12.0	9.5
Penis	—	—	—	—	0.0	0.0	0.1	0.2
Urinary system	2.0	0.6	0.2	0.3	0.9	1.3	3.4	7.1
Urinary bladder	0.0	0.0	—	0.3	0.6	0.9	2.4	4.6
Kidney and renal pelvis	1.9	0.6	0.2	0.1	0.2	0.4	0.9	2.4
Ureter	—	—	—	—	—	—	0.1	0.1
Eye and orbit	1.1	0.2	0.1	0.1	0.1	0.2	0.3	0.3
Brain and nervous system	3.8	2.8	2.1	2.2	2.7	2.8	4.3	4.6
Thyroid	0.0	0.0	0.2	0.8	1.1	1.6	2.7	3.2
Other endocrine	1.3	0.2	0.2	0.3	0.3	0.2	0.2	0.4
Hodgkin's disease	—	0.9	1.4	4.3	5.5	5.3	4.4	4.1
Non-Hodgkin's lymphomas	0.8	1.6	1.8	2.1	2.0	2.7	4.0	7.6
Multiple myeloma	—	—	—	—	0.0	0.0	0.2	0.4
Leukemias	6.7	3.5	3.1	2.6	2.1	2.3	2.8	3.9
Lymphocytic leukemia	5.4	3.0	2.1	1.8	0.9	0.7	0.6	0.7
Acute lymphocytic	5.4	3.0	2.1	1.7	0.8	0.6	0.5	0.4
Chronic lymphocytic	—	—	—	—	0.0	0.0	0.0	0.3
Granulocytic leukemia	0.8	0.3	0.7	0.6	0.9	1.5	1.8	2.6
Acute granulocytic	0.4	0.2	0.4	0.4	0.4	0.9	0.9	1.7
Chronic granulocytic	0.2	—	0.1	0.2	0.4	0.5	0.7	0.8
Monocytic leukemia	0.1	—	0.0	0.1	0.1	0.0	0.1	0.1
Acute monocytic	0.1	—	0.0	0.1	0.1	0.0	0.1	0.1
Chronic monocytic	—	—	—	—	—	—	—	—
Other leukemia	0.4	0.2	0.2	0.1	0.2	0.2	0.4	0.5
Ill-defined/unknown	0.5	0.1	0.2	0.3	0.6	0.7	1.2	1.9

From the National Cancer Institute: Annual Cancer Statistics Review Including Cancer Trends 1950-1985. Bethesda, MD, 1988.

APPENDIX TABLE 13-1 (continued)

40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
137.5	239.4	436.4	782.7	1233.0	1830.3	2483.1	3101.1	3576.3	3669.4
8.2	17.9	30.9	51.0	63.8	76.4	83.7	80.5	85.9	90.0
22.6	49.3	97.1	180.9	291.2	432.1	598.6	769.6	926.6	1026.9
1.1	2.6	5.5	12.8	18.8	25.0	29.6	32.2	30.8	32.2
3.1	6.2	11.6	21.1	31.1	50.1	67.2	78.5	116.4	141.8
0.8	1.2	1.6	2.6	3.5	4.7	7.1	6.8	7.3	6.0
8.5	18.2	36.7	66.6	118.6	182.7	268.2	368.7	446.2	513.8
3.9	10.0	21.9	41.6	65.0	93.9	120.6	141.5	162.6	151.1
0.4	0.5	0.9	1.9	2.3	2.7	3.0	4.4	4.5	4.3
0.6	1.3	3.1	5.9	9.4	13.1	17.7	21.3	25.6	21.3
0.1	0.1	0.4	0.9	1.8	3.4	5.0	9.5	8.8	13.9
0.4	0.9	1.2	3.0	4.1	7.5	9.4	14.3	18.7	20.3
3.0	7.3	13.1	22.7	33.9	45.1	66.7	86.0	98.7	111.9
0.5	0.6	0.6	0.8	1.1	1.5	1.7	2.3	3.1	4.0
24.2	57.9	124.7	236.3	347.6	483.9	597.6	641.0	610.4	445.0
0.6	0.9	1.1	2.3	2.6	2.9	3.8	4.4	4.3	5.0
2.8	6.8	16.1	27.2	36.2	43.9	44.4	41.9	36.9	25.2
20.2	48.8	106.0	203.3	303.3	428.9	538.8	582.2	557.4	407.5
0.3	1.1	1.3	2.6	4.5	6.7	9.1	11.6	10.2	6.3
0.6	0.4	0.7	1.1	1.7	1.9	2.3	3.5	1.7	1.0
2.3	2.7	3.8	3.9	4.8	5.8	7.6	12.7	11.1	18.9
14.8	17.9	21.2	25.8	29.0	32.7	33.0	36.2	38.3	42.2
0.5	0.6	1.1	2.0	2.2	3.5	4.2	5.5	5.9	6.3
8.6	12.1	31.7	86.6	203.8	393.9	636.2	873.1	1069.6	1154.1
1.3	5.6	26.4	82.1	199.2	388.7	630.4	865.2	1059.4	1138.8
6.8	5.3	4.0	2.6	2.3	1.3	1.0	1.2	1.2	1.3
0.4	1.0	1.2	1.6	1.8	3.1	3.9	5.2	6.4	10.3
14.8	28.9	49.8	87.0	135.1	190.9	248.5	322.5	384.1	394.9
8.6	16.3	31.7	57.4	92.3	138.5	184.1	240.6	301.1	326.1
5.9	12.3	17.1	27.3	37.8	46.4	54.3	67.5	69.6	56.5
0.1	0.2	0.6	1.7	3.3	4.4	6.9	10.0	9.0	6.0
0.7	0.9	1.2	1.4	2.6	2.2	4.1	4.4	5.4	3.7
6.9	8.9	10.7	15.9	19.3	25.0	24.8	28.1	21.8	14.9
3.5	3.7	4.4	4.7	5.2	6.6	5.0	5.7	5.0	6.0
0.4	0.5	0.7	0.6	1.5	1.8	1.3	0.9	1.2	0.3
3.7	3.9	4.0	4.6	3.8	5.8	6.2	5.1	7.1	4.6
11.1	13.7	22.0	27.2	39.9	52.1	65.7	84.4	101.5	88.0
1.5	2.3	4.5	8.8	14.3	20.3	25.2	40.5	43.3	45.8
5.0	7.3	13.1	19.0	30.4	43.1	65.2	89.2	122.4	151.1
1.4	2.3	5.0	8.6	14.0	17.6	28.3	33.8	48.5	67.4
0.4	0.6	0.6	0.8	1.0	1.1	1.9	1.2	4.0	3.3
1.0	1.6	4.2	7.6	12.6	15.7	25.6	31.3	43.1	60.8
2.4	3.4	5.4	7.0	10.5	17.8	24.5	39.0	53.5	60.1
1.4	2.2	3.3	4.2	6.1	10.7	14.8	23.4	29.6	32.5
0.8	1.1	1.6	2.5	3.3	5.5	8.0	12.2	16.8	21.6
0.1	0.3	0.4	0.4	1.0	1.2	0.8	2.4	4.0	3.3
0.1	0.2	0.3	0.2	0.8	1.1	0.6	1.9	3.1	2.3
—	0.0	—	0.0	0.2	0.1	—	0.3	—	0.3
1.1	1.2	2.2	3.0	4.9	6.4	11.5	13.9	16.3	20.3
3.2	6.2	11.7	23.6	34.1	49.5	69.2	91.1	128.5	164.7

APPENDIX TABLE 13-2. Average Annual Age-Specific Cancer Incidence Rates per 100,000 Population by Site, SEER Program, 1981-1985: White Females

	<5	5-9	10-14	15-19	20-24	25-29	30-34	35-39
All sites	17.4	9.6	10.7	19.3	28.5	53.5	91.1	154.7
Oral cavity and pharynx	0.0	0.2	0.2	0.5	0.3	0.7	1.4	2.1
Digestive system	1.0	0.0	0.3	0.3	0.8	1.6	4.0	8.7
Esophagus	—	—	—	—	—	0.0	—	0.0
Stomach	—	—	—	0.1	0.0	0.1	0.4	1.1
Small intestine	—	—	—	0.0	0.1	0.0	0.1	0.3
Colon	—	—	0.1	0.1	0.3	0.6	1.7	3.9
Rectum	—	—	—	0.1	0.2	0.2	0.8	1.7
Anus and anal canal	—	—	—	—	—	0.0	0.1	0.2
Liver	0.5	—	0.2	0.1	0.1	0.3	0.2	0.3
Gallbladder	—	—	—	—	—	—	—	0.1
Other biliary	—	—	—	—	—	0.0	0.1	0.1
Pancreas	0.0	—	—	0.0	0.0	0.1	0.4	0.8
Retroperitoneum	0.4	0.0	0.0	—	0.0	0.1	0.1	0.2
Respiratory system	0.4	0.1	0.1	0.2	0.3	0.8	1.6	5.9
Nasal cavity, sinuses, ear	0.1	0.1	—	0.0	0.0	0.1	0.1	0.3
Larynx	—	—	—	—	0.0	0.1	0.1	0.3
Lung and bronchus	—	—	0.1	0.1	0.2	0.6	1.3	5.3
Pleura	—	—	—	—	0.0	—	0.0	—
Bones and joints	0.2	0.7	1.2	1.1	0.5	0.5	0.4	0.3
Soft tissue	1.6	0.3	0.6	1.0	0.8	0.8	1.1	1.4
Melanoma of skin	0.0	0.1	0.1	1.5	3.5	7.8	11.8	14.1
Breast	—	—	—	0.1	0.9	8.0	26.1	66.0
Female genital system	0.1	0.2	0.7	1.9	4.7	12.3	19.8	28.0
Cervix uteri	0.0	—	—	0.3	2.0	7.6	11.8	14.0
Corpus and uterus, NOS	—	0.0	0.0	0.1	0.1	0.6	2.5	5.9
Ovary	—	0.1	0.6	1.3	1.9	3.3	4.3	7.0
Vagina	0.1	—	—	—	0.2	0.2	0.2	0.2
Vulva	0.0	—	0.0	0.0	0.2	0.2	0.5	0.7
Urinary system	1.9	0.7	0.1	0.3	0.2	0.7	1.3	2.9
Urinary bladder	0.0	0.0	—	0.2	0.1	0.4	0.5	1.5
Kidney and renal pelvis	1.9	0.7	0.1	0.1	0.1	0.3	0.7	1.3
Ureter	—	—	—	—	—	—	0.0	—
Eye and orbit	1.3	0.2	0.1	0.0	0.0	0.2	0.3	0.2
Brain and nervous system	2.9	2.7	1.7	1.7	1.6	2.7	3.0	3.7
Thyroid	—	0.2	0.9	2.6	5.9	8.5	9.3	9.1
Other endocrine	1.0	0.3	0.1	0.1	0.1	0.1	0.2	0.2
Hodgkin's disease	—	0.2	1.4	4.6	5.4	4.9	3.8	2.6
Non-Hodgkin's lymphomas	0.2	0.2	0.4	1.0	1.2	1.7	3.0	3.6
Multiple myeloma	—	—	—	—	—	—	0.1	0.4
Leukemias	6.1	3.3	2.3	2.1	1.6	1.5	2.6	3.0
Lymphocytic leukemia	5.2	2.9	1.5	0.9	0.5	0.3	0.4	0.7
Acute lymphocytic	5.2	2.8	1.5	0.9	0.5	0.3	0.4	0.4
Chronic lymphocytic	—	—	—	—	—	—	0.1	0.3
Granulocytic leukemia	0.5	0.3	0.6	0.9	0.9	1.0	1.7	1.9
Acute granulocytic	0.5	0.2	0.4	0.7	0.5	0.7	1.0	1.3
Chronic granulocytic	0.0	—	0.2	0.2	0.2	0.3	0.4	0.5
Monocytic leukemia	0.2	—	0.1	0.1	0.0	0.1	0.2	0.1
Acute monocytic	0.2	—	0.1	0.1	0.0	0.1	0.1	0.1
Chronic monocytic	—	—	—	—	—	—	—	—
Other leukemia	0.2	0.1	0.1	0.2	0.2	0.1	0.3	0.3
Ill-defined/unknown	0.4	0.1	0.2	0.2	0.2	0.2	0.9	1.8

From the National Cancer Institute: Annual Cancer Statistics Review Including Cancer Trends 1950-1985. Bethesda, MD, 1988.

APPENDIX TABLE 13-2 (continued)

40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
247.4	394.4	549.5	761.4	1029.1	1256.6	1475.3	1644.8	1827.9	1876.0
3.3	7.7	11.7	19.6	26.4	30.1	28.1	28.6	27.8	29.5
18.8	39.5	75.3	121.2	185.5	272.7	388.0	524.6	655.2	729.4
0.2	0.6	2.0	4.0	6.5	7.4	8.9	11.1	12.4	13.3
1.5	3.1	5.4	7.6	12.9	17.5	27.8	42.6	54.7	68.1
0.3	1.1	1.4	2.0	2.0	2.8	3.6	4.4	5.8	5.4
8.5	18.3	34.7	57.7	86.7	136.4	193.4	278.7	346.9	390.1
4.0	8.7	16.7	26.2	37.2	50.5	70.8	82.6	97.6	106.0
0.5	0.9	2.0	2.6	3.2	4.0	4.7	4.5	6.7	5.1
0.6	0.5	1.6	2.2	3.1	4.0	6.5	7.9	8.7	10.5
0.4	0.5	1.6	2.3	4.3	6.6	9.7	14.0	19.0	21.8
0.3	0.4	1.5	1.3	3.3	4.3	6.9	9.4	13.7	14.0
2.0	4.4	7.7	13.8	24.2	36.8	52.3	63.5	84.7	88.1
0.2	0.4	0.3	0.6	1.0	0.8	1.1	2.6	1.4	1.2
17.0	37.3	70.5	111.2	153.8	181.2	189.6	159.9	137.6	98.0
0.3	0.5	0.9	0.8	1.8	1.6	1.8	2.5	2.6	1.7
0.8	2.5	3.6	5.1	7.0	8.3	7.3	5.3	3.6	2.5
15.6	33.9	65.7	104.3	144.4	169.6	178.9	150.2	128.7	92.7
0.3	0.1	0.2	0.6	0.5	1.1	1.3	1.6	2.2	0.4
0.3	0.5	0.5	0.5	1.2	1.4	1.5	1.3	2.5	1.7
1.8	1.2	2.1	2.8	3.9	4.5	5.0	5.1	9.3	7.6
14.5	16.7	17.1	18.1	17.7	16.0	18.4	19.3	21.4	22.0
114.5	174.0	201.2	252.0	303.9	344.3	372.0	389.0	400.3	395.0
40.6	65.9	95.1	129.1	184.4	202.7	207.1	190.9	176.9	161.0
14.3	15.0	14.9	16.2	17.2	17.2	17.3	16.8	16.1	19.0
12.1	25.8	47.0	70.9	109.2	123.1	118.9	99.9	82.1	64.1
12.3	21.9	29.3	36.0	49.9	53.2	58.1	55.2	55.6	49.4
0.6	0.8	0.6	1.5	2.2	1.9	2.8	4.0	5.1	5.8
0.8	1.5	2.4	2.6	3.4	5.3	7.7	12.2	15.5	20.1
6.2	11.5	16.6	27.0	43.4	56.6	73.3	89.7	105.3	110.1
2.9	5.9	9.1	14.6	25.6	32.8	46.1	55.1	72.1	82.7
3.4	5.4	7.0	11.5	16.1	21.4	23.4	29.6	28.3	23.0
—	0.1	0.2	0.7	1.0	1.6	2.7	3.4	3.1	2.7
0.6	0.9	0.5	1.7	1.4	2.8	2.5	2.1	2.0	2.1
4.5	4.9	8.8	9.7	13.5	17.0	16.5	16.8	16.1	6.9
9.3	9.4	9.2	8.7	9.3	7.9	9.4	7.0	9.0	6.3
0.3	0.2	0.7	0.7	1.0	0.8	1.3	0.7	0.8	0.3
1.7	1.4	2.0	2.2	2.8	3.1	4.3	4.4	3.9	3.4
6.5	9.6	15.1	22.6	30.1	38.8	53.3	66.0	68.9	66.0
0.7	1.6	3.7	5.2	9.8	14.7	19.2	24.3	29.1	28.5
3.3	5.1	7.5	11.1	15.0	24.1	32.1	41.5	62.3	75.8
0.9	1.3	2.4	3.5	6.3	10.0	14.0	17.7	24.8	32.4
0.6	0.5	0.4	0.3	0.5	0.7	0.6	1.4	1.3	1.7
0.3	0.7	1.9	3.1	5.4	9.2	12.7	15.4	22.0	28.6
1.8	3.1	3.9	5.6	6.5	10.2	14.5	17.7	25.3	28.9
1.0	1.7	2.6	3.8	4.1	6.6	9.2	10.2	14.3	16.1
0.6	1.2	1.2	1.4	1.7	2.5	3.9	5.7	7.6	9.3
0.2	0.2	0.2	0.4	0.4	0.7	0.4	0.8	1.9	2.1
0.1	0.2	0.2	0.3	0.3	0.6	0.4	0.7	1.2	1.0
0.0	—	—	—	0.0	—	—	—	0.5	0.5
0.5	0.5	0.9	1.5	1.9	3.2	3.1	5.4	10.3	12.4
2.8	6.1	11.3	16.9	25.0	36.2	51.6	70.3	94.1	127.2

APPENDIX TABLE 13-3. Average Annual Age-Specific Cancer Incidence Rates per 100,000 Population by Site, SEER Program, 1981-1985: Black Males

	<5	5-9	10-14	15-19	20-24	25-29	30-34	35-39
All sites	10.7	8.4	9.9	14.4	18.3	22.2	43.8	75.5
Oral cavity and pharynx	0.4	0.2	0.7	0.5	0.9	0.7	3.7	8.7
Digestive system	0.2	0.4	0.2	0.2	0.5	2.9	7.9	14.0
Esophagus	—	—	—	—	—	0.2	0.8	1.1
Stomach	—	—	—	—	—	0.2	0.4	3.4
Small intestine	—	—	—	—	—	0.4	—	0.3
Colon	—	—	0.2	0.2	0.2	0.9	2.9	5.6
Rectum	—	—	—	—	—	0.9	1.2	1.1
Anus and anal canal	—	—	—	—	—	—	—	—
Liver	—	0.2	—	—	0.4	0.4	2.1	0.8
Gallbladder	—	—	—	—	—	—	—	—
Other biliary	—	—	—	—	—	—	—	0.3
Pancreas	—	—	—	—	—	—	0.2	1.4
Retroperitoneum	0.2	0.2	—	—	—	—	0.2	—
Respiratory system	0.6	0.6	0.2	—	0.5	1.1	4.1	11.5
Nasal cavity, sinuses, ear	0.2	0.2	—	—	0.2	—	—	—
Larynx	—	—	—	—	—	—	0.6	1.1
Lung and bronchus	—	—	0.2	—	0.2	0.9	3.1	9.8
Pleura	—	—	—	—	—	0.2	—	—
Bones and joints	0.2	0.4	0.9	2.3	0.4	0.4	0.4	1.4
Soft tissue	0.7	0.2	0.7	0.5	1.1	1.6	2.3	1.4
Melanoma of skin	—	—	—	—	0.2	—	—	0.6
Breast	—	—	—	—	—	—	—	0.3
Male genital system	0.2	—	0.2	0.7	2.0	2.5	1.7	4.2
Prostate gland	—	—	—	—	—	—	—	1.4
Testis	0.2	—	—	0.5	2.0	2.5	1.4	1.7
Penis	—	—	—	—	—	—	0.2	0.3
Urinary system	2.0	1.2	0.4	0.2	0.5	1.4	2.9	3.6
Urinary bladder	—	—	—	0.2	—	0.5	0.6	1.1
Kidney and renal pelvis	2.0	1.2	0.4	—	0.5	0.7	2.3	2.5
Ureter	—	—	—	—	—	—	—	—
Eye and orbit	1.5	0.2	—	—	—	0.2	0.2	0.6
Brain and nervous system	1.7	2.5	1.4	3.1	1.1	0.7	3.1	1.4
Thyroid	—	—	—	0.4	0.4	0.4	0.6	2.2
Other endocrine	0.6	—	—	—	0.2	—	0.6	0.3
Hodgkin's disease	—	0.4	1.1	2.3	4.4	3.0	3.1	3.4
Non-Hodgkin's lymphomas	0.4	0.8	1.4	1.1	2.0	2.7	5.4	6.7
Multiple myeloma	—	—	—	—	—	—	0.6	2.2
Leukemias	2.0	1.6	2.7	2.7	3.0	2.2	2.5	5.6
Lymphocytic leukemia	1.7	1.2	1.8	1.4	—	0.2	—	1.7
Acute lymphocytic	1.7	1.0	1.8	1.4	—	0.2	—	1.1
Chronic lymphocytic	—	—	—	—	—	—	—	0.6
Granulocytic leukemia	0.2	0.4	0.9	1.1	2.3	1.8	2.5	3.4
Acute granulocytic	0.2	0.4	0.7	0.4	1.2	0.9	0.6	1.4
Chronic granulocytic	—	—	0.2	0.7	1.1	0.7	1.9	2.0
Monocytic leukemia	—	—	—	—	—	0.2	—	0.3
Acute monocytic	—	—	—	—	—	0.2	—	—
Chronic monocytic	—	—	—	—	—	—	—	0.3
Other leukemia	0.2	—	—	0.2	0.7	—	—	0.3
Ill-defined/unknown	0.4	—	—	0.2	0.5	0.5	0.4	4.2

From the National Cancer Institute: Annual Cancer Statistics Review Including Cancer Trends 1950-1985. Bethesda, MD, 1988.

APPENDIX TABLE 13-3 (continued)

40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
185.0	376.0	689.7	1182.5	1739.3	2315.5	3050.3	3294.1	4068.2	3433.6
24.1	49.6	68.3	95.1	86.2	74.7	65.8	44.8	67.9	39.3
47.9	92.1	182.8	283.7	422.4	533.5	707.1	831.6	1078.3	914.5
12.4	24.1	49.0	65.3	86.2	83.8	75.8	73.5	41.5	39.3
5.8	15.6	32.0	40.0	66.3	93.0	114.9	141.6	222.4	151.5
1.1	2.2	2.8	6.3	4.0	4.6	7.8	7.2	—	5.6
13.2	25.5	42.9	77.0	129.8	178.3	262.1	362.0	456.2	381.5
6.9	8.0	19.8	32.2	48.8	61.0	78.1	82.4	147.0	112.2
—	1.3	1.4	2.4	1.7	3.0	3.3	9.0	3.8	11.2
2.2	2.7	8.0	13.2	18.7	33.5	36.8	19.7	26.4	5.6
0.7	—	0.5	1.5	0.6	3.0	6.7	7.2	11.3	11.2
—	0.9	1.4	2.9	4.0	3.0	10.0	10.8	7.5	11.2
5.5	11.6	25.0	39.5	59.5	66.3	109.3	107.5	154.6	168.3
—	—	—	1.0	1.7	0.8	1.1	1.8	3.8	—
52.6	134.6	253.0	444.5	567.5	707.3	801.9	679.3	667.3	460.1
1.1	1.3	1.4	2.9	1.7	1.5	5.6	7.2	11.3	11.2
9.1	16.1	24.5	43.4	59.0	58.7	59.1	48.4	18.9	33.7
41.7	116.7	226.6	393.4	503.4	644.0	733.9	614.7	629.6	403.9
0.4	0.4	0.5	3.9	2.3	3.0	3.3	7.2	7.5	11.2
0.4	0.4	—	1.5	1.1	—	3.3	1.8	—	—
3.7	4.9	1.4	1.9	5.1	9.1	10.0	7.2	3.8	5.6
—	1.8	0.9	0.5	3.4	3.8	—	3.6	11.3	5.6
—	1.8	1.4	5.4	2.3	1.5	7.8	7.2	15.1	5.6
4.8	13.0	52.8	158.4	389.5	644.0	1032.8	1206.2	1583.5	1408.2
2.6	11.2	51.4	155.0	384.9	638.7	1027.2	1197.2	1576.0	1402.6
0.7	0.4	—	0.5	1.1	—	—	—	—	5.6
1.5	0.9	1.4	1.9	2.8	3.8	4.5	9.0	7.5	—
9.9	21.0	40.5	61.4	83.3	133.4	162.8	179.2	192.3	213.2
4.8	9.4	19.3	30.7	44.2	83.1	99.3	114.7	124.4	157.1
4.8	11.6	19.3	28.8	37.4	45.7	53.5	44.8	56.6	50.5
0.4	—	0.5	0.5	0.6	1.5	5.6	5.4	—	5.6
—	0.4	0.5	—	1.1	0.8	—	—	—	11.2
6.9	6.7	8.5	7.3	15.9	11.4	12.3	9.0	11.3	5.6
2.9	3.1	1.4	4.9	4.0	3.8	3.3	3.6	—	5.6
0.4	1.3	0.9	1.0	2.3	—	—	1.8	—	—
2.9	4.0	0.9	1.5	4.0	3.0	4.5	5.4	3.8	22.4
7.3	8.5	15.5	19.5	27.8	38.9	43.5	43.0	49.0	16.8
3.7	9.8	14.1	29.7	34.6	49.5	49.1	93.2	124.4	50.5
7.7	8.9	11.8	19.0	29.5	38.1	55.8	44.8	101.8	84.2
2.2	2.2	5.7	6.8	11.9	13.7	32.3	30.5	49.0	33.7
0.7	—	0.5	—	—	—	1.1	3.6	7.5	—
1.5	1.3	5.2	6.8	11.3	13.0	30.1	26.9	41.5	33.7
4.4	5.8	3.3	8.8	14.2	17.5	15.6	12.5	37.7	39.3
4.0	1.8	0.9	3.4	6.2	9.9	6.7	9.0	22.6	22.4
0.4	3.1	2.4	4.9	7.4	7.6	5.6	3.6	11.3	16.8
—	—	0.9	1.5	0.6	0.8	—	—	—	5.6
—	—	0.9	1.5	0.6	0.8	—	—	—	5.6
—	—	—	—	—	—	—	—	—	—
1.1	0.9	1.9	1.9	2.8	6.1	7.8	1.8	15.1	5.6
8.0	10.7	31.6	45.8	55.6	59.4	88.1	125.5	150.8	173.9

APPENDIX TABLE 13-4. Average Annual Age-Specific Cancer Incidence Rates per 100,000 Population by Site, SEER Program, 1981-1985: Black Females

	<5	5-9	10-14	15-19	20-24	25-29	30-34	35-39
All sites	17.2	7.7	9.3	12.3	17.1	38.5	88.1	154.3
Oral cavity and pharynx	—	—	0.5	0.7	0.5	0.3	1.1	4.1
Digestive system	1.5	—	0.2	0.5	1.0	2.7	4.8	13.9
Esophagus	—	—	—	—	—	—	0.2	1.2
Stomach	—	—	—	—	—	0.6	0.7	1.7
Small intestine	—	—	—	—	0.2	—	—	0.2
Colon	—	—	—	—	0.3	1.1	2.4	7.3
Rectum	—	—	—	—	—	0.8	0.6	1.9
Anus and anal canal	—	—	—	—	—	—	—	0.5
Liver	0.6	—	0.2	0.4	0.3	—	—	0.2
Gallbladder	—	—	—	—	—	—	—	—
Other biliary	—	—	—	0.2	—	—	—	—
Pancreas	—	—	—	—	0.2	0.2	0.7	0.7
Retroperitoneum	1.0	—	—	—	—	—	—	—
Respiratory system	—	—	—	—	0.2	0.5	1.8	6.3
Nasal cavity, sinuses, ear	—	—	—	—	—	0.2	—	—
Larynx	—	—	—	—	—	—	0.2	1.2
Lung and bronchus	—	—	—	—	—	0.2	1.5	5.1
Pleura	—	—	—	—	—	—	0.2	—
Bones and joints	0.4	0.2	0.9	0.7	0.2	0.5	0.6	0.7
Soft tissue	2.1	0.6	0.9	1.4	0.2	0.8	1.3	0.7
Melanoma of skin	—	0.2	—	—	—	—	0.4	0.5
Breast	—	—	—	—	1.5	12.2	39.8	73.0
Female genital system	0.2	0.6	1.1	2.5	6.1	12.1	21.9	32.1
Cervix uteri	—	—	—	0.7	2.6	7.6	14.7	22.1
Corpus and uterus, NOS	—	—	—	—	—	1.1	1.5	3.9
Ovary	—	0.6	1.1	1.4	2.5	2.3	4.4	4.4
Vagina	0.2	—	—	—	0.2	—	0.2	0.2
Vulva	—	—	—	—	—	0.5	0.6	1.5
Urinary system	3.3	1.0	0.5	0.9	0.8	0.5	1.5	1.2
Urinary bladder	—	—	—	0.4	0.2	0.2	0.4	0.7
Kidney and renal pelvis	3.3	1.0	0.5	0.5	0.7	0.3	0.9	0.5
Ureter	—	—	—	—	—	—	—	—
Eye and orbit	1.1	—	—	—	—	—	—	—
Brain and nervous system	2.5	2.8	1.5	0.5	1.0	1.1	1.3	1.2
Thyroid	—	—	0.2	0.5	1.8	2.7	3.9	3.9
Other endocrine	0.4	0.2	—	0.2	0.2	—	—	0.7
Hodgkin's disease	—	0.2	0.9	1.3	0.8	1.4	1.5	2.4
Non-Hodgkin's lymphomas	0.6	0.4	0.2	0.5	1.3	1.3	2.4	2.9
Multiple myeloma	—	—	—	—	—	—	0.7	1.0
Leukemias	4.8	1.4	2.0	1.6	1.5	1.3	2.0	4.4
Lymphocytic leukemia	4.2	0.8	0.5	0.4	—	0.2	0.2	0.2
Acute lymphocytic	4.2	0.8	0.5	0.4	—	0.2	0.2	—
Chronic lymphocytic	—	—	—	—	—	—	—	0.2
Granulocytic leukemia	0.2	0.4	1.1	1.1	1.3	0.8	1.7	2.9
Acute granulocytic	0.2	0.2	0.5	0.5	1.0	0.6	0.7	1.9
Chronic granulocytic	—	0.2	0.2	0.4	0.3	0.2	0.7	0.7
Monocytic leukemia	0.2	—	0.2	0.2	—	0.2	—	—
Acute monocytic	0.2	—	0.2	0.2	—	0.2	—	—
Chronic monocytic	—	—	—	—	—	—	—	—
Other leukemia	0.2	0.2	0.2	—	0.2	0.2	0.2	1.2
Ill-defined/unknown	0.4	—	0.4	0.2	—	0.3	1.5	3.9

From the National Cancer Institute: Annual Cancer Statistics Review Including Cancer Trends 1950-1985. Bethesda, MD, 1988.

APPENDIX TABLE 13-4 (continued)

40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
269.9	389.9	514.1	755.0	925.9	1102.4	1378.6	1514.7	1891.1	1695.3
8.8	17.5	21.0	29.5	22.0	16.7	19.7	16.2	12.8	14.6
31.9	60.1	99.1	162.7	230.5	328.5	466.6	523.7	736.8	697.6
3.3	7.8	15.9	17.9	24.4	21.3	19.7	11.5	19.2	14.6
2.3	7.0	7.1	13.7	19.6	34.0	51.1	61.1	108.6	124.4
1.0	1.6	3.2	2.1	3.3	5.8	9.4	4.6	4.3	4.9
13.4	21.7	37.7	72.4	105.7	156.7	229.0	259.6	347.1	309.8
4.9	7.0	13.1	24.6	28.2	46.7	51.9	70.4	80.9	78.1
2.0	1.6	2.8	3.7	4.3	2.9	5.5	1.2	10.6	7.3
—	1.2	2.4	4.2	4.8	6.9	7.9	13.8	4.3	17.1
0.3	0.8	2.0	3.7	2.9	3.5	4.7	11.5	19.2	7.3
—	—	0.8	0.4	2.4	2.9	5.5	5.8	8.5	14.6
4.2	10.1	13.5	18.3	33.5	46.7	77.9	83.1	129.9	112.2
0.7	1.2	0.4	1.2	1.0	0.6	2.4	—	2.1	—
29.3	58.6	85.6	123.2	158.3	159.1	147.9	151.1	134.2	102.4
0.3	1.2	—	0.8	1.4	0.6	1.6	—	6.4	—
2.0	5.0	8.3	7.9	10.5	8.1	6.3	5.8	6.4	—
27.1	52.0	77.3	114.0	146.3	148.7	140.1	144.2	119.3	97.6
—	0.4	—	—	—	1.7	—	1.2	—	2.4
1.0	0.4	0.4	—	1.0	0.6	—	1.2	2.1	2.4
1.6	1.9	2.8	3.3	4.3	6.9	9.4	12.7	10.6	—
—	1.2	1.2	0.8	2.9	3.5	0.8	4.6	—	9.8
114.8	149.0	158.2	209.3	223.8	244.9	307.7	305.7	389.7	302.5
46.0	53.2	75.7	108.2	141.1	155.0	183.3	205.3	215.1	231.7
31.6	29.1	33.3	34.1	34.0	41.5	51.1	56.5	59.6	87.8
7.2	9.3	19.0	38.3	63.1	68.6	77.9	73.9	89.5	85.4
4.9	11.6	17.4	27.1	35.4	35.7	40.1	56.5	38.3	39.0
0.7	1.2	2.0	3.3	3.8	5.8	8.7	5.8	14.9	9.8
1.3	1.2	2.8	2.9	3.3	—	3.9	8.1	2.1	4.9
5.9	8.5	17.4	30.4	34.9	36.9	47.2	63.4	83.1	73.2
1.0	1.2	5.9	15.0	17.7	24.2	26.8	33.5	49.0	56.1
4.6	5.8	9.5	13.3	13.9	12.1	18.9	25.4	29.8	17.1
—	—	—	—	—	—	1.6	1.2	2.1	—
0.7	—	0.4	—	0.5	—	—	—	—	—
2.6	1.2	5.2	4.2	7.7	9.8	7.9	12.7	14.9	—
6.2	7.8	5.2	8.7	5.7	5.8	8.7	1.2	6.4	12.2
—	0.8	0.4	1.2	1.0	2.3	—	—	—	—
1.0	0.4	1.2	1.7	1.4	2.3	2.4	2.3	2.1	—
3.3	8.9	7.5	13.7	18.7	32.3	30.7	36.9	38.3	34.1
3.3	4.7	11.5	13.7	18.2	26.5	44.1	47.3	63.9	46.3
3.3	4.3	6.7	10.8	21.0	21.3	29.9	48.5	42.6	56.1
—	1.2	1.6	3.7	6.2	7.5	11.8	24.2	19.2	19.5
—	0.4	0.8	0.4	0.5	1.7	0.8	—	—	—
—	0.4	0.8	3.3	5.3	5.2	11.0	23.1	17.0	14.6
2.6	2.3	5.2	5.4	10.5	11.5	13.4	16.2	17.0	22.0
2.0	1.6	3.2	2.9	6.7	5.2	4.7	9.2	10.6	12.2
0.7	0.8	2.0	2.5	3.3	4.6	7.9	5.8	6.4	9.8
—	—	—	0.4	1.0	0.6	1.6	—	—	2.4
—	—	—	0.4	1.0	0.6	1.6	—	—	—
—	—	—	—	—	—	—	—	—	—
0.7	0.8	—	1.2	3.3	1.7	3.1	8.1	6.4	12.2
9.8	8.5	14.7	31.6	32.5	50.1	70.0	80.8	138.4	112.2