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Evolution of Cancer Epidemiology

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INTRODUCTION

As the 20th century passes into history, it seems timely to reflect upon current directions and progress in epidemiologic studies of cancer. The most important legacy of cancer epidemiology to date is the general recognition that an array of exogenous exposures are responsible for most cancer occurrence (1). Evidence supporting this conclusion includes: 1) the notable variation in cancer incidence internationally, 2) migrants' and/or their descendants' frequent development of cancer rates characteristic of the new area of residence, and 3) etiologic studies demonstrating a substantial fraction of cancer arising from exogenous exposures.

An important watershed was a 1981 article by Doll and Peto estimating the proportion of US cancer deaths due to major categories of exposures (1). The two most important categories were nutritional factors (estimated to be responsible for approximately 35 percent of cancer occurrence) and tobacco use (30 percent); others included reproductive factors/sexual behavior (7 percent); occupation (4 percent); alcohol drinking (3 percent); geophysical factors, including ionizing radiation and ultraviolet radiation from sunlight (3 percent); pollution (2 percent); iatrogenic exposures (1 percent); food additives (<1 percent); industrial products (<1 percent); and other and unknown factors. In an ongoing debate, some epidemiologists have questioned the entire premise of these estimates; others proclaim their continuing accuracy, while a few suggest rigorous reevaluation at periodic intervals to direct cancer epidemiologic research priorities.

Differences as well as similarities between cancer epidemiology and other areas of epidemiology have changed over time. Prior to the second half of the 20th century, epidemiologists focused on infectious diseases, the leading cause of death for centuries before and continuing up to World War II. With the advent of effective infection control and treatment measures in the 20th century for many (but not all) infectious diseases, mortality rates declined. As the leading causes of mortality shifted from infectious diseases to chronic diseases in developed countries, epidemiologic theory and study methods evolved to feature the notion of multiple causes associated with chronic diseases. More recently, the distinctions between chronic disease epidemiology and infectious disease epidemiology have begun to blur as a growing number of infectious organisms have been etiologically linked with cancer and other chronic diseases. Blurring of the boundaries has resulted as the multicausal theory of chronic disease etiology has expanded to include not only multiple exposures leading to a given chronic disease outcome but also social, cultural, community-level, and historical factors contributing to disease determinants. Thus, the methods initially developed for epidemiologic investigation of infectious diseases and then enhanced to assess suspected risk factors for chronic diseases have been developed further, and they increasingly incorporate a combination of epidemiologic, molecular, and laboratory approaches to the evaluation of a variety of agents suspected in the etiology of chronic diseases.

This review consists of two major components. The first component examines aspects of descriptive epidemiology and methodologic issues, while the second focuses on a few important carcinogens, cancer outcomes, and cancer prevention strategies. A recurrent theme is the need for continued evolution of the thinking guiding the overall approach as well as the specific methods utilized in descriptive studies, analytical investigations, and more recently the genetic and molecular components of cancer epidemiologic studies. A second major theme is the need for ongoing dialogue between investigators in pertinent scientific disciplines and cancer epidemiologists to develop jointly effective strategies with which to maximize the scientific value of etiologic and prevention research, given limited financial resources.

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Abbreviations: HPV, human papilloma virus; SEER, Surveillance, Epidemiology, and End Results.

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Four key strategies are suggested. The first is to develop internationally agreed upon standards for population-based cancer registries. The second is to establish several types of international centralized resources (or expand the scope of activities within existing international agencies), including offices with expertise in cancer registration, cancer epidemiologic methods, and field research activities, and libraries (with both paper and electronic versions) of protocols, questionnaires, and all other types of data collection materials. Ideally, each of these resource organizations would maintain state-of-the-art web sites to provide training and research materials that could be downloaded, and message boards for questions and answers by expert consultants. The third strategy is to establish dedicated methodologic research units to improve the quality and cost-effectiveness of cancer epidemiologic studies. The fourth strategy is to move beyond closer collaboration within the limited context of classical and/or molecular epidemiology by extending etiologic investigations of a hypothesis or related hypotheses to include a carefully integrated, seamless series of epidemiologic and experimental studies that are conducted by a tightly conjoined team of epidemiologists, molecular biologists, toxicologists, and other laboratory scientists from a wide array of disciplines.

Underscored in this paper's conclusion is the need for closer collaboration among epidemiologists, an increased role for cancer epidemiologists in various aspects of risk assessment, and improved clarity of risk communication. Finally, some policy aspects of cancer epidemiology are considered, using examples described earlier in the paper. Readers can find comprehensive reviews (2–5) and alternative points of view (6–8) elsewhere. Some important issues in cancer epidemiology (such as nutritional factors and diet) that are touched upon only briefly in this paper are addressed in more detail by other authors in this volume of *Epidemiologic Reviews*. This paper presents the author's personal perspectives on challenges in cancer epidemiology.

DESCRIPTIVE EPIDEMIOLOGY

Cancer registration

Since the first population-based cancer registries were established in 1935 in Connecticut and in 1943 in Denmark, the numbers and uses of cancer registries have increased dramatically. The International Agency for Research on Cancer, a part of the World Health Organization, has assembled data from many cancer registries into an ongoing series on cancer incidence. The International Agency for Research on Cancer has also coordinated the development of specialized, standardized classification systems for adult (9, 10) and childhood (11) cancers. These efforts and the requirements for inclusion in *Cancer Incidence in Five Continents* (12) have improved the quality of cancer registration worldwide, and increasingly permit comparisons of incidence (13) and time trends (14) among populations.

Cancer incidence in the United States was initially estimated in population-based surveys during 1947–1950 (15) and 1969–1971 (16). Since 1973, data have been collected in nine long-standing registries included in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program. Recently, geographic regions with higher proportions of minority groups have been added (17), such that SEER now covers approximately 14 percent of the US population.

The number of population-based cancer registries has increased substantially during the past three decades in developed countries, but has lagged in developing countries. Existing high quality population-based registries monitor the changing cancer patterns and trends for only a small proportion of the populations that have recently undergone dramatic lifestyle alterations in Asia and Africa. Major political changes, such as the dismantling of the former Soviet Union and concordant changes in many parts of eastern Europe, have also impacted adversely upon cancer registration. Newly established population-based cancer registries and some older ones fail to identify or delay registering a substantial proportion of incident cancer cases (particularly those seen only in physicians' offices or at institutions outside the geographic catchment area of the registry). Many registries lack adequate quality control procedures. Medical care practices, public health policies, and legal requirements within a geographic region can also impact adversely on the quality of cancer incidence data if a large proportion of cases are not histopathologically confirmed or physicians are not legally required to report incident cancers.

To increase the quality of population-based registries worldwide, it would be helpful to establish internationally accepted, minimum accreditation standards for certification and to take advantage of the current efforts at the International Agency for Research on Cancer and the expertise of other groups producing high quality work on the descriptive epidemiology of cancer to establish an international centralized unit of cancer registry expertise. The latter might consist of a staff, comprising both long term and visiting experts with extensive cancer registry experience, who would provide frequent, short term training courses, longer term assistance, and site visits for accreditation and

consultation. Ideally, such a unit could also identify and test scientifically valuable and cost-effective strategies for implementing rapid surveillance, quicker adoption of the most recent and clinically useful cancer classification systems, and long term active follow-up of registered cancer patients. These activities could substantially increase the clinical utility of cancer registries. An international unit could also assist in establishing new cancer registries to monitor populations exposed to the accidental or industrial release of carcinogens, populations with high rates of specific cancers, and special populations (e.g., persons with childhood cancer, familial cancer, or genetic or other disorders that predispose them to high rates of cancer).

Uses of cancer registry and other types of descriptive data

Numerous studies have shown that comparisons of descriptive patterns among population subgroups and among populations internationally may provide useful hypotheses about cancer etiology. Most descriptive epidemiologic studies analyze cancer incidence data and report patterns and trends according to year of diagnosis or death (cross-sectionally) (12, 17). These types of analyses have contributed useful information about incidence and mortality risks by age, gender, race, ethnic group, geographic region, and time period, and have provided many useful etiologic leads about cancer occurrence. Sometimes, although not sufficiently often, changing patterns and trends have been explored further through assessment of longitudinal effects and secular patterns for successive birth cohorts (18). There is growing recognition that age-period-cohort assessment may provide substantially more incisive information than cross-sectional data for clarifying the likely pattern of exposure (according to the time period in calendar years and to the age(s) in years at the time of exposure) in members of successive birth cohorts.

Increasingly, cancer registry data have also been examined alone or in combination with population survey or administrative data. As an example of a growing number of studies assessing the effects on cancer incidence of new screening, diagnostic, or treatment procedures, Kricker et al. (19) used New South Wales, Australia, cancer registry data to assess secular trends in female breast cancer incidence according to the patient's age and the size of the malignant tumor at diagnosis, preceding and subsequent to introduction of mammographic screening. Registry data have also been linked with administrative data to estimate cancer risk following hospitalization for diagnosis and/or treatment of certain medical conditions (20) or subsequent to collection of census information about occupation or industry of employment (21). Registry data have been used in Sweden to examine childhood cancer risks associated with prenatal and perinatal medically related exposures (22). With the growing number of cancer registries and computerized databases, linked-registry analyses should be utilized increasingly to provide new leads about cancer etiology, although privacy laws or other legal restrictions may curtail such efforts. Cancer registry data have been used to compare childhood leukemia incidence in Europe and parts of the former Soviet Union before and after the 1986 Chernobyl nuclear accident (23); to evaluate whether lower latitude (a proxy for sunlight exposure) is associated with a higher incidence of non-Hodgkin's lymphoma (24); and to pinpoint geographic regions with especially high or low incidence (25). Cancer registry incidence data, in conjunction with survey information, have also been used to estimate the attributable fraction of cancers due to a specified exposure or agent (26) and to identify new etiologic leads, although such ecologic comparisons can be fraught with biases that may be difficult to characterize (27).

RECENT DEVELOPMENTS IN METHODS

Outcomes

Prior to the 1990s, clinically evident cancer was the primary outcome examined in cancer epidemiologic studies. As knowledge has accumulated about the molecular pathway(s) and corresponding precursors of different cancers, cancer epidemiologists have begun to evaluate a broader range of endpoints that correspond to their study objectives. While incident clinically diagnosed cancer may be the most appropriate outcome for evaluation of late stage cancer promoters, cancer precursors may be more relevant for assessing agents that accelerate or interrupt events earlier in carcinogenesis. The long-standing strategy of focusing solely on clinically overt cancer outcomes (28) or, to a substantially lesser extent, on known precursors (29) is beginning to shift as cancer epidemiologists simultaneously assess risk or protective factors for both clinically evident cancer and any known precursors for that cancer in the same population (30). Cancer epidemiologists should consider a variety of early outcomes (31), known precursors (32), and clinically diagnosed cancer and related outcomes (33) in epidemiologic studies utilizing novel approaches to examine gene-environment interaction in carcinogenesis.

Among the increasing number of cancer precursors being evaluated in epidemiologic studies are Barrett's esophagus (preceding adenocarcinoma of the distal esophagus); adenomatous polyps (preceding colorectal carcinoma); cervical, vulvar, and anal intraepithelial

neoplasia (preceding invasive anogenital neoplasms); dysplastic nevi (preceding melanoma); breast fibrocystic disease (preceding breast cancer); benign thyroid tumors (preceding thyroid cancer); and myelodysplastic syndromes (preceding acute myeloid leukemia). A growing body of evidence supports similarities in risk factors for colorectal adenomas and colorectal carcinomas (34), but further experimental and epidemiologic research is needed to clarify whether the other cancer precursors listed above share similar etiologic risk factors with the corresponding clinically manifest cancer outcome.

Exposures

The concept that a disease may be associated with a person's environment has been known since the time of Hippocrates. Yet, statistical approaches for quantifying public health measures were not employed before Graunt (in 1662) and later Farr (in 1837 and then yearly in the Annual Reports of the Registrar General) utilized quantitative methods to measure mortality (35, 36). A historic milestone was reached in 1855 with the first report of a "natural experiment" for assessing the relation of exogenous exposures to disease. In a critical series of observations, John Snow tested and confirmed a hypothesis linking ingestion of contaminated water to subsequent mortality from cholera more than 10 years before the specific causal organism was identified (37). Although early epidemiologic studies focused on identification of causal agents (mostly infectious organisms), other characteristics were recognized as etiologically important (including organism-related features such as transmissability, personal factors such as sociodemographic characteristics and prior immunologic experience, and extrinsic environmental factors) (38). With the shift in emphasis from infectious diseases to chronic diseases, there has also been an evolution in the concept of "cause," defined as "an event, condition, or characteristic that preceded the disease event and without which the disease event either would not have occurred at all or would not have occurred until some later time" (38, p. 8). The notion of "cause" evolved with recognition of the complexity of causation. The ever growing number of postulated carcinogens includes some categories containing a diversity of exposures (geophysical, occupational, diet, reproductive) and others that are more homogenous (alcohol, benzene), although each is often comprised of additional subgroups. Agents that increase or decrease risk of cancer include dietary and nutritional factors (macro- and micronutrients, vitamin supplements, alcohol), tobacco products, certain medical conditions and treatments, reproductive factors, physical activity, and many others. Rothman (38) has pointed out that carcinogenic agents represent only one dimension of the notion of "cause," with other components that may comprise a "sufficient cause" also including the mechanism or route of exposure, the subject's external and internal environments, and the subject's genetic makeup. More recently, factors that may enhance or reduce cancer risks have been postulated to include important behavioral, lifestyle, and physiologic factors such as stress, social networks, religion, and recreational activities. Many key aspects of the causal constellation remain unknown or poorly understood, however, even for the best studied carcinogens such as tobacco. The extremely informative role of experimental animal and in vitro studies in contributing to hazard identification in cancer occurrence is illustrated in the valuable monograph series *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* (39), which is compiled by the International Agency for Research on Cancer. These monographs critically evaluate human, experimental, and mechanistic information to classify agents according to their likelihood of carcinogenicity in humans (e.g., definitely, probably, or possibly carcinogenic or not carcinogenic).

Growing range of issues evaluated

Cancer epidemiologists have long been concerned with exposures, effect modifiers, and host susceptibility characteristics, since these may be causally associated with cancer outcomes. In the past several decades, cancer epidemiologic studies have expanded to include an even broader range of issues. For example, the success of many cancer treatments has spawned qualitative (40) and quantitative (41, 42) assessments of the risk of second malignancies following specific treatments. Research on tobacco- and alcohol-related aerodigestive tract malignancies has been extended to evaluate these exposures in relation to multiple and/or second primary cancers at these anatomic sites (43). Another rapidly growing area is chemoprevention, defined as the prevention of cancer through treatment with agents that prevent malignant disease or treat premalignant lesions. Although cancer chemoprevention research, particularly the use of randomized clinical trials, has dramatically increased during the past 20 years, only a few published studies are considered to have been of sufficient quality and size to be regarded as potentially definitive (44–48). More needs to be accomplished in understanding carcinogenesis, in developing and testing chemoprevention agents for efficacy (49), and in evaluating the benefits and risks of treating persons who are free of symptomatic disease (45, 49), in addition to designing and conducting better studies. Cancer epidemiologic studies are

increasingly exploring possible interactions of known or likely carcinogens with one (gene-environment interactions) or more (gene-gene interaction) host genetic characteristics that may modify risk factor associations (50). As additional polymorphisms are identified, the number of epidemiologic studies examining potential interactions can be expected to grow. Other examples of the increasing range of topics, as described below in this paper, include cancer epidemiologic studies that are: evaluating and testing new methodologies; critically examining an increasing number of biologic markers of exposure and outcome; assessing increasingly sophisticated proxy measures of exposures from the distant past; attempting to identify risk factors for earlier precancerous and intermediate outcomes; and focusing on genetic and/or environmental determinants of behaviors, such as cigarette smoking, that are known risk factors for cancer outcomes.

Expansion of data sources and methods for exposure assessment

Interviews and medical or workplace records are widely used, but cancer epidemiologists are also turning to more direct environmental or biologic measures of exposure. There have been few rigorous investigations of the accuracy and reproducibility of data obtained from questionnaires (51–54), records (55), and measurements taken in workplace and residential settings (56, 57). Further methodologic studies are therefore needed. Industrial hygienists, experimental scientists, and engineers frequently obtain physical or chemical measurements as part of their jobs, but, other than in radiation epidemiology, few areas in cancer epidemiology have incorporated such measurements within retrospective or prospective epidemiologic investigations. Therefore, only a small number of cancer epidemiologists have grappled with a wide range of related issues, such as the choice of a measurement device suitable for epidemiologic field research, regular instrument calibration, development of a measurement protocol that approximates current (or ideally, past) relevant human exposure, appropriateness of the exposure metric selected, and temporal aspects of measurement (including sampling frequency, interval, and duration) (58). While the potential for DNA markers of exposure (including DNA adducts and DNA fingerprints) has been widely heralded, there have been only a few examples of carcinogens that have clear one-to-one relations with specific mutational spectra (59). Several technical (the limited number of DNA bases that could potentially demonstrate mutations) and temporal (the subject's age and the calendar date of exposure cannot be determined from such mutations) factors limit the value of such measures of exposure.

For development of a measurement protocol that best approximates current or past personal exposures, studies should be undertaken to compare personal dosimetry with a spectrum of different area measurements. When choosing between available measurement instruments for cancer epidemiologic field studies, a variety of critical parameters must be considered and ideally evaluated in pilot studies. Important characteristics include the sensitivity of the device, the reproducibility of measurements, and the similarities and differences between each instrument under consideration in relation to availability, accuracy of exposure measurement, logistic feasibility, and cost considerations. Other considerations include the difficulty and frequency of required calibration; the frequency and cost of periodic instrument checks (by the manufacturer or another specialist) for assessment of the accuracy of measurements and other important aspects of operation; the ease of use by epidemiologic field staff; the acceptance of the device by subjects (based on size, time required for measurement, and adverse effects produced by the device, such as noise or dust); and the ease of transferring data from the instrument and summarizing the data in computerized files. The characteristics of the instrument selected will also need to be compared with the measurement device(s) used in prior or concurrent research. Shipping of measurement devices (between the investigator, the study coordinating center or the manufacturer, and the field staff) also requires evaluation of the most cost-effective approaches and strategies for preventing damage en route.

As the use of biomarkers in cancer epidemiologic studies has expanded, investigators have increasingly been required to evaluate the accuracy of these markers in predicting exposure or outcome (60). The first phase of such studies should include laboratory evaluation of the dose-response curve, sensitivity at low doses, specificity of the exposure, and reproducibility of the assay. Subsequent testing should be carried out in epidemiologic investigations to assess population sensitivity and specificity, individual variation, predictive value, biologic relevance, logistic feasibility, and cost. Shipping and storage of biologic specimens also require evaluation of the most cost-effective approaches, strategies for preventing damage, and methods needed for maintaining the viability of specimens.

The spectrum of exposures and biomarkers of exposure as well as the development of new exposure assessment methods must be broadened if identification of etiologic factors is to continue to progress. More comprehensive paradigms are needed for expo-

sure assessment in order to expand the definition of what constitutes "exposure," to increase the time period evaluated to cover the entire life span (and even gestation for many exposures), to incorporate greater precision in defining individual exposure windows, to assess exposure changes over time, and to examine interactions among exogenous and endogenous exposures that also evolve with age and time. Essential to the development of more complete and accurate exposure assessment constructs is the necessity for combining similar exposures from different settings (e.g., ionizing radiation exposures from medical, occupational, and residential environmental settings). As understanding of the specific molecular steps and pathways in multistage carcinogenesis is clarified, epidemiologists will need to develop tailored approaches for assessing risk and protective factors characterizing progression or lack of progression at each subsequent stage.

Mathematical modeling and statistical methods

Mathematical modeling of carcinogenesis. Decades before detailed delineation of the molecular steps involved in carcinogenesis, hypotheses about the underlying biologic mechanisms were translated into mathematical equations. Informative experimental studies of carcinogenesis and cancer mortality data were mathematically modeled in the 1950s, when the two-stage model was first introduced by Armitage and Doll (61). Knudson's observations on the characteristics of childhood retinoblastoma (62), the incidence and growth patterns of breast cancer and other cancers, and other experimental and observational evidence were considered to be consistent with the two-stage model (63). More recent mathematical modeling efforts, focusing primarily on chemical carcinogenesis data from experimental studies (64), will also (hopefully) be extended to incorporate breakthroughs in the understanding of human carcinogenesis. As the carcinogenic pathways identified become increasingly numerous and complex, mathematical modeling may be a helpful adjunct with which to clarify the biologic basis of carcinogenesis in conjunction with the biologic samples and other data collected periodically from large cohorts enrolled in long term follow-up studies.

Selected aspects of statistical methods. As in other areas of epidemiology, statistical methods utilized in cancer epidemiology have addressed the important methodologic problem of confounding, initially by stratification (65) and subsequently by regression methods (66). Regression analysis has been employed in both case-control (67) and cohort (68) studies. Other important statistical applications have been created for use in cancer screening studies, in evaluation of temporal and spatial clustering, and in assessment of genetic transmission of cancer susceptibility. Available statistical methods should be utilized and additional methods developed for characterizing the cancer risks of birth cohorts using the longitudinal approach; for estimating the effects of time-dependent exposures on cancer risk; for evaluating temporal and/or geographic clustering (69); for assessing the thousands of genetic variables in individuals and populations identified by new technologies; and for comparing cancer registry data with administrative data to generate new leads for cancer epidemiologic research (70).

Meta-analysis and pooled analysis. Meta-analysis is a method of analyzing epidemiologic data using information (generally only the published results) obtained from several studies, and pooled analysis is defined as a strategy for combining data (often raw data) from more than one study for evaluation (71). These techniques, used originally to clarify results from randomized clinical trials, are increasingly being employed to estimate cancer risks associated with low dose exposures based on observational studies (72). In contrast to the small likelihood of systematic differences among randomized populations, systematic differences can occur readily among the populations evaluated in observational studies (72). Meta-analyses of observational studies are limited in their ability to evaluate adequately the consistency of results within and between studies or to control for potential confounding. Even if the corresponding raw data are combined in pooled analyses, there is no way to carefully assess or appropriately control for such important methodologic problems as selection bias. Pooled analysis has been used to assess potential effect modifiers, such as combined effects on risk of aerodigestive cancers in relation to smoking and alcohol ingestion. Less commonly, pooled analyses combine data from populations with a wide variation in exposures. The growing utilization of meta-analysis and pooled analysis for observational study data should be critically evaluated to prevent misuse and inappropriate interpretation, to establish guidelines for appropriate use, and to develop better statistical approaches for summarizing results from a body of epidemiologic studies on a given topic.

Genetic studies: evolution in study designs and use of genetic markers

As studies have elucidated the alterations in the genetic control of cellular processes that lead to cancer at the molecular level, it has become apparent that multiple alterations in the major groups of genes (dominant

oncogenes and tumor suppressor genes) are required to produce cancer (73). Although dominant oncogenes appear to be involved in a high proportion of cancers in humans, with few exceptions it is mutations in tumor suppressor genes that cause inherited forms of familial cancer. Hereditary cancer is due to a germinal mutation that is inherited from a parent and observed in all somatic cells of susceptible family members, although at the molecular level, both familial and sporadic forms of cancer often derive from the same genes. In addition to the autosomal dominant genes whose loss of function predisposes to cancer, there are disorders associated with cancer susceptibility and loss of gene function that are inherited in an autosomal recessive manner (including such generic examples as DNA repair disorders and disorders of genomic instability). On a population basis, however, Mendelian disorders conferring notably increased risks of cancer account for only a small proportion, with potentially 80 percent of common cancers being probably due to gene-environment interactions (74). Animal data, pharmacogenetic data, and very limited human data demonstrate notable variability among individuals in their ability to metabolize exogenous and endogenous carcinogens, and variation in susceptibility to DNA damage and repair. Cancer epidemiologic studies have begun to incorporate testing of a growing array of genetic markers whose early carcinogenic and other biologic effects are only partially or poorly understood. The expanding number of types of markers evaluated includes: markers representing important germline lesions (such as heritable genetic mutations of the p53 tumor suppressor gene and those of mismatch repair genes, the latter playing a leading role in promoting or inhibiting carcinogenesis); markers of early biologic effects (such as cytogenetic aberrations, somatic cell mutations, cytotoxicity, immunologic alterations, or markers of altered messenger RNA expression); and markers of genetic susceptibility (such as polymorphisms responsible for chemical activation or detoxification, DNA repair, or genomic instability).

Earlier study designs. Investigations of cancer genetic epidemiology have evolved in the past few decades. Initially, investigators evaluated rare genetic syndromes in a single family (or a few families) with multiple first or second degree relatives affected by one type of cancer or related cancers (75). Subsequently, researchers at some referral institutions established registries of multiply affected families for clinical studies of familial and genetic determinants of cancer (76). In recent years, epidemiologists have included increasingly sophisticated familial and genetic components within comprehensive case-control investigations (77). While it may be methodologically advantageous to evaluate the entire spectrum of familial and genetic determinants of one or more cancers within a population-based setting, such an approach may not be financially or logistically feasible. This strategy may also be affected by the declining level of participation characterizing more recent population-based case-control efforts (78).

Newer study designs. Recent epidemiologic studies have only begun to utilize novel study designs. As an example, the kin cohort cross-sectional study design was developed to estimate the effect of one or more mutations in a major gene (such as *BRCA1*) on cancer penetrance by comparing the cancer histories of relatives of carriers of the mutation and relatives of noncarriers (79, 80). While it is not as methodologically rigorous as detailed evaluation of all first and second degree relatives of specified cancer cases and controls within a population-based investigation, the kin cohort study is characterized by higher participation rates and notably lower costs than the population-based approach. In one application of this approach, more than 5,300 Ashkenazi Jewish volunteers in the Washington, DC area were enrolled, and the breast, ovarian, and prostate cancer risks among those with and without the 185delAG and 5382insC mutations in the *BRCA1* gene and the 6174delT mutation in the *BRCA2* gene were estimated (80).

Although research is still in the early stages, an increasing number of cancer epidemiologic studies suggest that genetic polymorphisms related to activation or deactivation of carcinogens (81) or to DNA repair capability (82) may affect an individual's risk of cancer associated with carcinogens such as tobacco. Unfortunately, much of the existing epidemiologic literature on this general topic is limited by gaps in knowledge about the role of known and unidentified allelic variants and by poor study design, inadequate sample sizes, poor participation rates, and conflicting results (83). Interpretation is also problematic for genetic polymorphisms characterized by modest associations with the cancer under investigation if the primary exposure, although a known powerful carcinogen, demonstrates no evidence of an association with the cancer under study (because the sample of cases and/or controls is unusual). To elucidate the interplay of genetic polymorphisms with known carcinogenic exposures and to eliminate the methodologic, logistic, and cost-related difficulties associated with poor participation by controls, the innovative case-only design was proposed to screen for gene-environment interaction (84). Two required assumptions—i.e., independence between exposure and genotype in the population (85, 86) and independence of gene frequencies (87)—may limit the situations in which the case-only methodology can be used.

Gene-environment interactions and transgenerational effects

Since diethylstilbestrol was identified as the first human transplacental carcinogen (when a high risk of vaginal clear cell adenocarcinoma was observed among daughters of US and European women who had been treated with diethylstilbestrol to prevent spontaneous abortion (88)), there has been growing interest in disentangling the roles of genetic versus environmental factors in offspring of mothers and fathers exposed to a variety of carcinogens. For diethylstilbestrol and other suspected carcinogens whose effects may be transplacental or transmitted via germ cell damage, cancer risks in the offspring and, if possible, in the parents (89) should be carefully quantified and long term follow-up continued. Several such populations are currently being monitored. For example, offspring of the Japanese atomic bomb survivors exposed to radiation in utero have shown no excess of childhood cancer or any evidence of an excess in early adulthood (90). With regard to children and adults treated for cancer, reproductive patterns should be monitored and offspring evaluated for the occurrence of cancer and congenital anomalies (91). Offspring of workers employed in nuclear power plants have been found to have no overall cancer excess, except possibly a small increase in leukemia among children whose fathers had a cumulative dose of at least 100 mSv (92). In a Chinese study, significant excesses of acute lymphoblastic leukemia and brain tumors were observed among the offspring of fathers who smoked cigarettes during the preconception period and nonsmoking mothers (93).

Implications for cancer epidemiology of automated genetic marker assessment

Newer laboratory technologies will permit simultaneous testing of thousands of genetic markers. While this will provide vast new opportunities for cancer epidemiologists, careful thought will be required to select biologically meaningful markers for study and to utilize appropriate study designs. Studies will need to include sufficient sample sizes, appropriate comparison groups, high participation levels, suitable methods of data analysis, and state-of-the-art laboratory methods with adequate quality control features and bioinformatics capability for orderly and accurate evaluation of data and interpretation of results.

Establishment of resource centers to support cancer epidemiology field research

The rapid discoveries in genetics, molecular biology, related fields, and laboratory technology have outpaced the corresponding developments in epidemiologic methods and field research strategies necessary for cancer epidemiologists to usefully incorporate many new advancements. On the other hand, there is a critical need to apply the many new discoveries within epidemiologic studies, since this will be vital to evaluate the experimental findings in humans. Empirical and field studies are urgently needed to develop and test new methods and data collection strategies for incorporating the burgeoning discoveries from related fields within cancer epidemiologic research. For example, alternative study designs are essential for assessing possible environment-environment, gene-environment, and gene-gene interactions. Better strategies are needed to minimize the serious problems derived from the use of proxy respondents for highly fatal cancers in adults or for childhood cancers. Validation studies are also necessary to improve exposure estimates derived from distant points in time. Better approaches are also critical for obtaining large quantities of DNA and other biologic materials from close to 100 percent of participants; improvements are needed to reduce pain from venipuncture and to minimize any adverse health, psychological, or economic effects. New methods should be developed and tested for transporting and storing biologic specimens for long periods without degradation of lymphocytes, other cells, or important markers. In addition, methodologic studies are essential to evaluate and quantify the effects of potential biases and to develop effective strategies for minimizing such biases.

To assist cancer epidemiologists worldwide in employing the most effective and efficient strategies for evaluating the ongoing explosion of new knowledge and laboratory developments in genetics and molecular biology, a few centralized resources could be established to provide consultation, training (in study design, field research strategies, data analysis, and interpretation of results), and "library" facilities. Such resources might include a few experts in genetic and cancer epidemiology, statistical genetics, and possibly bioinformatics as permanent staff, with supplemental assistance being provided by visiting epidemiologists, molecular biologists, geneticists, immunologists, and other relevant experimental scientists. Such resource centers could help establish high standards for cancer genetic epidemiologic research to encourage better quality individual studies and, ultimately, pooling of data from multiple high quality studies. The permanent staff could also help oversee pooled analyses, conduct methodologic research, and pilot-test new approaches for many aspects of cancer genetic epidemiologic research studies.

SELECTED CARCINOGENS AND ASSOCIATED CHALLENGES

Identification of causes may not be sufficient to reduce the associated cancer burden: tobacco and cancer

A triumph of cancer epidemiology was the conclusive demonstration of cigarette smoking as the major cause of lung cancer (94–97). Subsequent studies have quantified dose-response relationships. Data from the American Cancer Society's Cancer Prevention Study II suggested that tobacco smoking causes 95 percent of lung cancer in males and 92 percent in females (98). Smoking has also been estimated to cause 20 percent of all cancers (except skin cancers) worldwide (99).

Unfortunately, the recent downturn in lung cancer and other smoking-related cancers among males in the United States (100) and a few other countries does not represent current or likely future patterns for most men worldwide. Among persons who have quit smoking, a substantial decrease in lung cancer risk occurs within 5–15 years after cessation, and lung cancer rates have declined among populations that have sustained lower smoking rates for 20 or more years (such as US adult males) (101). A dramatic decline in smoking prevalence among US males, from 51.9 percent to 27.0 percent between 1965 and 1995, was paralleled by a smaller decrease among US women (from 33.9 percent to 22.6 percent), although both the peak prevalence and recent prevalence were lower in women than in men. While these achievements provide some cause for optimism, recent survey results are worrisome. For example, between 1995 and 1997, the rate of the decline slowed for US Caucasians and minority populations, leveling off at a 24.7 percent prevalence overall. Persons in more recent US birth cohorts have begun smoking at progressively younger ages (98). In addition, the average number of cigarettes smoked per day and the duration of smoking in years have been rising steadily among US smokers, even though tar content has declined. This pattern has been more pronounced in women than in men. Particularly bleak have been the 25 percent and 80 percent increases in cigarette smoking among White and African-American US high school students, respectively, between 1991 and 1997 (102), despite extensive educational, public health, and political efforts. Data from US nationwide surveys reveal that physicians ascertain adolescents' smoking status at 72 percent of visits but rarely provide counseling about the dangers of smoking (103). Other ominous trends include the 75 percent increase in tobacco use worldwide during the 1970s and 1980s (104) and the growing epidemic of tobacco-related cancers and causes of death in China (105) and parts of eastern and central Europe (104). Worldwide, the prevalence of tobacco use is at an all-time high, with an estimated 900 million men and 200 million women (including 700 million men and 100 million women in developing countries) currently smoking (104).

On the one hand, epidemiologic investigations are providing invaluable information about familial and genetic, molecular, host-related, and tobacco type-specific aspects of smoking-related carcinogenesis (106). On the other hand, the record level high prevalence of smoking among persons in many developing countries as well as among US adolescents and the likely forthcoming surge in tobacco-related cancer occurrence in these populations suggest that thousands of epidemiologic studies have had little impact upon key determinants of smoking for these populations. Cancer epidemiologists should participate in future efforts to evaluate the environmental and genetic determinants of smoking behavior as well as the cultural, societal, political, legislative, and economic determinants. Cancer epidemiologists should also contribute methodologic and other expertise to the development of prevention strategies, particularly for children and adolescents.

Low dose exposures: quagmires and quandaries

Ionizing radiation. Atomic bomb survivors. Current understanding of long term carcinogenic effects of acute radiation exposure is largely derived from studies of cancer incidence and mortality among the atomic bomb survivors in Hiroshima and Nagasaki, Japan (107–113). Detailed reconstruction of individual radiation doses for 94,000 survivors has linked radiation from the atomic bombs with many different types of cancer. Although cancer risks vary by anatomic site, histology, and estimated dose, radiation from the bombs accounts for approximately 5–8 percent of the cancer risk to date among survivors (112).

Therapeutic radiation. Studies of patients receiving therapeutic radiation have also provided useful quantitative information about cancer risks associated with moderate to high radiation exposures. Organ doses can often be reconstructed for patients who have been treated with radiation therapy and, to a lesser extent, for populations that have been occupationally exposed to ionizing radiation, but there are numerous difficulties in reconstructing past exposures (113, 114).

Unresolved issues. The greatest quandary for radiation epidemiologists is that the general population is mostly concerned about prolonged, low dose environmental ionizing radiation, whereas the most detailed data available are for moderate to high dose acute exposures from the Hiroshima and Nagasaki atomic bomb explosions and medical treatments. Although

ionizing radiation is one of the best studied carcinogens, unresolved issues include extrapolation of risks from high dose rates to low dose rates, from adult males to females or children, from ill persons to healthy ones, and from occupational exposures to residential exposures (e.g., radon risks based on studies of uranium miners) (115–117). For example, valid estimates of lung cancer risk associated with residential radon exposure could not be derived solely from studies carried out in homes, since so few cancers are associated with the very low exposures characterizing most homes (115); yet several problems limit straightforward extrapolation of lung cancer risk estimates from studies of uranium miners to risks associated with residential radon exposure, including the high prevalence of smoking among the miners and their substantial exposure to dust and other air pollutants. Despite these difficulties, the Committee on the Biological Effects of Ionizing Radiation (BEIR VI) estimated that approximately one in 7–10 lung cancer deaths overall (e.g., 15,400–21,800 of the estimated 157,400 annual lung cancer deaths in ever and never smokers) and 2,100–2,900 of the 11,000 annual lung cancer deaths in nonsmokers in the United States are due to radon (115). A related controversial topic is the interaction of tobacco smoking and radon exposure, since smoking is the cause of most lung cancer internationally. Despite gaps in knowledge (limited data from epidemiologic studies and an absence of valid biologic markers of exposure), the available information suggests synergism between the two agents, consistent with an interaction that is less than multiplicative (116). Debate has focused on the contribution of indoor radon exposure to lung cancer risk among smokers, in view of the extremely high attributable risks due to smoking. Lung cancer mortality risks in relation to residential radon exposures of never smokers are also difficult to estimate accurately, because mortality rates in this group are substantially lower than overall rates in the general population and because of the many other sources of uncertainty (117).

Promising new populations. Valuable new data may be generated from analytical studies of childhood leukemia and of thyroid cancer arising in persons who were children residing in the Ukraine, Belarus, or Russia at the time of the 1986 Chernobyl accident. These data will only be useful, however, if accurate dose reconstruction and high participation rates prove to be possible. While ecologic studies (118, 119) can offer an alternative to the expense and complexity of utilizing a cohort follow-up approach, difficulties arise when ecologic study findings differ markedly from the results of analytical studies (120). Since the recognized limitations are substantial (121), ecologic studies should be employed only to suggest new hypotheses or if analytical studies are unfeasible.

Ionizing radiation and other exposures—cancer clusters. A more general problem not unique to ionizing radiation exposures is the issue of potential cancer clusters. One of the more frustrating examples has been the cluster of leukemia arising in young people living close to the Sellafield nuclear fuel reprocessing plant in the United Kingdom (122). Although incidence is significantly higher than expected, the very low environmental radiation levels are unlikely to be responsible for the excess (123), and no other proposed explanations (124, 125) have been confirmed. Ecologic studies evaluating childhood leukemia and other cancers among populations proximate to nuclear plants, including the detailed investigation following the 1979 accident at the Three Mile Island nuclear facility in Pennsylvania (126), have all shown little evidence of excess risks. Nevertheless, population exposures from routine nuclear plant operations, nuclear plant accidents, and fallout continue to cause great public concern.

Low dose exposures—a strategy for moving forward. A strategy that might be utilized for studies of low dose radiation (or other types of low dose exposures) would involve joint efforts among epidemiologists, dosimetrists, and radiobiologists (or epidemiologists and laboratory scientists for other types or exposures). These specialists could collaboratively design a series of epidemiologic and experimental studies that would incorporate radiation dosimetry and biomarker evaluation. Such multidisciplinary efforts could be initiated at the planning stage and then continue through analysis. A multidisciplinary approach could also extend to development of economically feasible biologic markers for measuring low dose exposures and long-lived exposure effects.

Cancer viruses and vaccination: the valleys and vertices of hope for prevention

Hepatitis viruses and liver cancer. Among all types of cancer combined, liver cancer ranks fifth internationally. Although the attributable risks for liver cancer associated with chronic hepatitis B and C virus infection vary among populations, it has been estimated that persistent infections with these two viruses combined account for more than 80 percent of liver cancer cases worldwide (127, 128). Estimated relative risks for hepatocellular cancer range from 5 to 148 and from 1.1 to 52 among persons who are seropositive for hepatitis B surface antigen or hepatitis C virus antibodies, respectively (127).

Hepatitis B. Most cases of hepatitis B virus-associated hepatocellular cancer occur in conjunction

with cirrhosis of the liver, after decades of chronic hepatitis, following asymptomatic infection during early childhood or the perinatal period (129, 130). The prevalence of cirrhosis has been reported to be very high among patients with chronic hepatitis B (approximately 81 percent) and hepatitis C (approximately 76 percent) who develop hepatocellular cancer (131). Studies from Europe suggest that risk of hepatocellular carcinoma is low among persons infected with hepatitis B virus who experience sustained remission and compensated cirrhosis based on virologic and liver disease parameters (127, 129). Populations vary in their levels of hepatitis B endemicity. The highest prevalence is observed in China, Southeast Asia, and western and central Africa; midlevel prevalence is seen in eastern and southern Europe, the Middle East, and southern Asia; and low prevalence is observed in North and South America, northern Europe, Australia, and New Zealand (129). More than 80 percent of liver cancer cases occur in developing countries. Age at infection varies with population prevalence of seropositivity and is the major determinant of carrier status (128, 131). The hepatitis B vaccine is more than 70 percent effective for populations characterized mostly by perinatal infection and more than 85 percent effective for populations in which childhood and adult infection predominate (129). Early childhood vaccination against hepatitis B virus could lead to elimination of as much as 60 percent of liver cancer cases associated with chronic hepatitis B infection (132).

Hepatitis C. Hepatitis C virus infection is the most common chronic bloodborne infection in the general US population, with close to 2 percent, or 4 million persons, demonstrating evidence of past or current infection (133); an estimated 170 million persons are infected worldwide (129). In developed countries, transfusion of blood and blood products was an important source of hepatitis C virus transmission prior to the early 1990s, but at present most hepatitis C virus transmission is related to high risk drug use and sexual exposures (133). In the United States, the annual number of newly acquired acute hepatitis C infections declined from an estimated 180,000 per year in the mid-1980s to an estimated 28,000 per year in 1995. Nonetheless, there is a large reservoir of chronically infected persons, including those who received multiple blood transfusions prior to the early 1990s, renal dialysis patients, persons with blood clotting disorders, prisoners, and cancer survivors (133, 134). Although most acute infection is asymptomatic, acute infection often leads to chronic infection; within 10 years, approximately 20 percent of persons with chronic hepatitis C go on to develop cirrhosis (135). Hepatocellular cancer develops in 1–4 percent of patients with hepatitis C-induced cirrhosis per year (135). Immunoprophylaxis for hepatitis C virus infection is unlikely to be developed soon because of the virus' genetic heterogeneity and propensity to mutate.

Barriers to reducing the incidence of hepatitis-related liver cancer. Despite extensive knowledge about the epidemiology of hepatitis and an effective vaccine against hepatitis B, important barriers to reducing virus-associated hepatocellular cancer remain. Economic barriers may limit widespread vaccination in poorer populations, although some Asian countries have implemented universal infant vaccination. In economically well-off populations, there is generally no systematic testing or efforts to achieve complete immunoprophylaxis in high risk subgroups. Not well understood are the precise mode of transmission of hepatitis B virus during childhood and the factors preventing successful immunization in some vaccinated persons. Subsequent to the use of more accurate tests for identifying hepatitis C antibodies in donor blood in the early 1990s, a decline occurred in new-onset hepatitis C virus infection. Nevertheless, because of the severity and chronicity of the liver disease and related conditions caused by hepatitis C virus, the number of associated deaths is expected to dramatically increase over the next few decades. Epidemiologists should encourage implementation of routine screening of subgroups at high risk of hepatitis C to prevent transmission by infected persons, to limit exposures to other known liver toxins, and to institute therapy for chronic active hepatitis. Other barriers to reduction of hepatitis-associated hepatocellular cancer could be addressed by epidemiologic research that evaluated further the role of potential effect modifiers such as alcohol, acetaminophen, other medications, and various solvents in the occurrence of virus-induced hepatocellular cancer and related nonmalignant precursors.

SELECTED CANCER OUTCOMES AND PREVENTION STRATEGIES

Cancer epidemiology as a public health discipline

While epidemiologists often focus on identification of high *relative risks* (such as those observed for breast cancer among genetically susceptible populations with *BRCA1* mutations), public health practitioners are more concerned with ascertaining preventable carcinogens responsible for substantial *attributable risks*, even if the associated relative risks are modest. From the public health standpoint, identification of etiologic factors responsible for 5 percent of the attributable risk for lung cancer is more important than identification of factors causing 50 percent of the risk for a very rare

malignancy. Since the long term goal of cancer epidemiology is ultimately to prevent all cancers, cancer epidemiologists should certainly expend major effort in identifying factors that account for large attributable risks, but they should not restrict their activities to an exclusive focus on causes of common cancers. In addition, epidemiologists should evaluate suspected causes of cancers that are rapidly increasing in incidence (such as non-Hodgkin's lymphoma), exposures that are of major concern to the public (such as residential pesticides and low level ionizing radiation), and potential risks from devices whose usage is dramatically increasing (such as cellular telephones). It is also noteworthy that etiologic studies of certain very rare cancers (such as retinoblastoma) (136) and rare familial cancer aggregations (such as Li-Fraumeni syndrome) (137) have identified important genes and mechanisms of carcinogenesis that have had profound implications and have led to broad insights for cancer causation. The examples discussed below illustrate some etiologic aspects and cancer prevention issues for a few common cancers.

The optimist's view

A striking development of the past few decades is the expanding purview of cancer epidemiology. The boundaries of the field no longer encompass limited types of outcomes, exposures, and methods employed in descriptive and analytical observational studies. Advances in cancer epidemiology have been deeply influenced by developments in related fields such as molecular biology and genetics, virology, immunology, pathology, occupational medicine, toxicology, public health, and statistics. Conceptual advances include recognition of the potential importance of in utero and perinatal risk factors for a diversity of adult cancers (including adenocarcinoma of the vagina, brain tumors, and potentially breast, testicular, prostate, and other cancers), while the seemingly endless possibilities afforded by continuing discoveries in molecular biology and genetics have barely begun to be exploited.

Recent breakthroughs in the identification of causal factors and enhanced understanding of the multistage processes involved in tumor development are nowhere better exemplified than for cervical cancer, as briefly described below. The long-running community-wide efforts to promote sun protection in Australia beginning in the early 1980s and prevention efforts begun in the 1990s in other parts of the world (summarized below) provide hope for further improvement in the favorable mortality and incidence trends characterizing cutaneous melanoma among persons in more recent birth cohorts.

Cervical cancer: a triumph of cancer epidemiology. Cervical cancer is the second most common type of cancer among women worldwide (12). Since the discovery of a successful method for cervical cytologic screening and the establishment of broad-based screening programs, incidence and mortality have progressively declined for decades in developed countries (although rates recently began to plateau or even increase somewhat among younger women in several countries, including the United States) (138, 139).

Descriptive and analytical studies revealed a strong association of cervical cancer with sexual behavior more than 30 years ago. These epidemiologic studies ultimately spurred the discovery by laboratory scientists of a possible role of human papilloma virus (HPV) infection in cervical cancer. Despite the laboratory-based discoveries, detailed understanding of this relation was limited until the introduction of polymerase chain reaction-based DNA amplification provided the major measurement technique necessary for clarifying the epidemiology and natural history of HPV-induced cervical carcinogenesis (138). An essential step in this process was the clear determination of the reliability of the HPV measurement (139). Also critical was recognition of the pivotal role and importance of chronicity of infection as well as the multistage development of cervical carcinoma.

Approximately 90 percent of cervical carcinomas worldwide have been found to be caused by infection with at least one of 15 genital types of HPV (139). Venereal transmission peaks in late adolescence through very early adulthood in the United States. The epidemiologic evidence fulfills all of the established epidemiologic criteria for causality, with case series worldwide demonstrating the same 10–15 types of HPV, and virtually no negative studies. Epidemiologic understanding of the multistage pathogenesis of HPV-induced cervical cancer, although not yet complete, surpasses that of virtually any other malignancy. Using various molecular epidemiologic approaches, new prevention strategies are proving to be extremely effective, and primary prevention of cervical cancer through HPV immunization of the general population now appears to be a promising possibility.

Skin cancer: improvements in prevention. For several decades prior to the mid-1980s, the incidence and mortality of cutaneous melanoma rose steadily throughout most countries with primarily Caucasian populations (140). Typical rates of increase ranged from 3–7 percent annually from the mid-1960s to the mid-1980s in most of these countries (140), with recent increases in the United States averaging 3.3 percent per year during 1990–1996 (141). Ultraviolet radiation exposure from the sun has long been linked

with cutaneous melanoma because of the higher risks observed in fair-skinned persons, those with blond or red hair, those who sunburn or freckle easily, those residing in lower latitudes, and patients with xeroderma pigmentosum (a genetically inherited condition characterized by deficient repair of ultraviolet damage to DNA) (142). In a systematic review of 29 case-control studies of melanoma and sun exposure, Elwood and Jopson (142) found a significant overall excess risk associated with intermittent exposure, significantly reduced risks in relation to substantial occupational sun exposure, and significantly increased risks linked with sunburn in childhood and adolescence and, to a lesser extent, in adulthood. Although the highest incidence rates internationally were seen in Australia, migrants who moved from countries of low incidence to Australia or other areas with high incidence generally experienced lower rates of melanoma than native-born residents (141). This finding and data from most case-control studies have suggested that childhood exposures might be of particular importance (142, 143).

Community-wide public education campaigns were undertaken in Australia in the early 1980s and were initiated in the mid-1980s to early 1990s in other countries (144). These campaigns promoted reduction of outdoor exposures during midday in summer, use of protective clothing and hats, and application of sun block as an adjunct. Studies have documented that knowledge, attitudes, and behavior aimed at sun reduction have dramatically improved in Australia, and sunburn prevalence has also been reduced (144, 145). In addition, cutaneous melanomas are being diagnosed at earlier stages, as documented by the increasing relative probability of being diagnosed with an in situ neoplasm rather than a thin invasive lesion, between 1984–1986 and 1990–1992 among patients with melanoma whose cancers were reported to the South Australian Cancer Registry (145).

Worldwide, some increasingly favorable signs are also apparent. Although mortality rates were increasing in 22 developed countries between 1955 and 1985, most of these countries (including the United States) have experienced declines in mortality from cutaneous melanoma among persons aged 20–44 years since 1985 (146). Age-period-cohort analyses of incidence data have shown a declining incidence of cutaneous melanoma among cohorts born since 1930 in Canada (147) and among males (but not females) in recent birth cohorts in Connecticut, based on data from 1950–1989 (148). English and Milne (149) suggest that declines or stabilization in the incidence of cutaneous melanoma beginning in the mid-1980s may have originated with behavioral changes initiated in the mid-1960s, assuming that recent sun exposure is of little importance in the etiology of this malignancy. Regardless, sun protection behaviors are still woefully inadequate in the United States and western Europe, as evidenced by the increased prevalence of sunburn during 1986–1996 in the United States (150) and an increased duration of recreational sun exposure among young Europeans using sunscreen with a higher sun protection factor (151).

Achieving the promise of advances in molecular genetics: the role of cancer epidemiology. It has been argued that any current assessment of key issues and critical gaps in cancer epidemiology will be irrelevant within a few years, when it should become possible to review an individual's genetic blueprint and ascertain the summation of all past carcinogenic exposures, as manifest in specific mutations, deletions, viral insertions, and other molecular changes. On the other hand, the landmark discoveries of the occurrence and sequence of the specific mutations and allelic losses in colorectal carcinogenesis by Vogelstein and colleagues (152) have not clarified the specific etiologic factors or the functional processes responsible for these changes.

Cancer epidemiologic research and complementary experimental studies will be essential for identifying causal agents and the associated carcinogenic processes. Cancer epidemiologists are just taking the first steps toward unraveling the complex, interactive processes by which exogenous agents interact with an individual's evolving genetic makeup in the process of carcinogenesis. Epidemiologic studies strongly suggest that different types of cancer vary according to the specific types of exogenous agents and genetic markers and the innumerable potential gene-environment interactions. Skeptics may argue that these notions are overly simplistic and assume a static structural and functional characterization of the genomic DNA. It is important for cancer epidemiologists to recognize that not only is temporal change a frequent characteristic of exogenous exposures, but also dynamic change and instability are fundamental features and defining aspects of the human genome (and human biology in general).

The pessimist's view

Prostate cancer: causes are hard to identify. The etiology of prostate cancer is poorly understood (153), although intriguing clues are suggested by the dramatic differences in age-adjusted incidence among racial and ethnic groups (12–14). Studies of migrants have also shown changing incidence patterns, often within one or two generations (153). The lower rates among African Blacks than among US Blacks and

among native Japanese or Chinese than among Japanese Americans or Chinese Americans suggest that variation in rates may be related to changes in exogenous factors as migrants adopt lifestyle and other exposures characteristic of their new country of residence. The lower international variability in latent prostate cancer in autopsy series compared with clinically manifest occurrence may suggest lower international variation in initiators compared with late stage risk factors (154).

Postulated risk factors include age, lifetime (beginning in utero) hormonal exposures (153, 155, 156), and the interrelated dietary factors, weight, and body fat distribution. Venereal disease and sexual activity have been linked to prostate cancer in some studies (157).

The dramatic international variation in incidence suggests that multicenter studies including men of Asian, Caucasian, and African origin may be extremely helpful, yet relatively few studies have incorporated such comparisons in their design (153). Biochemical and epidemiologic evidence suggests that androgens, particularly testosterone and dihydrotestosterone, play a role in prostate cancer etiology (153, 155, 156). Particularly promising are recent studies focusing on genes involved in androgen biosynthesis, activation, transport, and metabolism (153, 155). A specific mutation in the steroid 5-α-reductase (*SRD5A2*) gene, which converts testosterone to dihydrotestosterone, may be linked with the significantly higher risk of prostate cancer in African-American and Hispanic men than in Caucasians and the significantly lower risk in native Japanese men (160) than in Caucasians (158, 159). An intriguing earlier finding of higher serum testosterone and estradiol levels in early pregnancy among pregnant Black women compared with pregnant White women (156) deserves further investigation, although laboratory methods for measuring hormone levels must be carefully evaluated for reproducibility and accuracy (161).

Genetic determinants of hormonal factors and age-related changes in hormone profiles (from the fetal period to old age) should be evaluated in large US cohorts with sufficient numbers of Black, Caucasian, Hispanic, and Asian-American men to explore age-related changes in hormone profiles and interrelations with nutritional factors, anthropometric characteristics, sexual activity, and venereal and other genitourinary infectious diseases in relation to risk of prostate cancer in these racial/ethnic subgroups (153, 155, 156, 159, 160). All but two existing Asian cohorts (Japanese atomic bomb survivors and Japanese men in Hawaii, the latter including only 8,000 men) were established quite recently. A variety of other cancers and other serious disease outcomes could be evaluated in such cohorts in conjunction with a broad range of other exogenous exposures and endogenous factors.

Also important to monitor are the dramatic changes in both incidence and mortality trends of prostate cancer that have occurred for decades and continue to the present. From 1968–1972 through 1983–1987, prostate cancer incidence rose steadily among White and African-American men in the United States, as well as in England, Italy, Japan, Sweden, and other countries (162). While this trend was ascribed in part to improved detection, mortality also increased in several (though not all) of these countries during this time period (162). Following approval of the prostate-specific antigen test in 1986 by the US Food and Drug Administration for monitoring of disease status in patients with prostate cancer, the test was increasingly performed on men not previously diagnosed with this malignancy. An initial acceleration in the increasing incidence of prostate cancer during 1989–1992 was followed by a dramatic decline in the incidence of distant stage disease and then in the incidence of earlier stage disease that has continued through the most recent year of observation (163). From 1969 through the early 1990s, prostate cancer mortality rose, with an acceleration of the rising mortality trend for Whites and African Americans beginning in 1987 and 1988, respectively, followed by a downturn starting in 1991 and 1992, respectively (163, 164). Since the downturn began, the annual rate of the decline has accelerated steadily for Whites and has continued to decline at approximately 11 percent per year for African Americans (164). The reason(s) for these welcome downturns in prostate cancer mortality have been debated, but they have been ascribed by some to dramatically increased application of the prostate-specific antigen test to healthy men (164). Recent improvements in the survival of prostate cancer patients also reflect the increased use of prostatectomy, improvements in early detection by transrectal ultrasound, and perhaps new hormonal approaches to therapy (164).

Breast cancer: difficult to prevent, although much is known about its etiology. Three hundred years ago, Ramazzini (165) first reported the relation of reproductive history to the occurrence of breast cancer among nuns. Accumulating evidence from epidemiologic, clinical, and experimental studies suggests that estrogen compounds, metabolites, and possibly other chemicals with estrogen-like or antiestrogen activity or progestins play key roles in breast cancer etiology (49, 166, 167). There is notable variation in age-adjusted incidence, with the highest rates being observed among Caucasian women in North America and northern Europe and the lowest rates being seen in

China and Japan (12). The substantial international differences do not appear to derive from variation in genetic susceptibility, since Japanese migrants and US Blacks have substantially higher rates of breast cancer than native Japanese (168, 169) and African Blacks (170), respectively. Breast cancer risk increases with age, with a rapid rise from late adolescence to approximately age 50 years (corresponding to the average age at menopause), followed by a change in the slope corresponding to a more gradual increase (166). Other key risk factors include early age at onset of menarche, late age at menopause, late age at first pregnancy, a history of breast cancer in first degree relatives (particularly if these relatives developed breast cancer during the premenopausal years), biopsy-confirmed benign proliferative breast disease, and probably use of exogenous estrogens, short menstrual cycle length, and consumption of three or more alcoholic drinks per day (166, 167). Caucasian race, obesity, and use of estrogen replacement therapy are associated with increased risk in postmenopausal women. The relations of physical activity, dietary fat, total calories, and lactation with risk of breast cancer are inconsistent. It has been estimated that known risk factors account for approximately 55 percent of breast cancer incidence (171).

Two groups of inherited susceptibility genes appear to play a role in breast cancer. The first category includes genes whose breast cancer-associated germline variants confer a high absolute degree of risk but which are rare and account for a low attributable risk in the general population. Examples include *BRCA1*, *BRCA2*, *TP53*, *PTEN*, *MSH2*, *MSH1*, and *STK11*. The second category consists of common genes that encode enzymes involved in the metabolism of steroid hormones or the metabolism of carcinogens or are involved in DNA repair. This category of genes confers low to moderate absolute risk but a moderate to high attributable risk. Examples are *CYP1A1*, *CYP2D6*, *CYP2E1*, *GSTM1*, *HRAS1*, *NAT2*, and *ATM* (172).

While the antiestrogenic drug tamoxifen clearly reduces risk of a second primary breast malignancy in postmenopausal women (173), the recommendation that high risk women should consider using tamoxifen for primary prevention is more controversial. A single, albeit well conducted, large study (49) provides the major direct evidence supporting such use of tamoxifen, while the side effects of tamoxifen include increased occurrence of cancer of the endometrium, thromboembolic disorders, and menopausal symptoms (49, 173). Raloxifene, a selective estrogen receptor modulator with antiestrogenic effects, notably decreased the risk of estrogen receptor-positive breast cancer but not estrogen receptor-negative breast cancer in one large randomized trial, with no increase in endometrial cancer but an excess of thromboembolic disease (174).

Based on our current understanding of breast cancer etiology, it is also unclear how to reduce some of the key risk factors linked with breast cancer without producing potentially deleterious effects. For example, encouraging early childbearing because of the dramatic reduction in risk associated with having a first full term pregnancy prior to age 20 could have adverse health, educational, social, emotional, economic, and other implications. Further lowering of risks by eliminating at least 50 percent of the ovulatory cycles between menarche and a woman's first full term pregnancy could probably not be accomplished without drugs whose long term effects could include bone loss and other serious adverse effects. It is also premature to consider testing women for mutations in the genes conferring high absolute risk, since the only effective therapy currently available is bilateral mastectomy. Thus, although substantial knowledge has accumulated about etiologic factors for breast cancer, the consequences of early modification of key risk factors are potentially harmful. The results of initial chemoprevention trials require replication and consideration of serious side effects.

Further epidemiologic research is also needed to identify causes of the substantial proportion of breast cancer that remains unexplained. For example, investigation is needed to characterize genetic and environmental determinants of the specific hormonal patterns that increase risk on the population level and the individual level. Epidemiologists should pursue further the interrelations among dietary fat, total calories, consumption of fruits and vegetables, physical activity, and anthropometric characteristics (including body weight, body composition, and stature) at specified time points during subjects' lifetimes. Multicenter studies that enroll subjects from populations with substantial variation in diet, physical activity, reproductive variables, and other exposures are needed to clarify reasons for the notable differences in breast cancer incidence. The compelling evidence from migrant studies, particularly the rise in rates among first and second generation immigrants from Asian countries (168, 169, 175), and data demonstrating excess mammary tumors among the adult offspring of animals treated with carcinogens during pregnancy (176) have led to a hypothesis that risk of adult breast cancer may be related to high estrogen exposure in utero (177). Results from a limited number of epidemiologic studies using proxy indicators of prenatal estrogen exposure are largely consistent with the hypothesis, but

additional studies that utilize valid measures and explore the potential role and mechanism for estrogens and other possible agents during the prenatal, early childhood, and adolescent periods are clearly needed (178). Epidemiologic studies will also need to evaluate the major genes associated with high risks of breast cancer, as well as the many genes suspected of conferring low to moderate risks. Additional chemoprevention trials of tamoxifen, raloxifene, and other compounds with fewer serious side effects than tamoxifen are already under way for testing the efficacy of these agents in reducing the occurrence of primary breast cancer in high risk populations.

CONCLUSION

The advent of a new century provides the stimulus for refocusing our vision and implementing bold new initiatives in cancer epidemiologic research. Although the purview of cancer epidemiology has expanded notably during the past few decades, cancer epidemiologists will need to further broaden their activities if progress is to continue. New hypotheses and conceptual advances from within and outside of the field will be essential for any forward leap. Many of the new approaches will require extensive collaboration among a wide range of scientists. The growing trend of cancer epidemiology to become more biology-based will necessitate closer integration of efforts between epidemiologists and experimentalists. Epidemiologic studies of the behavioral determinants (cigarette smoking, excess alcohol consumption, overeating) of some of the major categories of cancer etiology (tobacco, alcohol, excess calories) are clearly among the most important initiatives for the new millennium. Because these behaviors are increasingly recognized to derive from a complex mixture of heritable and environmental origins (179), it is difficult to understand how epidemiologic studies of these behaviors would be considered to fall within the province of public health practitioners but not considered particularly relevant to good clinical research and practice (180). In our zeal to incorporate the exploding amount of data from molecular genetics, biology, and microbiology within cancer epidemiologic studies, it will also be critical to continue embracing the population-level perspective. Recent history and innumerable examples have underscored the value of the population perspective in virtually all elements of epidemiologic research (181, 182). It is important to remember that many of the recent discoveries on causes of cancer (e.g., hepatitis B virus and liver cancer or HPV and cervical cancer) derived directly or indirectly from epidemiologic analytical studies that followed up findings from systematic comparisons of cancer incidence within and among populations internationally (12, 14, 26, 34, 100, 129, 181).

Although independent epidemiologic investigations in diverse populations will be essential for testing the reproducibility of results, greater cooperation among epidemiologists will be required to enable detailed comparisons of study results and to clarify reasons for differences in findings. The increased use of the strategy of pooling data to resolve questions about rare tumors or cancer subtypes and to obtain more precise estimates of small increases or decreases in risk will require close collaboration, not only in analyzing and interpreting the pooled data but also in planning the original studies, to maximize overlap and consistency in key features of the studies. Closer collaboration will not obviate the ongoing requirement to critically evaluate and honestly acknowledge the limitations inherent in individual studies as well as pooled observational data.

Results of cancer epidemiologic studies will be assuming a more central role in risk assessment in the coming millennium. To that end, epidemiologists should identify and develop constructive approaches for addressing the critical gaps in knowledge, the limitations of existing exposure assessment approaches, the design problems of existing studies, the important biases, and the many sources of uncertainty characterizing the body of relevant epidemiologic studies. Because epidemiologic studies provide the only information about dose-response relationships in humans, one could argue that cancer epidemiologists should be closely involved in identifying relevant epidemiologic studies to be utilized and/or excluded from risk assessments. In addition, cancer epidemiologists should play a more important role in interpreting high dose to low dose extrapolation. Cancer epidemiologists should also be more involved in identifying sources of uncertainty.

Scientific and media reports of cancer epidemiologic studies have dramatically risen in number during the past decade. To assist the general public and the media in understanding findings, cancer epidemiologists will need to clearly communicate key epidemiologic concepts and principles of interpretation. Among the critical concepts that will have to be defined is the difference between a mere statistical association and a causal association with biologic meaning. Clarification of this will require cancer epidemiologists to clearly describe the key criteria that distinguish causal associations from noncausal ones (38, 183). Cancer epidemiologists will also need to provide detailed interpretations of the meaning of small increases in cancer risk, distinguishing true cause-and-effect relations from associations due to chance or to undetected bias. Related to this will be the need to convey when small relative risks may be etiologically important and the impact of small increases or decreases in risk upon

incidence and mortality, assuming that causality has been established. Clear and meaningful examples will help illustrate these concepts for the public and the media. Other recurrent topics that should be addressed in communications with laypersons or the media include: the key characteristics of different study designs, eligibility criteria for selecting study subjects, ascertainment of data sources, methods for exposure assessment, and interpretation of the results of a single study, meta-analysis, or pooled analysis. The epidemiologist should also be able to clarify how epidemiologic studies differ from laboratory studies and from clinical trials. It will be important for epidemiologists to communicate not only the results and conclusions of specific studies but also the associated limitations and data uncertainties. Above all, it will be critical for cancer epidemiologists to explain a study's contribution to existing scientific evidence. Improvements in communication will also require cancer epidemiologists to listen more closely to concerns about known and suspected cancer risk factors as expressed by members of the public, the media, and policy-makers. Cancer epidemiologists should play a central role in the ongoing dialogue directed at identifying and correcting misperceptions about cancer risk factors (184).

The role of epidemiologists in setting public health agendas, policy-making, and advocacy has been much debated (185–188). Regardless of one's position, most epidemiologists will agree that findings from cancer epidemiologic studies will be used as the basis for public health practice, prevention strategies, and current and future policy objectives. What are the key public health and policy challenges facing cancer epidemiology at the turn of the millennium? From the profession's lengthy experience in clarifying the relation between tobacco use and cancer risk, it is apparent that identification of cancer causes may not be sufficient to reduce the cancer burden associated with those causes. Although further epidemiologic research is certainly warranted to evaluate factors characterizing individual susceptibility and tobacco-gene interaction(s), cancer epidemiologists also can play a key role by contributing their expertise on any of a large number of other fronts to the advancement of the ultimate goal of eliminating tobacco use. Some of us will be in the forefront of setting policy or even enacting or lobbying for new legislation on tobacco control, whereas others will focus exclusively on enlarging the database, either through application of epidemiologic methods to the identification of behavioral determinants or through evaluation of the molecular basis of increased susceptibility. Regardless of the approach taken, cancer epidemiologists should strive to promote the elimination of tobacco use, expending their greatest efforts on the prevention of use by children and adolescents and the cessation of use among young to middle-aged adults (98, 101).

On the brink of an explosion of new knowledge in human molecular genetics, we are faced with frequent efforts to limit the use of biologic specimens and limit access to medical records. Cancer epidemiologists should aggressively oppose such restrictions while vigilantly maintaining subjects' rights to confidentiality and privacy. Breakthroughs in the understanding of important aspects of carcinogenesis are likely to occur if a very broad range of efforts are pursued, regardless of the rank order of the cancer or related outcome under investigation. However, public health and policy goals require that we maintain a quantitative understanding of the role of various carcinogens in causing cancer in our own and other populations. Regular updates of the approach used by Doll and Peto (1) could help to clarify the population attributable risks for carcinogenic exposures. Implementation of this type of approach, using broader definitions for exposure and outcome, could provide some guidance to policy-makers, although many other considerations discussed above should also inform decision-making. In addition to widespread utilization of all possible cancer risk reduction strategies on a population basis, we might also envision a future in which routine preventive medical care will include characterization of an individual's risk of cancer by identifying that person's (and perhaps his or her potential offspring's) unique susceptibilities and resistance to various exogenous agents. Provided that disclosure of such information is restricted to the patient, the individual could use such information to choose a healthy diet and lifestyle and seek to avoid harmful environmental and occupational exposures. On a population level, the timely and ongoing synthesis of data across studies and extrapolation of findings to the population (particularly to subgroups at high risk) could inform and guide policy-making for disease prevention and treatment services and for additional scientific research needs.

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