Epidemiology in the Study of Cancer

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GLOSSARY

age adjustment a procedure for standardizing incidence or mortality rates with respect to a common age distribution, so as to minimize age-related biases when comparing rates over time or between two or more populations.

carcinogen adducts macromolecular complexes resulting from the chemical interaction of specific carcinogens with DNA or with proteins.

case–control study an epidemiological study that starts by identifying patients with the disease of interest (cases) and a suitable group of persons without the disease (controls). The relation between hypothesized risk factors and the disease is then studied by comparing cases and controls with respect to the distributions of exposures to the risk factors.

cohort study an epidemiological study that ascertains the distributions of exposures to hypothesized risk factors in a subset of the population (the cohort) and then correlates these distributions with the future occurrence of a disease of interest.

cross-sectional study an epidemiological study that identifies through a survey the joint distribution of a disease (or precursor lesion) and its putative risk factors in a subset of the population.

ecologic study an epidemiological study that attempts to demonstrate the relation between a risk factor and a disease of interest by analyzing populations as the units of observation. This type of study is also known as aggregate or correlational analysis.

population-based tumor registry an organization, usually affiliated with a health department or university, that collects data on all new cases of cancer occurring in the entire population of a defined geographical area, such as a city, a metropolitan area, a state, or a province.

relative risk a measure of epidemiological effect that is calculated by taking the ratio of the risk of disease (or death) among those exposed to the risk among those not exposed to the putative risk factor. It is frequently designated as risk ratio.

Cancer epidemiology is the scientific discipline that studies the occurrence of human neoplastic diseases, their risk factors, and how they are distributed in populations. Cancer epidemiology also encompasses the study of clinical outcomes in human cancer, such as disease recurrence, second tumors, and death, as well as of their determinants, the so-called prognostic factors. Well-accepted discoveries from epidemiological investigations coupled with experimental evidence from other disciplines form the mainstay of cancer prevention and have revealed, for example, the role of tobacco smoking, diet, and environmental exposures, and that of screening. In primary prevention, we are concerned with the elimination or reduction of the impact of risk factors, so that cancer risk will be reduced in populations. In secondary prevention, the focus is on early detection of cancer, its precursor lesions, or its signs, so as to reduce the morbid consequences of overt neoplastic disease. If clinically evident cancer ensues despite the latter prevention strategies, there is still a tertiary level of prevention, which concerns itself with the improvement in duration and quality of patient survival by reducing the risk of unfavorable clinical outcomes.

I. INTRODUCTION

Cancer is a group of diseases of long latency; the time elapsing from beginning of exposure to a carcinogenic insult to clinical onset of the disease may well exceed 20 years. This contrasts with the generally much shorter latency periods for infectious diseases. Another tenet in cancer epidemiology is that there are multiple causes for neoplastic diseases when one interprets cancer occurrence in populations. Cancer is frequently referred to as a group of diseases of multifactorial etiology. This also contrasts with infectious disease epidemiology, where one generally deals with one cause—the putative microbial agent—and perhaps a number of cofactors that affect the transmissibility and pathogenicity of the microorganism.

Cancer epidemiology has evolved to amalgamate the traditional role of disease surveillance, commonly referred to as descriptive epidemiology, with that of analytical epidemiology, which searches for causes and determinants of cancer occurrence and outcome. It has gradually become an interdisciplinary discipline reaping the benefits of progress in other medical specialties, as well as in statistics. From the early days of simple disease surveillance using vital statistics, cancer epidemiology has progressed by encompassing the study of etiology and prognosis of cancer with increasingly more sophisticated methods. During the 1960s and 1970s, research designs became well delineated (cohort, case–control, cross-sectional) and methods of exposure assessment using structured questionnaire-based interviews were perfected. Methods of statistical data analysis amenable to the study of disease risk given various candidate causes were developed in the 1970s (e.g., logistic and proportional hazards models). Because of their sophistication and complex, calculation-intensive nature, these methods initially enjoyed a restricted use, and only in centers equipped with mainframe computers. During the 1980s, however, the introduction of inexpensive, powerful microcomputers, permitted widespread access to these methods.

Also starting in the 1980s, there have been important developments in the biomedical sciences, particularly in molecular biology, which came to play a key role in cancer epidemiology by allowing more precise and accurate assessment of exposure and host susceptibility in field studies. Detecting DNA adducts, measuring oncogene amplification, and testing a tumor for the presence of viral DNA, to name a few of the procedures, became part of the standard set of methods used in conducting an epidemiological investigation. The latter developments also expanded the horizons of cancer epidemiology, by allowing the study not only of causes but also of their mechanisms in cancer development.

Despite the latter advances, epidemiology remains at its core the simplest and most direct way to study the causes of cancer in humans. The foundations of good epidemiological work remain the same as they were more than a century ago, namely, meticulous data collection, strong quantitative skill, and ability to reason logically across scientific disciplines.

II. DESCRIPTIVE CANCER EPIDEMIOLOGY

A. Sources of Data

The surveillance of cancer risk in populations has traditionally relied on the use of mortality statistics, as the primary widespread source of data, and on morbidity statistics from population-based tumor registries, as a secondary, more restricted source. Mortality and morbidity statistics are commonly represented as rates, expressing, respectively, the numbers of deaths or of new cases of cancer of a specified type per 100,000 population per year. Age- and sex-specific rates refer to the same calculation in a given sex and age group in the population. Because the distribution by age, which is the strongest determinant of cancer risk, varies considerably across populations, it is important that we factor out its effect when comparing rates in different regions or rates over time in the same region. This is accomplished by performing an age adjustment (also commonly referred to as age standardization) of the crude rates. Age-adjusted rates are thus the best estimates because they are not biased with respect to age.

Many countries maintain active surveillance of cancer mortality, which can be used for time trend studies and geographical comparisons. However, incidence rates represent the best epidemiological indicator of cancer occurrence because they reflect more closely the risk of disease, which allows better monitoring of the effects of changes in prevalence of risk factors and of the impact of screening and other interventions. Unfortunately, the establishment and maintenance of population-based tumor registries is an expensive and complex undertaking, which restricts the availability of morbidity data to developed countries only or to selected areas in developing countries.

For those types of cancer of low survival expectancy within a relatively short period, such as pancreas, stomach, and lung cancers, the trend in mortality rates will closely follow that of incidence rates. However, for other types of neoplasms of better prognosis, mortality and incidence rates will differ considerably. Medical progress in terms of early diagnosis and treatment, which will tend to improve the average survival expectancy for a given cancer type, will affect the temporal parallelism between incidence and mortality figures. Intercountry comparisons based on mortality rates are also affected because of geographical differences in availability of screening, distribution of cancer stages at diagnosis, and quality of medical care, conditions that influence survival directly. Nevertheless, mortality rates represent important indirect indicators of cancer occurrence and, to a certain extent, may be more useful markers of the economic burden of cancer in a population.

Population-based registries collect limited information on all new cases of cancer occurring in a given region. With few exceptions, these registries do not collect data on patient survival or on other clinical outcomes and treatment. Many large cancer treatment centers, on the other hand, do maintain tumor registries that record all relevant clinical information on patient cohorts for prognostic studies of cancer survival. However, the patient populations recorded in these so-called hospital-based registries are often not representative of the general population. Therefore, although useful in clinical epidemiology studies of cancer outcome, data from hospital-based registries need to be supplemented with those from population-based registries in studies that require an unbiased view of the distribution of risk factors in a given area.

B. The Most Frequent Types of Cancer

The International Agency for Research on Cancer (IARC), the branch of the World Health Organization dedicated to the study of cancer and situated in Lyon, France, in collaboration with the International Association of Cancer Registries, provides periodic compilations of worldwide cancer incidence from all qualified population-based registries. These compilations represent the best source of data for descriptive epidemiology studies of cancer. However, since many regions are not covered by registries, IARC investigators have used indirect estimates of incidence based on the age- and sex-specific cancer mortality in these areas to supplement the morbidity database. This method provides an overview of the worldwide burden of cancer, which allows investigators to identify high risk areas for individual types of cancer. Considering

the wide geographical variation in quality of these statistics, it is important that one treats the resulting figures as estimates.

The latest of these analyses used data for 1985 and indicated that lung cancer was the most frequent of all neoplasms (Fig. 1), accounting for approximately 12% of all incident cancer cases worldwide. It is by far the most common cancer in men, with 18% of all occurrences, but ranks fifth (6%) among all female cancers. Lung cancer risk is highest among North American males, the age-standardized rate being 74 per 100,000 men. North American women are also at high risk, with 29 new cases per 100,000 women, and lung cancer is the third most common female cancer in this region. Lung cancer rates have been increasing in most countries, a result of the pandemic of tobacco smoking among men, initiated after the First World War, and among women, accompanying the social changes in the late 1940s and 1950s.

As shown in Fig. 1, the second most common anatomic location of cancer was stomach, with about 10% of all incident cases, regardless of gender. Stomach cancer is the second most common cancer in men (12%), ranking fourth (8%) among women. It is noteworthy that stomach cancer used to be the most common cancer worldwide. In fact, it still ranks first in China, Japan, and elsewhere in Eastern Asia, in both men and women, and among men only, in tropical South America. However, gastric cancer rates have been steadily declining in most countries; between 1980 and 1985, it dropped from first to second place in rank, as lung cancer rates continued to increase globally. The decline in gastric cancer rates have been largely ascribed to the improvement of food preservation methods by wide-scale adoption of domestic refrigeration since the 1930s and 1940s. This hypothesis finds support in the prevailing theory of gastric carcinogenesis, which considers the role of bacterial induced conversion of nitrates from foodstuffs into nitrosamines, which act as carcinogens.

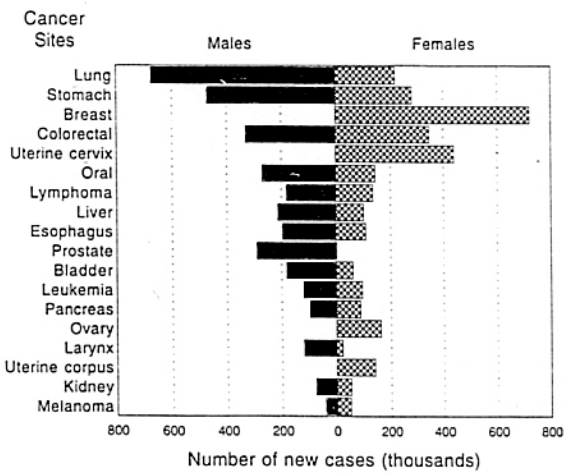

FIGURE 1 Worldwide incidence of 18 major types of cancer around 1985. Number of new cases are specified according to sex. From Parkin *et al.* (1993).

Irrespective of sex, breast cancer is the third most common human cancer worldwide (Fig. 1), with more than 700,000 new cases every year. It is, however, the most frequent female neoplasm. Colorectal cancers rank fourth (680,000 new cases annually) for both sexes combined and third in individual analyses of male and female incidence. Invasive cancer of the uterine cervix is the fifth most common human neoplasm but the second most important among women, with an estimated 440,000 new cases every year.

The incidence of the 18 sites of cancer displayed in Fig. 1 comprises nearly 85% of the combined occurrence of clinically important cancers worldwide. Missing from such a list is the incidence of nonmelanoma skin cancers, which are likely in fact to be the most common of all human neoplasms. Why is it then that such an important type of cancer has been omitted from the above analysis? The reason is that statistics on nonmelanoma skin cancers are only irregularly kept by tumor registries, because these tumors are generally diagnosed by clinical examination, and the affected persons are typically treated as outpatients. Therefore, one cannot rely on case identification through hospital inpatient registration or pathology records. As prognosis for squamous or basal cell skin cancers is excellent, with better than 95% cure rate, mortality rates are a poor indicator of the occurrence of these diseases. In the few places where adequate enumeration of cases is conducted, for example, Australia and Canada, age-adjusted rates range between 100 and 200 per 100,000 annually.

Also excluded from most cancer incidence statistics is enumeration of the so-called preinvasive or *in situ* cancers. It has become conventional in cancer epidemiology to report only on invasive cancers, which denote epithelial tumors that are advanced enough

to have spread to the adjacent connective tissue with breakage of the underlying basement membrane. For certain cancers that can be easily detected by screening, such as cervical cancer (by Pap smear screening) and breast cancer (by mammography), many cases are detected at the intraepithelial stage (intraductal, in the case of breast cancer). As these lesions are usually subclinical, they would not be detected in the absence of active screening, and thus their inclusion in cancer incidence statistics would affect comparability of data among regions differing in terms of screening coverage.

The relative importance of the 18 types of cancer analyzed varies considerably across geographical boundaries. Figure 2 shows the combined numbers of new cases of cancers in both sexes, separately for developed and developing countries, according to the IARC compilation for 1985. In developed countries, the commonest cancer site was the lung (15%), followed by the colon and rectum (13%), breast (12%), and stomach (9%). On the other hand, stomach cancer ranked first in developing countries (11%), followed by lung (9%) and cervical cancers (9%), which were nearly equal in frequency. The frequency of breast cancers (298,000) in developing nations was slightly less than that of oral cancers (301,000), which comprised the fourth most common group of neoplasms in such countries, with nearly 8% of all occurrences. Interestingly, oral cancers were of relatively lesser importance in developed countries, with only 3% of all occurrences, giving oral cancers a ranking of eighth among all clinically important neoplasms. A reverse trend is found in the occurrence of prostate cancers, which ranked fifth in importance (6%) in developed countries but represented only 2% of all cancers (fifteenth in rank) in developing countries.

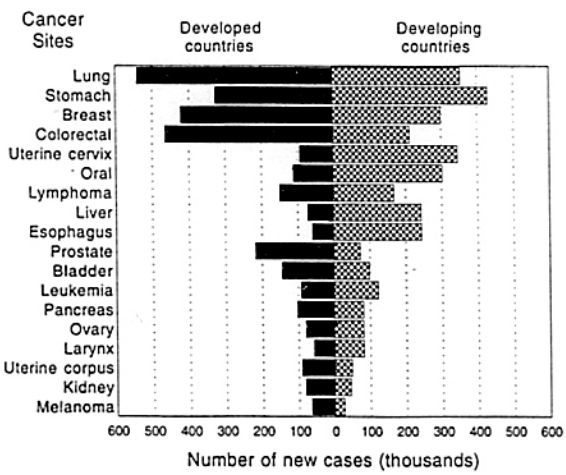

FIGURE 2 Worldwide incidence of 18 major types of cancer around 1985. Numbers of new cases for both sexes combined are shown separately for developed and developing countries. From Parkin *et al.* (1993).

C. High and Low Risk Regions

Table I shows the two highest and the two lowest risk regions and the respective sex-specific age-adjusted incidence rates for each of the 18 types of cancer presented in Figs. 1 and 2. As discussed earlier, because rates are standardized by age the differences observed cannot be accounted for by the obvious discrepancies in age distributions that exist among the various populations.

The estimated lifetime risk for developing a clinically important cancer in a high risk region such as North America is in the 25 to 35% range (nearly one in four women and one in three men), defining lifetime as being from birth to age 74. The cumulative risks of individual sites of cancer can also be high, approaching 10%, as in the case of lung cancer among men and breast cancer among women, in North America.

The incidence ratios between highest and lowest risk areas for all combined sites of cancer, including other anatomical sites not listed among the 18 shown in Figs. 1 and 2 (except nonmelanoma skin cancer), are in the 3- to 4-fold range (Table I). When we consider the individual sites of cancer, however, incidence ratios are much greater, frequently exceeding 10-fold or even approaching 100-fold differences, as in the case of skin melanoma. Such geographical variations form the basis for the widely held belief that primary and secondary prevention strategies can potentially achieve substantial reductions in cancer incidence, which would have as the upper bounds for risk reduction the very ratios discriminating highest from lowest risk regions. Evidently, such a statement implies the assumption that the only differences among the various continents or regions listed in Table I that could influence risk are related to environmental, dietary, and lifestyle causes of cancer. However, populations do differ considerably in terms of race and

TABLE I

Age-Standardized Cancer Incidence Rates[a] in High and Low Risk Regions

Cancer site	High risk regions	Incidence		Low risk regions	Incidence	
		Male	Female		Male	Female
Mouth/pharynx	Southern Asia	25.1	14.9	Western Africa	3.5	2.6
	Tropical South America	18.7	4.9	Eastern Asia, Japan	4.5	1.8
Esophagus	Southern Africa	40.7	12.1	Western Africa	1.2	1.6
	Eastern Asia, China	22.1	12.1	Central America	2.9	1.2
Stomach	Eastern Asia, Japan	74.8	35.2	Northern Africa	6.0	4.0
	Eastern Asia, other	55.0	25.3	Southern Asia	7.5	4.0
Colon/rectum	North America	48.2	36.5	Western Africa	2.5	2.5
	Oceania	45.1	35.8	Southern Asia	4.3	3.5
Liver	Eastern Asia, other	34.5	9.3	Central America	1.8	1.3
	Western Africa	22.6	7.7	Oceania	2.2	0.8
Pancreas	Eastern Europe	9.0	5.8	Western Africa	1.0	1.2
	Eastern Asia, Japan	9.1	5.2	Southern Asia	1.1	0.7
Larynx	Western Asia	15.0	2.3	Western Africa	1.5	0.2
	Northern Africa	13.3	1.8	Middle Africa	2.2	1.1
Lung	North America	73.6	28.9	Western Africa	2.5	1.1
	Northern Europe	60.5	18.7	Eastern Africa	3.8	1.3
Melanoma	Oceania	21.3	21.9	Southern Asia	0.3	0.2
	North America	9.5	8.3	Eastern Asia, other	0.3	0.3
Breast	North America		84.8	Western Africa		11.1
	Western Europe		64.7	Eastern Asia, China		14.6
Uterine cervix	Southern Africa		46.8	Western Asia		7.6
	Eastern Africa		45.6	Southern Europe		9.0
Uterine corpus	North America		18.0	Southern Asia		1.3
	Western Europe		10.9	Western Africa		1.9
Ovary	Northern Europe		12.2	Eastern Asia, other		3.0
	North America		11.8	Temperate South America		3.5
Prostate	North America	61.3		Eastern Asia, China	1.2	
	Oceania	39.7		Eastern Asia, other	2.3	
Bladder	North America	23.0	6.2	Southern Asia	2.9	0.6
	Northern Africa	21.9	6.0	Southeastern Asia	3.9	1.6
Kidney	North America	10.4	5.2	Middle Africa	1.0	0.7
	Eastern Europe	9.4	5.3	Southern Asia	1.2	0.6
Lymphoma	North America	19.4	13.7	Southern Asia	4.8	2.6
	Oceania	16.2	11.6	USSR	5.9	3.7
Leukemia	North America	10.1	6.8	Western Africa	1.3	2.6
	Oceania	9.6	6.2	Southern Asia	2.7	1.7
All sites (except skin)	North America	342.9	277.6	Western Africa	82.2	89.9
	Western Europe	306.2	226.5	Southern Asia	106.6	111.1

[a]From Parkin *et al.* (1993). Rates adjusted to the age structure of the world population.

ethnic composition, and genetic characteristics markedly influence cancer risk, both directly and indirectly, by interacting with the plethora of environmental determinants known to affect cancer risk. Also difficult to measure is the effect due to socioeconomic factors, another important element to vary across geographical regions. Although not affecting cancer incidence directly, socioeconomic characteristics play a risk factor role by their influence on the distribution of known causes of cancer in the population.

Some of the geographical risk differentials are ostensibly suggestive of the underlying causes. For instance, the elevated risk of oral cancer in India is linked to the widespread habit of betel quid chewing, and that of liver cancer in the Gambia and in China is associated with the high prevalence in these countries of chronic hepatitis B infection. High incidence rates of cervical cancer in Africa and South America are possibly linked to a combination of factors including high fertility, poor nutrition, and a low screening rate for precursor lesions.

D. Trends in North America

Neoplastic diseases represent the second leading cause of death (after heart diseases) irrespective of gender in both the United States and Canada. However, cancer ranks first among all causes when one considers the burden of disease on society on the basis of the numbers of person-years of life lost.

Cancer incidence coverage in the United States is provided by the Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute, which collects data from nine population-based registries. The SEER program has been in operation since 1973 and covers a nonrandom 10% of the country's population, which allows adequate sampling of the risk experienced by ethnic minorities in different metropolitan areas and states. Detailed information on cancer mortality by site has been available since 1930 for the whole country based on deaths reported to the U. S. Division of Vital Statistics. Trends in cancer mortality are regularly published by the American Cancer Society, in its annual Cancer Statistics series.

Figure 3 shows the mortality trends among males since 1930 for selected sites of cancer. Because rates

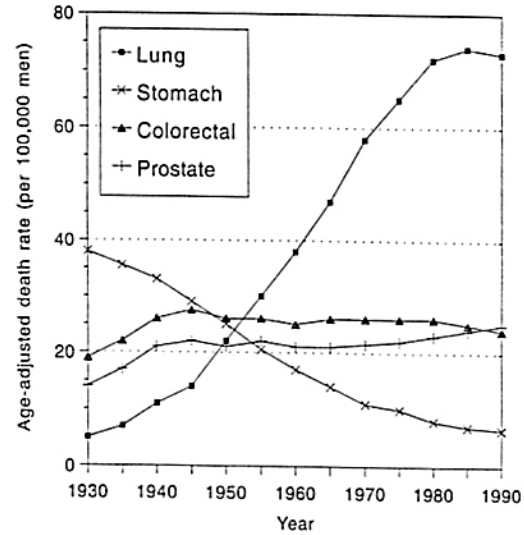

FIGURE 3 Mortality rates due to selected cancers among U.S. males since 1930. From Boring *et al.* (1993).

are adjusted for age (to the 1970 U. S. population), one need not worry about possible shifts in age distribution of the population as the underlying cause for the trends. The most remarkable feature in Fig. 3 is the marked increase in mortality from lung cancer over the past 60 years, resulting from the smoking epidemic that started around the time of the First World War. Lung cancer deaths increased 15-fold since 1930, from a position of relatively lesser importance among all neoplasms to become the most common cause of cancer death in the late 1950s. In the 1980s, more than twice as many American males died of lung cancer than from any other neoplasm. More recently, lung cancer mortality seemed to have reached a plateau, with a dampening in the rate of increase starting in 1980. It is expected that rates will actually start to decline, as a reflection of the success of smoking cessation programs, targeting men in particular, which were initiated in the late 1960s.

Also striking is the dramatic decline in gastric cancer deaths since 1930 (Fig. 3). This disease was the most common underlying cause of cancer death before 1945, with rates that were exceeded only by those of lung cancer after that time. Nowadays, cancer of the stomach is the cause of only 3% of the deaths due to neoplastic diseases. Although impossible to prove historically, it is likely that the decline of stomach cancer in the United States may be due to the univer-

sality of domestic refrigeration and improvements in agricultural distribution.

Mortality rates for colorectal and prostate cancer increased until 1945 and remained mostly constant thereafter, except for recent trends of a slight decline, for colorectal cancer, and a slight elevation, for prostate cancer (Fig. 3). Although not entirely clear, it is possible that the decrease in colorectal cancer mortality may be consequent to a combination of a falling incidence and of improved treatment results due to early detection and advances in surgery and radiotherapy. The increase in prostate cancer mortality is parallel to the increase in incidence.

Figure 4 shows the death rate trends for five of the sites of cancer with highest impact on female mortality during the past 60 years. The evolution of lung cancer rates among women is a dramatic illustration of the effects of the smoking epidemic, which started much later in the U. S. female population, after the Second World War. Lung cancer had only a small impact on female mortality before 1950. Since 1985, however, it has become the most common cause of death from neoplastic diseases, when the lung cancer death rate surpassed that of breast cancer. Since smoking cessation programs started much later among women than among men, the current levels of lung cancer mortality are still increasing as a reflection of the parallel increases in smoking prevalence among women during the liberal social changes of the 1960s and 1970s. Although smoking prevalence has declined among women (from 33 to 23% over 1974 to 1990), it will take a few more years before the effect becomes apparent in the national rates of lung cancer.

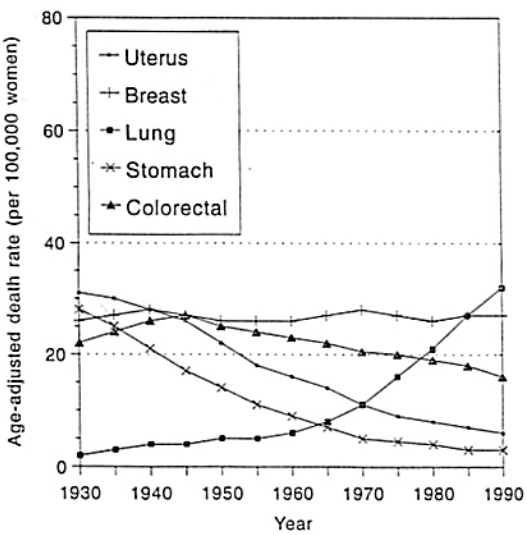

FIGURE 4 Mortality rates due to selected cancers among U.S. females since 1930. From Boring *et al.* (1993).

Considering the high expectation for the secondary preventive value of mammography screening in North America, it is somewhat surprising that breast cancer mortality has remained fairly stable since 1930 (Fig. 4). It should be emphasized, however, that the stability in death rates has persisted despite a moderate increase in breast cancer incidence for the last 20 years (about 1–2% per year). This indicates that early detection by screening coupled with improved treatment may be offsetting the excess incidence. Nevertheless, the concern still exists that the impact of screening on the reduction of mortality by breast cancer may never attain the same level of success of cervical cancer screening by cytology, where disease can in fact be arrested at a precursor lesion state before becoming invasive. For breast cancer, even detection by a sensitive screening method such as mammography fails to turn out enough very early lesions to the point of making a difference in the overall mortality. For many of the malignant breast tumors detected by screening, the increased patient survival after diagnosis may not necessarily translate into a diminished probability of death from breast cancer. This is commonly referred to as lead time bias of a screening program. The survival time stopwatch in these patients is started earlier than among those diagnosed without screening. Unless treatment can make a difference, the natural history of the disease will follow unaltered.

The gradual increase in breast cancer incidence is also evident in other Western industrialized nations. This may reflect the declining fertility rates in successive birth cohorts in these populations. Since the late 1950s, there has been a tendency for women to have fewer and fewer children and to have the first full-term pregnancies at increasingly older ages. These reproductive characteristics have been found to be associated with increased risk of breast cancer in epidemiological studies.

The same pronounced decrease seen in stomach cancer rates among men is also evident among women (Fig. 4). This disease was second only to uterine can-

cer as cause of cancer deaths in the 1930s. Gastric cancer rates in women decreased by a factor of 10 over the years 1930–1990. A similar pattern of decrease is also seen for uterine cancer. In the 1930s, the vast majority of these deaths were due to cervical cancer, which is in fact the type of uterine cancer whose incidence has been declining most conspicuously. Nowadays, about 40% of uterine cancer deaths are due to cervical carcinomas and 60% are due to endometrial cancer and other unspecified uterine cancers. The decline in cervical cancer incidence and mortality has been ascribed to the wide availability of screening by cytology in the U. S. female population. Of all secondary prevention methods in cancer, the Pap smear cytology is by far the most proven, with a definite impact in populations where screening programs have been introduced.

Colorectal cancer death rates increased until 1945 and then began to decline thereafter (except among blacks), in a consistent and gradual fashion, as a reflection of the parallel decrease in incidence and improved survival (Fig. 4). The reasons for the decrease in incidence are not clear, however, as an opposite trend has been seen in many Western countries.

Also worth mentioning is the trend for increased incidence and mortality due to skin melanoma (not shown in Figs. 3 and 4). Incidence rates have been increasing at a 4–6% annual rate among whites in the United States and Canada. This trend is likely to be consequent to an increase in intermittent sun exposure associated with recreational activities in Western countries, particularly since the 1960s.

For the most part, patterns of cancer morbidity and mortality prevailing in the United States are also seen in Canada, which has a nationwide cancer incidence reporting system covering virtually 100% of the population. Among males, mortality trends for the main sites of cancer have been the same as in the United States, except for colorectal cancer, whose constant increase in incidence among Canadian men has been largely compensated by improved survival with a consequent leveling off in mortality rates. Among women, the only remarkable difference between Canadian and U. S. patterns is with respect to the relative importance of breast and lung cancer. While beginning in the mid 1980s, lung cancer mortality in U.S. women topped that due to breast cancer, Canadian women are still on average more likely to die from breast cancer than from lung cancer. This situation will soon change, however, if present trends continue. Lung cancer deaths may become more frequent than those from breast cancer among Canadian women as early as 1994. In provinces such as British Columbia this has already happened.

E. Childhood Cancers

Excluding perinatal causes, cancer is the second most common cause of death among children under 15 years of age in the United States (after accidents) and the third in Canada (after accidents and congenital anomalies). Leukemias, lymphomas, and central nervous system tumors comprise over 50% of all childhood malignancies. Altogether, the annual cancer incidence and mortality rates are, respectively, about 15 new cases and 4 deaths per 100,000 children aged 0–14 years. Except for Hodgkin's disease, the incidence of childhood cancers has steadily increased since the mid 1970s in North America. Fortunately, the increases in incidence have been more than compensated by dramatic improvements in survival expectancy for most childhood tumors, which has caused mortality rates to decline during the same period. An American child diagnosed with cancer in 1960 had only a 28% probability of surviving 5 years, whereas the same survival expectancy was 67% in 1980.

F. Cancer Survival

Table II shows 5-year relative survival rates for cancers of selected anatomical sites, listed by race and sex for the United States and by sex for Canada. Survival expectancy varies considerably by organ affected as a result of distinct natural histories and differing degrees of treatment efficacy. The sex-specific survival rates for Canadians are closer to those among whites in the United States. Black–white and female–male differentials in survival have been the subject of intense scrutiny by epidemiologists. Racial and gender-related differences in extent of disease at diagnosis, as well as in the access to surgery, radiotherapy, and chemotherapy, may account for such survival differentials. The poor survival experience for some sites among blacks has been ascribed to socioeconomic factors,

TABLE II

Survival Expectancy[a] by Site after 5 Years Since Diagnosis of Cancer in the United States and Canada

	United States				Canada	
Anatomical site	White male	White female	Black male	Black female	Male	Female
Mouth and pharynx	52	56	27	43	58	64
Stomach	15	18	18	20	20	24
Colorectal	56	56	44	48	52	53
Pancreas	3	3	3	4	8	8
Lung	12	16	10	14	14	17
Melanoma	76	87	61	68	78	88
Female breast		78		64		73
Uterine cervix		67		57		70
Uterine corpus		84		55		86
Ovary		39		38		41
Prostate	75		62		70	
Bladder	80	75	63	49	80	74
Kidney	54	52	51	52	55	56
Brain	23	25	33	30	29	31
Lymphoma	51	52	42	49	53	52
Leukemia	35	37	28	29	39	39
All sites	47	57	33	44	46	57

[a]The 5-year relative survival rates are given as percentages. Data for the United States are from the SEER program during 1981–1986. Data for Canada are from the National Cancer Institute of Canada and refer to the province of Ontario during 1978–1987.

rather than race per se. Studies that examined the effect of socioeconomic factors after factoring out the discrepancies in stage and treatment have ruled out a prognostic effect for income or education. However, differences in survival by race seem to persist for cancers of the breast, bladder, and uterus even after controlling for disease extension and other factors.

III. EPIDEMIOLOGICAL METHODS IN STUDIES OF CANCER ETIOLOGY AND PROGNOSIS

A. Carcinogenicity Evaluation

By observing patterns of cancer occurrence in different populations and over time it is possible to formulate etiological hypotheses that can be tested in specifically designed studies, for example, the role of diet, tobacco consumption, and screening in explaining the variability in the risk of cancers of the stomach, oral cavity, and cervix. Once an etiological hypothesis is verified, however, how do we judge causality?

To obtain proof of a causal association between a risk factor and a particular cancer we have to merge the knowledge stemming from both laboratory studies and epidemiology. Whereas in the former it may be possible to prove experimentally that a given candidate substance or agent has the required carcinogenic properties, in the latter we verify whether the potential exposure to the putative carcinogen in human populations has a measurable effect in elevating risk of tumors. This is easier said than done, however, as there are hurdles in the way of designing, conducting, analyzing, and interpreting studies of carcinogenicity evaluation, both experimental and epidemiologicalal. Germane to this discussion is the definition of "cause." In a simple mechanistic sense we can define causes as being either necessary or sufficient, or both. This definition is somewhat applicable to the study of infectious diseases, where a microbial agent is a necessary

but perhaps not a sufficient cause of disease, which ensues as a result of the interplay between agent, host, and environmental factors. On the other hand, the situation is less clear for cancer, a group of diseases of multifactorial etiology, which ultimately result from the interaction between environmental (external) causes and the genetic (internal) makeup of the individual. None of the accepted causes of human cancer can be said to be necessary or sufficient.

Unlike most infectious diseases, cancer has a long latency period, which highlights the succession of time-dependent events that are necessary for normal tissue to develop into a malignant cellular proliferation and ultimately progress into clinically evident cancer. Carcinogenesis is, therefore, a multistage process where the final probability of disease development is a function of the combined probabilities of relatively rare events occurring in each stage. The likelihood of such events depends on factors related to the entry of the carcinogen into the body and to the target cells, to its metabolic activation, to binding with damage to relevant cell DNA (e.g., protooncogenes or tumor suppressor genes, or to other genes that control their function), and to the ability of the cell to repair such damage or to arrest cell division prior to repair. If the end result at this point is an initiated cell, other random events will take place before disease develops. Also to be considered as causes is the contribution of promoters that will favor cell proliferation with consequent selection of clones with malignant traits in the face of genetic (and biological) diversity of the affected tissue. Eventually, other factors will facilitate further progression of the disease to the point that tumor burden is massive enough to produce clinically manifested disease. Each one of the factors influencing the passage from one stage to the next in the above sequence contributes a causal role to cancer development, and, in theory, it should be possible to measure the effect of each cause on the overall risk of disease.

In consequence, what prevails today is an operational definition of cause, which entertains both scientific and public health issues. If sufficient evidence is obtained from epidemiological studies that are judged free of bias, then we need not await experimental proof of causality before public policy can be implemented with the aim of reducing or abolishing the exposure. Likewise, we can also provisionally accept as possible carcinogens those that have been discovered in the course of well-conducted laboratory studies, even before epidemiological observations are made to confirm that they may in fact pose a health threat to humans.

B. Study Methods

Table III lists the approaches used in evaluating a wide range of environmental carcinogens, with particular emphasis on the role of epidemiological methods. The experimental approaches outlined include the various *in vitro* assays of mutagenicity and genotoxicity using microbial probes and eukaryotic cell systems, as well as *in vivo* studies using suitable animal models. There has also been great hope for the use of computer-assisted analyses of the potential for carcinogenic properties inferred on the basis of the molecular structures of new pharmaceutical compounds. It is beyond the scope of this discussion to provide a detailed methodological account of the various study designs available today for cancer epidemiology investigations. What follows, therefore, is a brief and broad overview of the main study types.

The epidemiological methods are subdivided into two categories based on the nature of data collection, observational or experimental (Table III). Observational studies constitute the majority of all epidemiological designs. The first three designs, namely, case reports, morbidity/mortality monitoring, and ecological studies, are typically used to allow a first glance of possible exposure–cancer associations and to formulate hypotheses to be tested in further work. They are simpler to conduct since one generally uses data that have already been collected in the course of other investigations or of routine surveillance work. In ecological (or correlational) studies, we are concerned with the demonstration of a correlation between the degree of a putative exposure and cancer risk using as units of observation entire communities or even cities, states, or countries. It requires that we juxtapose two data sets, one containing the incidence or mortality rates and another containing the prevalence data on the suspected cause or a similar surrogate of the exposure. The well-studied association between subsequent cancer of the vagina in daughters of women

TABLE III
Approaches to Evaluation of Carcinogenicity and Other End Points in Natural History of Tumors

Approach	Type of data collection	Study design
Nonepidemiological	Experimental or mechanistic	*In vitro* short-term genotoxicity assays *In vivo* animal studies Structure–activity relationships
Epidemiological	Observational	Case reports Incidence/mortality monitoring Ecological studies Cross-sectional studies Case–control studies Cohort studies
	Experimental	Intervention trials Clinical trials

who took diethylstilbestrol during pregnancy or the role of diet in breast and colorectal cancers were originally proposed in case reports and ecological studies, respectively.

The greatest limitation of ecological studies is that they attempt to make inferences about exposure at the individual level on the basis of observations of entire groups—the so-called ecological fallacy. In addition, adjustment for confounders is frequently impractical or of dubious value in ecological studies. On the other hand, it is the only type of study that allows the analysis of a wider range of exposure levels on disease risk, since it can include observations from vastly different populations. Most studies using individuals as units of observation (i.e., case–control, cohort, and cross-sectional) are, by necessity, conducted in a single population, and will in consequence be restricted to a narrower range of observable exposure levels. This may be the reason why ecological studies correlating diet and cancer of the breast and colon in many countries illustrated a more clear-cut effect for dietary fat than subsequent case–control or cohort studies.

The other three observational study designs, namely, cross-sectional, case-control, and cohort (Table III), are more complex but provide a more in-depth probing of the suspected exposure–disease association. In cross-sectional studies, epidemiologists use a survey approach to identify cases of the disease and to quantify exposure to putative factors simultaneously in the population. The prevalence of the exposure in diseased subjects is then compared to that in nondiseased subjects. Cross-sectional studies are inefficient in studies of overt clinical cancer because very few cases turn out in a survey, which is completed within a relatively short period of time. It is most useful, however, in studies of precursor lesions or of intermediate endpoints, which are generally more prevalent in the population (e.g., studies of determinants of abnormal Pap smears or of cervical human papillomavirus infection in women). The caveat in cross-sectional studies is the lack of guarantee that the hypothesized exposure has in fact preceded the health event, since they are both ascertained simultaneously.

In case–control studies epidemiologists use a retrospective approach to collect data. Typically, incident cases of the disease are first identified through hospital and population-based registries. A control group consisting of cancer-free individuals is selected among inpatients of hospitals in the same area where cases were obtained or from census listings for the same geographical area. Histories of exposure to the putative risk factors are then obtained by interviewing both groups of subjects using a structured questionnaire. The interview has to be standardized to minimize biases introduced by the interviewer or by the patient (who may recall information differently depending on whether he or she is a case or a control). Relative risk (RR) estimates are then calculated by

computing the so-called exposure odds ratios for each category or intensity level of the risk factor investigated. To ensure maximum efficiency in the analysis and to avoid possible biases in the identification of risk factors, a common procedure is to match one or more controls to each case on the basis of age, sex, and/or other demographic characteristics.

In cohort studies the goal is the same, namely, to estimate the RR of disease given the exposure, but the design of the study follows a more natural prospective approach. Subjects are followed from the date of study entry, when exposure levels are ascertained, to the date of disease onset or death, or until termination of the study many years later. Incidence or death rates are calculated for the different exposure levels using as numerators the number of cases or deaths from the disease and as denominators the sum of person-years of follow-up in each stratum. The ratio between the rate for the exposed and that for the unexposed individuals is a measure of the magnitude of the association between risk factor and disease. Such a measure is known as rate ratio or risk ratio and is akin to the RR defined above for a case–control study. Cohort studies may vary depending on how they ascertain exposure and disease occurrence. Some are truly prospective in the sense that data collection takes place as events happen, whereas others follow the reconstructed cohort approach, where the study is conceived after the exposure and disease events have occurred. Many occupational epidemiology studies use the latter approach, because of the ease with which the onset of exposure in workers can be traced back in time using company records and the convenience of retrieving data on disease events by linking the exposure records to subsequent incidence or mortality databases maintained by tumor registries or health departments.

Much theoretical and empirical research has supported the notion that RR estimates obtained from case–control studies approximate those measured in cohort studies. These two research designs should be viewed as differing only with respect to the directionality and timing of data collection. Two particular variants of the classic cohort study that have become popular are the nested case–control or case–cohort designs. When the cost of ascertaining exposure is low (e.g., use of computerized company records or of self-administered questionnaires), the analysis can be extended to all subjects enrolled in the study. However, in studies of biomarkers of cancer risk requiring costly laboratory testing of biological samples, such as serum, hair, nail, or other specimens, it becomes prohibitive to obtain results in all subjects. The alternative is to store specimens indefinitely and assay only those from subjects whose outcome information is likely to be the most informative. In a cohort numbering thousands of individuals, testing would be done in all of the initial few hundred who developed cancer and only in a sample of the vast majority who remained disease-free. The sample of disease-free individuals can be randomly obtained from the cohort (case–cohort design) or matched to the cancer cases on the basis of characteristics that would help the analysis to be more efficient, for example, age, sex, and trimester of entry (nested case–control design). Acceptance of the case–control design in epidemiology comes from the demonstration that valid estimates of the RR are produced by the latter two variants of the cohort study, which in reality are nothing more than post hoc case–control analyses of data pertaining to selected cohort members.

The theory and practice of cohort and case–control studies have advanced considerably since the 1970s with the advent of statistical methods of multivariate analysis (e.g., the proportional hazards and logistic regression models) and, even more so, with the widespread use of computers for epidemiological data processing since the mid 1980s. Before these methods became available, RR estimates had to be obtained via cumbersome stratified analyses that allowed one to entertain the potential for confounding from one or two variables only. There was always the possibility that the magnitude of the estimated RR could be due to some residual secondary association between cancer risk and another confounding factor left unaccounted for in the stratification. With multivariate statistical tools it has become possible to estimate the RR for the desired exposures after adjustment by many potential confounding factors.

None of the complexities inherent to the design (e.g., matching, selection of controls) and analysis (e.g., multivariate statistics) in the previous study types exist in intervention and clinical trials (Table III). The latter two designs are the only instances

when epidemiologists can practice real experimentation with human subjects. Individuals are allocated in a random fashion to two or more groups where exposure to the intervention, clinical maneuver, or treatment is expected to vary. For instance, disease-free adults could be allocated to one of two types of diets (intervention) and be followed up for the occurrence of precursor lesions in the colon. Patients with a first cancer of the mouth can be given retinoic acid or placebo (treatment) and be compared with respect to their subsequent risks of recurrence or of second, metachronous cancers. Because assignment of group membership is random and the size of the trial is sufficiently large, one can expect that the only factor to change across groups is the actual intervention or treatment. In other words, the groups will be balanced with respect to the distributions of factors influencing the outcome, and, for this reason, the statistical analysis of the data from such trials can be rid of the complexities that are necessary only when one expects multiple confounding factors to be in operation. Besides affording the opportunity for experimental evaluation of the etiological or prognostic hypothesis, experimental trials also have the advantage of addressing the suspected cause–effect relationship in a time-coherent manner. However, other complexities exist in experimental trials. They are generally very costly because of the complex operational resources in patient management, treatment delivery, and data collection. Interestingly, whereas the randomized clinical trial has been the paradigm of study designs to advance our knowledge concerning cancer therapy, very few of the relevant etiological questions in cancer epidemiology have been addressed by intervention trials.

C. Common Framework for Research on Cancer Etiology and Prognosis

Table IV establishes the parallel between the two main axes of orientation in cancer epidemiology: etiological and clinical research. There is a common framework in terms of research architecture and statistical methodology that serves the two activities.

Traditionally, one thinks of the study of causes of cancer when describing the role of cancer epidemiology. It is on the basis of such discoveries as the roles of smoking, alcohol drinking, diet, and sunlight exposure in cancer risk that many of the current strategies for primary cancer prevention have been formulated. The goal in primary prevention is the reduction of cancer incidence. However, epidemiology also plays an important role in assessing the efficacy of secondary prevention programs, such as cancer screening, and in discovering prognostic factors of unfavorable outcomes, which forms the basis of tertiary cancer prevention. In secondary prevention, our main concern is with early detection of disease, so that neoplastic development may be arrested during the precursor lesion, preinvasive state. In tertiary prevention, the goal is the reduction of the risk of unfavorable clinical outcomes, such as recurrence and death.

In clinical epidemiological research, one is concerned with the characterization of prognostic factors that affect disease recurrence and patient survival. These prognostic factors are used to define risk categories to deliver more effective therapy and to allow appropriate surveillance of treatment failure or of disease recurrence during follow-up. More aggressive treatment may be given to those patients considered to be at higher risk of recurrence, whereas others with favorable characteristics may be spared the undesirable side effects of an aggressive regimen. Likewise, high clinical risk patients may be followed up more closely with more sensitive diagnostic workup methods, whereas low risk patients may be monitored on the basis of standard oncological schedules. It is easy to see the analogy between the latter rationale and its counterpart in etiological research, where we attempt to identify characteristics that place healthy individuals at an increased risk of cancer. Once discovered, we act on the knowledge of these characteristics to deliver risk modification programs and to target screening to high risk groups.

D. Laboratory Methods in Cancer Epidemiology

Given the above scenario for study designs, how does one measure the candidate etiologic or prognostic factors? The majority of epidemiological studies dealing with causes of cancer have resorted to questionnaire-based, structured interviews to elicit information to be analyzed as risk factors. Although

TABLE IV
Role of Epidemiology in Studies of Cancer Etiology and Prognosis

Study elements	Etiological research	Clinical research
Ultimate goal	Identify etiological factors	Identify prognostic factors
End points	Precursor lesion, cancer occurrence	Initial spread, cancer recurrence, death
Types of explanatory variables	Environmental, lifestyle, genetic, hormonal	Constitutional, stage, histopathology, treatment
Methods of study	Cohort, case–control, cross-sectional, intervention trial	Survival cohort, case–control, cross-sectional, clinical trial
Statistical analysis	Multivariate regression	Multivariate regression
Role in prevention	Primary, secondary	Tertiary, secondary

modern-day instruments for the assessment of diet and occupation are increasingly more refined and quantitative, the quality of the data is still dependent on the patient's ability to recall accurately the circumstances of the exposure. For variables such as diet, which constitutes a complex and ever-changing element in a person's life, it is exceedingly difficult to obtain an average estimate of past consumption for relevant items, and the resulting information is likely to be measured with some degree of error. Even if this error is random and of similar magnitude between cancer cases and their controls, the resulting RR estimate is most likely going to be biased toward the null hypothesis, that is, with an attenuation of the magnitude of the association between exposure and risk. Exposure mismeasurement is not always random and nondifferential, however, which complicates the exercise of predicting the direction and intensity of the resulting bias in effect estimation.

Epidemiologists have dedicated much energy to understanding the effects of misclassification in their studies and in proposing methods that attempt to mitigate the problem. Although a great deal has been produced on the statistical theory of misclassification in epidemiology, others have contributed by proposing exposure assessment methods that relied on laboratory measurements done on biological specimens. Biological markers (or biomarkers) now exist for a variety of objectives in etiological and prognostic studies, such as assessment of exposure intensity, genetic susceptibility, DNA repair capability, and immune response to tumor and viral antigens. Although far from ideal, since they seldom allow an estimate of cumulative exposure, these biomarkers have come to play an important role in epidemiological studies of cancer, particularly since the mid 1980s.

For a long time, many epidemiologists have held the belief that tumors do not contain traces of the carcinogens that caused them. This belief, which is a product of the inadequate laboratory tools of the past, has reflected on the black box nature of much of the epidemiological research on cancer. The use of biomarkers in epidemiology also stems from the need to cross interdisciplinary boundaries in cancer research. Progresses in allied scientific fields, such as molecular and cell biology and immunology, have generated crucial knowledge and a promising set of tools for the study of carcinogenesis and of the natural history of clinically overt cancer. Use of these tools in epidemiology not only helped to deal with the problem of misclassification of variables but also afforded for the first time the opportunity to probe more intimately the mechanisms of carcinogenesis and clinical progression.

Table V summarizes the most commonly used laboratory methods in cancer epidemiology. These techniques are grouped according to discipline and particular study objective. Molecular biology techniques, such polymerase chain reaction (PCR) amplification, can detect DNA sequences in host genes or in tumor viruses with high sensitivity and specificity. These techniques may eventually allow one to correlate particular carcinogenic insults with specific patterns of mutations in individual protooncogenes or tumor suppressor genes.

Use of the various biomarkers listed in Table V fills a continuum of end points in the assessment of the exposure–disease association. DNA and hemoglobin

TABLE V

Common Laboratory Techniques Used in Molecular Epidemiology Studies of Cancer Etiology and Prognosis

Field	Biomarker to be measured in specimens	Technique
Molecular biology	Specific DNA sequences (host or viral)	Southern blot hybridization, dot-blot hybridization, *in situ* hybridization, polymerase chain reaction
	Localization of specific DNA sequences in cells	*In situ* hybridization, polymerase chain reaction
	Specific RNA sequences or gene expression	Northern blot hybridization
	Allele losses or mutated forms of specific genes	Restriction fragment length polymorphism analysis, polymerase chain reaction, DNA sequencing
	Oncogene amplification	Southern blot amplification, dot-blot hybridization, polymerase chain reaction
Immunology/serology	Localization of antigenic epitopes in tissue	Immunohistochemistry
	Localization of mutated forms of gene products in cells	Immunohistochemistry
	Circulating antibodies or tumor antigens	Enzyme/radioimmunoassays
Biochemistry	Carcinogen–DNA adducts	Enzyme immunoassays, ^{32}P-postlabeling assays, fluorescence spectroscopy
	Carcinogen–protein adducts	Enzyme immunoassays, gas chromatography
	Nicotine metabolites	Enzyme immunoassays
	β-Carotene, retinol	High-performance liquid chromatography
Cytogenetics	Sister chromatid exchange	Staining and blind scoring
	Micronuclei	Staining and blind scoring
	DNA aneuploidy/hyperploidy	Flow cytometry
	Mutagen sensitivity/DNA repair capability	Bleomycin sensitivity assay, other G_2 assays
Histopathology	Grading of malignant traits in tumor tissue	Staining and blind scoring

adduct assays provide a measure of internal and biologically effective doses related to the exposure. Nucleic acid hybridization techniques can then be used to detect gene mutations, as the earliest biological effect of the exposure. Chromosomal alterations and micronuclei can be detected in the next step, as an indication that these DNA lesions have been assimilated during cell proliferation. As clinical disease becomes established, one can then analyze oncogene amplification or overexpression and tumor antigens as biomarkers of disease severity. Testing for markers of susceptibility may provide adjunct information along the latter sequence of end points.

As a result of laboratory-based etiological and prognostic research, we have begun to understand the nature of the association between cervical cancer and human papillomavirus (HPV). This virus infects the basal cells of the cervical epithelium, causing asymptomatic infections in about 20% of all sexually active women of reproductive age. A small proportion of these women will eventually harbor more persistent infections that will lead to cervical neoplasia. The HPV genome is virtually episomal (i.e., extrachromosomal) at this stage. Integration of the virus into the host genome is an important next step in the carcinogenesis. Following integration, the nuclear proteins encoded by the HPV E6 and E7 genes bind to the normal cellular proteins encoded by the p53 and Rb tumor suppressor genes. The interaction of E6 with p53 leads to the degradation of this host cell protein, with loss of its function. Since not all cervical cancers are initiated by HPV infection, we can observe the analogy of the latter mechanism to cervical carcinogenesis in the absence of HPV. Interestingly, HPV-negative tumors seem to have lost the p53 activity via a direct mutation in the gene, suggesting a carcinogenic effect similar to an environmental mutagen. Therefore, cervical tumors arising from a non-HPV-induced route would also originate via a loss of the p53 gene function but may not have necessarily the same rate of disease progression as compared to HPV-induced cancers. This could translate into dif-

ferent prognostic characteristics based on the presence of HPV in the primary tumor, which has been seen in some studies. Molecular epidemiology studies using PCR and other methods have contributed to the elucidation of the latter mechanisms, including the mode of acquisition of persistent cervical HPV infection. These methods will also be useful in verifying whether HPV-induced and HPV-independent cervical cancers are in reality arising from distinct risk factor profiles, for example, a sexually transmissible route in the former, and a relation with smoking or hormonal influences in the latter.

IV. FACTORS INFLUENCING RISK AND CLINICAL OUTCOME OF CANCER

A. Risk Factors

Table VI lists the accepted risk factors for the most frequent types of cancer. Each risk factor is presented along with the estimated magnitude of the association, given by the average RR from pertinent case–control and cohort studies. An association of high magnitude for a risk factor does not imply that the importance of the factor to society is necessarily high. The overall public health importance is gauged by the proportion of all cancers of the given type that can be attributed to the particular risk factor, a measure known in epidemiology as the population attributable risk proportion (also known as etiological fraction). To calculate this quantity we must know the prevalence of the exposure in the population and its associated RR.

Figure 5 illustrates the relation between the prevalence of the risk factor in the population and the proportion among all specified cancers that can be attributed to this factor, given various magnitudes of the causal association between exposure and disease. Consider, for instance, the magnitude of risk due to tobacco smoking in lung cancer (Table VI), which is invariably equated to relative risks of 10 and higher. Around 1965, when smoking could have influenced present-day incidence of lung cancer, approximately 40–50% of North American adults smoked, which gives us an attributable proportion in excess of 80%. As another example, consider the association between history of ulcerative colitis and colorectal cancer risk, which, as seen in Table VI, is of high magnitude (RR = 20). Ulcerative colitis is a rare clinical condition in the population, with a prevalence rate of less than 0.1%, which indicates that at most 2% of all colorectal cancers occurring in the population would be due to ulcerative colitis as a primary cause. It is easy to see also how an association of presumably low magnitude, such as that between hot maté drinking (maté is a type of tea widely consumed in southern South America) and oral cancer (RR = 1.5), can have a great regional impact on disease occurrence (Table VI). Maté is consumed by approximately 80% of all adults in parts of Southern Brazil, Uruguay, and Argentina. We can see from Fig. 5 that, at this level of exposure, about 30% of all oral cancers can be attributed to maté drinking, which makes for a sizable public health impact.

Not all factors listed in Table VI have been extensively scrutinized by carefully conducted case–control or cohort studies. Many compelling associations have been studied only by detailed case or autopsy series, ecological correlations, or small, exploratory case–control studies. Noteworthy examples are the associations between liver helminthic infection and liver cancer, malarial infection and Burkitt's lymphoma, schistosomiasis and bladder cancer, and vitamin deficiencies and esophageal cancer. In consequence, one cannot judge the degree of evidence for the latter associations as being strong or at the same level of those that are bolstered by results from in-depth epidemiological studies.

The role of genetic causes in cancer is difficult to quantify. Taken together, the occurrence of cancers in relatives of those with the disease has revealed that the contribution of inheritance to the overall incidence of cancer is low, perhaps around 5%. The importance of genetics in cancer causation is likely to be much greater, however, if one considers the interaction between environmental causes and the genetic makeup of individuals. This is the rationale for the development of biomarkers of cancer susceptibility, which are based on the assumption that normal individuals vary genetically with respect to their cellular DNA repair capability and, consequently, in their ability to respond to chemical and physical mutagens.

TABLE VI

Risk Factors for the Most Common Types of Cancer

Cancer site	Risk factor	Magnitude of risk	Degree of evidence
Lung	Tobacco smoking	+++	++
	Radon gas and decay products	+	++
	X and gamma radiation	+	++
	Asbestos	++	++
	Polycyclic aromatic hydrocarbons	+	++
	Arsenic	+	+
	Nickel and chromium compounds	+	+
	Diet low in vitamin A, β-carotene	++	+/−
	Air pollution	+	+/−
Stomach	Low socioeconomic class	++	++
	Salty, pickled, smoked foods	+	+
	Diet low in vitamins A and C	++	+/−
	Conditions leading to achlorhydria	++	++
	Blood type A	+	+
	Tobacco smoking	+	+/−
	Helicobacter pylori infection	++	+
Breast	High socioeconomic class	+	++
	Early menarche	+	++
	Late menopause	+	++
	Older age at first full-term pregnancy	++	++
	Nulliparity	+	++
	Breast cancer in first degree relatives	+++	++
	Previous breast cancer	+++	++
	History of benign proliferative disease	++	++
	Previous cancer of the endometrium or ovary	+	++
	X radiation	+	++
	High fat intake	+	+/−
	Postmenopausal obesity	+	+
	Long-term oral contraceptive use	+	+/−
	Estrogen replacement therapy	+	+/−
Colorectal	Familial adenomatous polyposis	+++	++
	History of ulcerative colitis	+++	++
	Diet low in fiber and vegetables	+	+/−
	Diet high in fat and meat	+	+/−
Uterine cervix	Low socioeconomic class	++	++
	Multiple sexual partners	++	++
	Early age at onset of sexual activity	+	+
	Cervical human papillomavirus infection	+++	++
	Tobacco smoking	++	+
	High parity	++	++
	Long-term oral contraceptive use	+	+/−
	Diet low in vitamins A and C	++	+
Mouth and pharynx[a]	Low socioeconomic class	++	++
	Tobacco smoking	+++	++
	Tobacco chewing	+++	++
	Alcohol drinking	+++	++
	Diet low in vitamins A and C	+	+
	Hot maté drinking (South America)	+	++
	Oral human papillomavirus infection	++	+/−

(*continues*)

TABLE VI—*Continued*

Cancer site	Risk factor	Magnitude of risk	Degree of evidence
Lymphomas[b]	Immunosuppression	+++	++
	Epstein-Barr virus infection (Africa)	++	++
	Malarial infection (African)	++	+/−
	Herbicide exposure	+	+/−
Liver	Chronic hepatitis virus infection (B and C)	+++	++
	Aflatoxin exposure	+	+
	Vinyl chloride (angiosarcoma)	+	++
	Alcohol drinking	+	+/−
	Tobacco smoking	+	+
	Liver fluke infestation (east Asia)	++	+
Esophagus	Low socioeconomic class	+	++
	Tobacco smoking	+++	++
	Alcohol drinking	+++	++
	Hot maté drinking (South America)	+	++
	Vitamin deficiencies	+	+
Prostate	Black race	++	++
	Diet high in fat	+	+/−
Bladder	Tobacco smoking	+++	++
	Aromatic armines	+	++
	Chlornaphazine/cyclophosphamide treatment	++	+
	Schistosoma haematobium infection	++	+
Leukemia	X and gamma radiation	+++	++
	Benzene	++	+
	Human T-cell leukemia virus 1 infection	+++	++
	Genetic abnormalities (e.g., Down syndrome)	+	+
Pancreas	Tobacco smoking	++	++
	Diabetes mellitus	+	+/−
Ovary	Nulliparity	+	++
	Early menarche	+	++
	Late menopause	+	++
	Nonuse of oral contraceptives	+	++
	Previous breast cancer	+	++
Larynx	Low socioeconomic class	++	++
	Tobacco smoking	+++	++
	Alcohol drinking	+++	++
	Asbestos	+	+
	Laryngeal papillomavirus infection	++	+/−
Uterine corpus	Nulliparity	+	++
	Early menarche	+	++
	Late menopause	+	++
	History of infertility	+	+
	Nonuse of combination oral contraceptives	+	++
	Unopposed estrogen therapy	+	++
	Obesity	+	+

(*continues*)

Continued

Cancer site	Risk factor	Magnitude of risk	Degree of evidence
Kidney	Tobacco smoking	++	++
	Obesity	+	+/−
	Heavy phenacetin analgesic use	+	+/−
	Aromatic amines	+	+/−
Melanoma	High socioeconomic class	+	+
	Ultraviolet radiation exposure	++	++
	Fair complexion skin	++	++
	Benign melanocytic nevi	++	++

[a]Except cancer of the nasopharynx.
[b]Only non-Hodgkin's lymphomas.

Some of the DNA repair deficiency syndromes would be represented in one of the extremes of the gradient of genetic instability. These syndromes, such as ataxia telangiectasia, dyskeratosis congenita, xeroderma pigmentosum, Fanconi's anemia, and Bloom's syndrome, are also known to confer a high predisposition to the development of various types of neoplasms. However, although these diseases have a clear hereditary basis, it remains to be proved that the levels of DNA repair efficiency in normal individuals also follows a hereditary pattern.

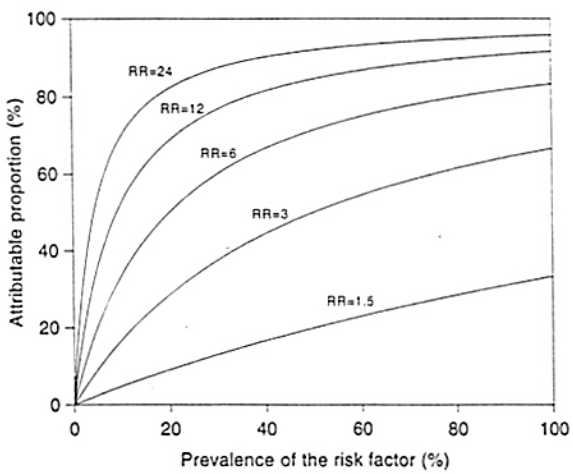

FIGURE 5 Proportions of all cancers occurring in the population that can be attributed to a given independent risk factor. The attributable proportion is estimated as a function of the prevalence of the risk factor in the population. Five different relative risk (RR) levels are assumed for the underlying magnitude of the exposure–cancer relationship.

B. Prognostic Factors

Much of the impetus in the search for prognostic factors of cancer survival came from the need to tailor therapeutic regimens to the risk of relapse anticipated for individual patients. The use of multivariate scores that subsumed the information from various prognostic factors became common during the late 1980s and early 1990s. It is hoped that such scores will allow more accurate prediction of prognosis than disease stage alone, as based on the tumor–nodes–metastasis (TNM) classification, which merely groups patients on the basis of the overall burden of disease. Since tumors will grow if left untreated, the TNM stage at diagnosis will reflect mostly the chronology of the neoplastic development, rather than its biology. Therefore, the search for prognostic factors that allow additional explanatory value with respect to survival is likely to discover markers of disease severity and rapid progression.

Constitutional factors, such as age, sex, race, and menopausal status, may play a prognostic role, depending on the site of cancer. In addition, some of the traits that are eminently linked to an aggressive neoplastic growth can be recognized histologically, such as degree of differentiation, necrosis, pleomorphism, vascular and lymphatic invasion, lymphocytic infiltrate, and mitotic grade. For breast cancers and malignant epithelial tumors in general, these characteristics may contribute independent prognostic information. For many cancer sites, regional lymph node involvement is the sole most important determinant

of survival, with a strong dose–response relation with the number of metastatic nodes.

Primary tumor cells that resemble more closely the tissue which originated them are generally associated with a less aggressive behavior. This has formed the basis for the testing of steroid hormone receptors and oncofetal antigens in tumors by biochemical and immunohistochemical techniques. More recently, there has been an active search for genetic markers of prognosis. Cancer progression is generally associated with a gain in genetic and phenotypic diversity in the primary neoplastic lesion, with consequent loss of important regulatory functions in the genome. Oncogene amplification and overexpression is an important next step. It has been hypothesized that the degree of amplification of certain oncogenes, such as c-*myc* and *erb-2–neu*, may help predict the probability of tumor recurrence. This has, in fact, been confirmed for many cancer sites, most notably in breast cancer, which is the most extensively studied of all human neoplasms.

See Also the Following Articles

BRAIN TUMORS: EPIDEMIOLOGY, MOLECULAR AND CELLULAR ABNORMALITIES; BREAST CANCER: MOLECULAR EPIDEMIOLOGY; GASTRIC CANCER: MOLECULAR AND CELLULAR ABNORMALITIES; LUNG CANCER: GENETIC EPIDEMIOLOGY; PROSTATE CANCER: EPIDEMIOLOGY.

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