The New Era of Cancer Epidemiology

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Introduction
Cancer epidemiology is at the threshold of a new era. Leading contemporary epidemiologists have recognized and begun to analyze this phenomenon from a historical perspective (1–4). We are not witnessing a staid science looking for rejuvenation but rather a vigorous discipline in search of full expression of its potential contribution to human well-being. Epidemiology has been appropriately described as a relatively new science that is still in its adolescence (5).

Cancer epidemiology attempts to interpret the distribution and determinants of the neoplastic diseases with the utilitarian aim of preserving human health. The new thrust comes mostly from two important developments. The first is the remarkable technological progress so skillfully being exploited to examine the complexities of the biological phenomena which precede and/or accompany the ultimate “end point” of invasive neoplasia. This is the field conventionally being identified as that of biomarkers. The second thrust is the increased ability to utilize new knowledge of causality and biomarkers to conduct prevention research. The epidemiological demonstration of causality has historically provided the basis for prevention. John Snow’s research on cholera led him to remove the handle of the Broad Street pump and stop the epidemic in London in 1848. The impressive progress made in cancer prevention in a relatively short time, counted in decades rather than in centuries, provides a strong stimulus to continue forward without being discouraged by the enormity of the task. Disease and death attributable to cancer will probably continue to be one of the most onerous human burdens in the twenty-first century.

In an attempt to bring into perspective today’s portrait of cancer epidemiology, this editorial will highlight some crucial contributions of classical epidemiology, comment on its apparent limitations, take a glimpse at the emerging new opportunities of modern science, mention possible new tools and new approaches, and dwell on the need for interdisciplinary collaboration to face the new challenge.

Historical Perspective
The basic tool of epidemiology is the quantification of events and experiences in human life. Opportunities to chart the social course of disease abound in the records of previous centuries. In a study of occupational health hazards published in 1700, Ramazzini recorded an excess of breast cancer in nuns and suggested that it was related to celibacy (6–7). Rigoni Stern studied death certificates for the city of Verona for the years 1760 to 1839 and described the relative frequency of cancer by site, age, sex, civil status, and certain professions (8–10). He provided the following account of the number of deaths from uterine and breast cancers:

<table>
<thead>
<tr>
<th></th>
<th>Uterine</th>
<th>Breast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuns</td>
<td>4</td>
<td>36</td>
</tr>
<tr>
<td>Other unmarried women</td>
<td>16</td>
<td>50</td>
</tr>
<tr>
<td>Married women</td>
<td>225</td>
<td>99</td>
</tr>
</tbody>
</table>

In his series breast cancer was 9 times more common than uterine cancer in nuns, 3 times more common in other unmarried women, but less than half as common in married women. The basic mechanisms underlying this peculiar distribution have yet to be understood. His findings apparently did not make an immediate impact in terms of generating further research. Only in recent decades, with more advanced epidemiological techniques, have the biological phenomena represented in his findings been explored in some depth, namely the possible role of sexually transmitted infectious agents in cervical carcinoma and the protective role of early pregnancy in breast carcinoma.

The lung cancer epidemic, brought about by the popularization of the smoking habit around the time of the first world war, has had a profound impact on cancer epidemiology. The link between tobacco and lung cancer was suspected as early as the 1930s by clinicians like Alton Ochsner and documented from pathology records by F. H. Mueller (12, 13). Mueller compared 86 male lung cancer patients seen at Cologne hospitals with 86 “normal persons.” Interviews with patients and relatives provided the following results:

<table>
<thead>
<tr>
<th></th>
<th>Lung cancer</th>
<th>Normal persons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-smokers</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>Moderate and heavy smokers</td>
<td>40</td>
<td>63</td>
</tr>
<tr>
<td>Very heavy and excessive smokers</td>
<td>43</td>
<td>9</td>
</tr>
</tbody>
</table>

This appears to have been the first case-control study of lung cancer, clearly showing a dose-effect relationship. But the real impact on cancer epidemiology was made by the seminal research of Doll and Hill (14) in Britain and of Wynder and Graham (14) and Levin et al. (14) in the United States published in 1950 and over the following years. Epidemiologists throughout the world then applied case-control methodology to study lung cancer and confirm and expand the results of these pioneering studies. The lung cancer epidemic also provided the opportunity to successfully apply the methodology of prospective cohort studies. The case studies of “one million men and women” gathered by American Cancer Society volunteers and published by Hammond and Horn (16), the follow-up of U.S. war veterans by Dorn (17), and the study of British doctors by Doll and Hill (18) are classics of this research. The remarkable similarity of the findings, including the “dose response” of these large but diverse cohorts followed for more than 20 years,
greatly strengthened the evidence needed to assign a cause-effect relationship between smoking and lung cancer. The epidemiological studies on smoking-related cancers provided the material for the Surgeon General’s 1964 report on smoking and health, a landmark consensus document (19). Smoking cessation and prevention activities were direct consequences of that report.

Lung cancer dominated cancer epidemiology for decades, but many other success stories resulted from the application of the epidemiological approach to other cancers, providing much of the current information on causality. Although these are too numerous to summarize, a few selected examples may highlight some areas of interest. The study of the role of the industrial revolution in cancer causation, a particularly difficult field because of the problems in documenting exposure (7), has provided some important contributions, such as those of Selikoff and Hammond (20), on the association of asbestos fibers with mesothelioma and their synergistic role in smoking-related lung cancer. Epidemiological studies have also contributed to the identification of “protective” factors, such as the frequent intake of fresh fruits and vegetables, which seem to exert their beneficial effect in several types of cancer through mechanisms still poorly understood. These findings are prominent in some major cohort studies such as the census-based Japanese cohort investigated by Hirayama (21) and the U.S. nurses studied by Willett (22). Major advances in the infectious etiology of human cancer have been made with cohort studies such as Beasley’s finding of a relative risk close to 100 for liver cancer in hepatitis B carriers of a Taiwanese cohort of civil servants (23). Hormonal influences in cancer causation, suggested by Ramazzini and Stern a long time ago, have been elegantly demonstrated by McMahon et al. (24), who reported that early full-term pregnancy protects against breast cancer. These results have found a possible mechanistic explanation in the studies of Russo and Russo (25) showing that the epithelial lining of breast ductules, which is highly susceptible to carcinogens, is hormonally transformed in late pregnancy into alveolar epithelium, which is highly resistant to carcinogens.

Scientists carrying out studies on the epidemiology of cancer and cardiovascular diseases have developed new methods to analyze data, such as the Mantel-Haenszel procedure and multivariate techniques, including logistic regression (26, 27). Descriptive epidemiology, an important base for the formulation of causal hypotheses, has been well served by the development and use of large data sets such as the Surveillance, Epidemiology and End Results program of the National Cancer Institute and the now classic series, Cancer Incidence in Five Continents, originated by the International Union Against Cancer and continued as a collaborative effort between the International Association of Cancer Registries and the International Agency for Research on Cancer. Some prominent members of this network of population-based cancer registries were greatly stimulated by William Haenszel, the head of the Biometry Branch of the National Cancer Institute. He also advanced the field by demonstrating the site-specific effects of transcultural migration on cancer incidence and mortality.

Limitations of Classical Cancer Epidemiology
The lung cancer epidemic was instrumental in launching cancer epidemiology as a distinct discipline. In other cancer sites, however, classical epidemiological techniques have provided a less dramatic contribution. The tobacco epidemic was unique; a mixture of over 3800 chemical substances containing at least 43 known carcinogens began to be inhaled regularly in large amounts by millions of persons within a defined time period throughout the world. In its impact, chronicity, and ubiquity this event is unique in human history. Other remarkable carcinogenic events affecting humans are more circumscribed, such as the atomic bombs which have induced well-studied cancer epidemics of lesser proportions. For the other major cancers affecting humanity at the present time, no such dramatic event has been identified. This is the case for gastric, colorectal, mammary, prostatic, pancreatic, bladder, and hematopoietic cancers. Some less widespread epidemics, such as that of liver cancer in some African and Southeast Asian populations, may also be associated with an overriding etiological factor such as the hepatitis-B virus. But it would appear that the multifactorial “web of causation” is much more complex for the other major cancers. The unanimity of findings on the tobacco-lung cancer association seen in international studies is not seen when other factors, such as fat intake in breast cancer, are tested by different epidemiologists. This lack of concordance does not negate the effect, but it does point to more complex associations which may require new approaches and/or refinements of epidemiological techniques.

Epidemiological studies have pointed to mechanisms less simple or direct than the tobacco-lung cancer association. One such mechanism is transplacental carcinogenesis, well illustrated by Herbst et al. (28) in their discovery of a miniepidemic of vaginal cancer in the daughters of women who took diethylstilbestrol during pregnancy. Synergistic effects such as those of asbestos and tobacco for lung cancer and smoking and alcohol for oral-pharyngeal cancer have been described (29, 30). Opposing actions between etiological factors are also suspected in the protective effects of fresh fruits and vegetables on lung and other cancers. The interplay of biological and physicochemical factors has recently been suspected, such as in the case of hepatitis B virus and aflatoxin in hepatocellular carcinoma and of Epstein-Barr virus and salted fish in nasopharyngeal carcinomas (31–34). The in situ formation of carcinogens, such as intra-gastric nitrosation of organic compounds, remains a distinct possibility. Epidemiological as well as experimental studies have pointed out that invasive cancer may be the final step in a prolonged multistep process. Berenblum’s (35) classical model of carcinogenesis requiring initiator and promoter forces acting sequentially, if analyzed simplistic with classical epidemiological techniques, may lead to the false conclusion that either the initiator or the promoter is not a carcinogen if taken out of sequence. Initiators and promoters have yet to be separated as individual sets of factors in human epidemiological studies. Berenblum’s model of carcinogenesis and its further development (37) has brought attention to the interplay of two key cellular events: mutation and proliferation. The importance of hyperproliferation is the focus of recent interest (37–39). The sufficiency of proliferative changes to transform normally differentiated tissues into neoplastic ones has been seriously challenged (40). The ongoing controversy is well illustrated by pointing out...
that normal hormones such as estrogens and androgens may increase cancer incidence in certain populations (41) which could lead to their classification as carcinogens. Trials are under way that attempt to counteract the “carcinogenic” effects of estrogens by chemoprevention (42). The importance of other factors in such a chain of events is illustrated by the fact that under certain circumstances estrogens may prevent breast cancer by contributing to the transformation from ductular to lobular epithelium (43). Classifying normal hormones as carcinogens may result from a narrow vision of a complex multifactorial and multistep process.

The lung cancer epidemic deemphasized the role of genetic predisposition. It seems clear that all men and women are susceptible to lung cancer if the dose of tobacco is high and prolonged enough and if competing risks of other diseases do not cause the demise of the host. Only recently have we learned that susceptibility may play an important role in certain individuals and that those individuals may be identified by the way they metabolize certain drugs such as debrisoquine (44). Epidemiologists with keen observational skills like Robert Miller (45) have identified special clinical associations such as congenital aniridia-hemihypertrophy and Wilms’ tumor and pointed to the need for the study of the interaction between genetic susceptibility and environmental forces, called “ecogenetics” by Mulvihill (46). Genetic susceptibility has been well established in retinoblastoma and has also been made evident by familial clusters of diverse tumors such as breast cancer, sarcomas, and gliomas in the Li-Fraumeni syndrome (47).

**Segments of the Chain of Causation**

Tobacco smoke is such a powerful carcinogen that classic epidemiological studies had no trouble connecting the exposure (tobacco smoke) to the final result (invasive lung cancer). But it has been well recognized that numerous events take place in the many years that elapse between the first exposure and invasive cancer and that many forces act at different points, either enhancing or retarding the progression of the carcinogenic process, the so-called modulation. Auerbach et al. (48) described in detail the process of metaplasia and dysplasia of the neoplastic bronchial epithelium. Isolating and describing such segments of the chain of causation is a new challenge for epidemiologists.

A complex hypothetical model of causation has been developed for stomach cancer, which has a “latent” or “incubation” period of several decades. Multidisciplinary research with an epidemiological orientation has documented the precancerous morphological changes and provided evidence for several etiological forces which seem to act at different points of the chain, as illustrated in Figs. 1–4 (49).

Before the epithelial cells of the gastric mucosa develop malignant characteristics and invade the neighboring tissues, at least 6 histological changes can be identified. The first two represent cell injury, repair (superficial gastritis), and gland loss (chronic atrophic gastritis). At these stages the epithelial cells preserve the original morphological phenotype. The subsequent steps express different phenotypes, apparently representing successive genotypic changes (mutations): the cells first resemble small intestinal epithelium (metaplasia of small intestinal type); colonic epithelium (colonic metaplasia) then expresses morphological nuclear abnormalities (dysplasia) and finally acquire the capacity to invade. When atrophy (chronic atrophic gastritis) sets in, the microenvironment of the gastric cavity is changed drastically, mainly as a result of the decreased secretion of hydrochloric acid and pepsin. An abnormal bacterial flora colonizes the mucosa. Many such anaerobic bacteria contain potent reductases which convert nitrate from...
food into nitrite, a very reactive molecule capable of nitrosating other nitrogen-containing substrata. In these chemical reactions organic compounds with the N=O (nitroso) bond are formed. Many such compounds are mutagenic and carcinogenic. Some nitrosocompounds are excreted in the urine. The so-called Oshima-Bartsch test (50) proves that in situ nitrosation does take place when nitrite and proline administered independently by mouth appear as nitrosopropine in the urine. It has been proposed that nitroso mutagens formed in the gastric microenvironment are responsible for the genotypic abnormalities observed in the advanced stages of the pre-neoplastic process in humans. This model provides an opportunity to postulate and test for etiological factors directed at specific points of the chain of causation.

The recently discovered bacterium Helicobacter pylori is a cause of chronic gastritis, which is very prevalent in many populations at high gastric cancer risk. In some such populations the gastritis is very severe and is present from childhood until old age (51). Food irritants, especially highly salted foods, are also capable of inducing gastritis. NaCl induces in experimental animals a state of hyperproliferation, which may potentiate the effect of carcinogens (52) (Fig. 2). The next step, atrophy or gland loss, is observed in some precancerous states such as the pernicious anemia syndrome, presumably due to circulating anti-parietal cell autoantibodies. In most populations such a syndrome is not a factor, and the cause of atrophy is not known. Epidemiological evidence in humans coincides with experimental studies linking mucosal atrophy to excessive salt intake (53, 54). The determinants of microenvironmental changes leading to excessive NO₂ production are the supply of NO₃ from food and drinking water and probably the dietary supply of reduced vitamin C (ascorbic acid), which blocks the nitrosation reactions (55) (Fig. 3). In the final stages, presumably driven by successive mutations, β-carotene may play a role as suggested by epidemiological and experimental evidence (56, 57). Other possible factors acting in the final stages are salt intake, which enhances experimental carcinogenesis, and ascorbic acid, which promotes fibroplasia and impedes tumor spread (58).

This model proposes that several etiological factors play specific roles in the chain of causation, at specific points of the chain and with a certain degree of interdependence. This is well illustrated by epidemiological studies addressing the nitrate factor. Nitrate ingestion (as measured by urinary excretion) has been correlated with precancerous lesions in Colombia. In England, however, nitrate ingestion correlated inversely with gastric cancer rates (59). Eisenbrant (60) has shown that nitrate intake results in excessive nitrite in the gastric cavity only in patients with chronic atrophic gastritis. Nitrate in Colombia is mostly found in water and in leguminous food such as fava beans containing a precursor which forms a highly mutagenic compound after nitrosation (61). In England, however, nitrate is mostly obtained from fresh vegetables which are associated with lower cancer risk. This example illustrates the intricacies of the interaction of etiological factors and biomarkers of precancerous changes. It also illustrates the need for close collaboration between epidemiologists and laboratory scientists.

The Need for Intermediate End Points: The Molecular Biology Revolution

In recent years cancer epidemiologists have been searching for events prior to invasive cancer which can be utilized to study cancer causation. Increasingly, classical epidemiological studies are including laboratory components intended to evaluate biological events accompanying or preceding invasive cancer (biomarkers). Names such as “genetic” (or “eco-genetic”), “biochemical,” “metabolic,” and “molecular” epidemiology are applied to refer to this new generation of approaches which combine epidemiology with laboratory sciences.

Prominent among these new approaches are attempts to provide epidemiological guidance to studies of the molecular biology of cancer and the precancerous process. Molecular biologists are increasingly utilizing human material (tumors, tissues, cells, biological fluids) to study the neoplastic process and are making substantial contributions to our understanding of the precancerous chain of events. These events occur in humans who belong to populations that clearly require epidemiological guidance in their interpretation and possible extrapolation to other human populations. New discoveries of
molecular abnormalities are being made at an almost overwhelming pace, reminiscent of the Koch-Pasteur era, in which species after species of bacteria were being discovered. Then as now, it took considerable epidemiological effort to sort out which of those bacteria are harmful, which are innocent bystanders, which play a beneficial role, and which could change from one status to another, mostly depending on the environment. Impressive progress has been made in the study of xenobiotics, their metabolism, their interaction with DNA, and their effects on cell-cell communication and other cell functions. A new and growing series of biomarkers is being developed which provides information on exposure, biological response, and host susceptibility. Chromosome abnormalities, micronuclei, DNA adducts, pharmacokinetic measurements, oncogene activation, sister chromatid exchange, and over 150 cytochrome P450 enzymes are just a few of the new tools that provide a fresh look at the problem of the "Achilles' heel" represented by the inability to document exposure in studies of environmental epidemiology (62). Scientists outside the field of molecular biology are waiting for a settling down of the explosive field of oncogene research, which has provided more findings than can currently be assimilated in a logical way to understand the human carcinogenic process.

A more immediately useful avenue relates to genes that negatively regulate cell division or abnormal cellular growth. The study of these "suppressor" genes has been important in the application of molecular genetic approaches to the study of inherited predisposition to cancer and of cytogenetic aberrations in affected individuals and their tumors. In familial retinoblastoma, a loss of the suppressor gene is inherited as an autosomal dominant predisposition (63) detectable as a deletion in chromosome 13 (64). Knudson's analysis of the age of diagnosis of unilateral and bilateral cases led to the now well-accepted "double deletion" hypothesis in which two distinct events are required for the initiation of the tumor (65). This has been further defined as genetically recessive predisposition through the use of DNA marker technology by Cavenee (66, 67) and utilized for premorbid detection of predisposed gene carriers (68). This paradigm has now been extended to other human cancers (69) and to the isolation of the retinoblastoma gene (70) and the in vitro abrogation of tumorigenicity in retinoblastoma cells (71). It has a number of corollaries that extend its explanatory power (72) and promise to provide important tools for the new epidemiology. A second major suppressor gene, p53, has been found to be either deleted or mutated in malignant neoplasms of different organs (73). Mutations of the p53 gene have been found in cells of unaffected members of families with the Li-Fraumeni syndrome, suggesting that the double deletion hypothesis is also applicable to this cancer family syndrome (74). A series of studies by Vogelstein et al. (75) has indicated that the formation of colorectal carcinoma is intimately associated with a cumulative series of genetic alterations. Epidemiologists have identified several risk factors for colorectal cancer, recently summarized by Bruce (76), but have not yet provided a comprehensive etiological hypothesis. It is hoped that epidemiologists and molecular biologists will together establish the chronology and interdependency (if any) of the etiological factors of colorectal cancer.

The fruitful interaction between epidemiologists and molecular biologists is well illustrated by the progress made in the understanding of the etiology of uterine cervical carcinoma. Descriptive and analytical epidemiology studies have pointed to sexually transmitted infectious agents as a major etiological factor. The same type of studies have focused on the human papillomaviruses and identified a subset, especially types 16 and 18, as linked to invasive carcinoma (77). Other types, such as 6 and 8, were linked to benign neoplasms. Molecular biologists have reported that types 16 and 18 have two oncogene products, E6 and E7 proteins. E6 will bind to p53, forming a complex that inactivates the suppressor gene. Similarly, E7 will bind and inactivate the retinoblastoma gene. It thus appears that the oncogenic function of papillomaviruses is mediated by their capacity to bind and inactivate two major tumor suppressor genes (78, 79). The immortality of Hela cells is apparently due to the fact that they are infected with papillomavirus 18 (80).

Cancer Epidemiology and Social Sciences

As expressed by Susser (1), "Epidemiology is a human science, inevitably entangled with society." Human populations are at the center of epidemiological activity as well as the beneficiaries of its discoveries. Understanding human behavior, especially as it relates to populations, is therefore essential in order to conduct epidemiological research and to apply new knowledge to prevent disease. Social aspects are frequently ignored in cancer epidemiology research and may be responsible for some of its shortcomings. It has taken decades for the epidemiological findings on the carcinogenic influences of smoking to exert an impact on society, enabling a reduction of smoking habits. There are still too many millions of smokers, too many legislators who fail to address the smoking problem, too much deceptive advertising, and too many adolescents starting nicotine addiction every day. Only through behavioral research will it be possible to improve this situation. The tobacco industry has been very successful in targeting high-risk populations and designing strategies for addiction. The mercenary use of scientific knowledge to stimulate a lethal addiction is harmful to society; it is the antithesis of epidemiology.

Fortunately, behavioral scientists (psychologists, physicians, sociologists) have joined the forces of epidemiology and made important contributions to cancer prevention. They have analyzed the components of smoking behavior, defined nicotine addiction, and devised strategies to decrease initiation and facilitate cessation of smoking. These efforts preceded and influenced positive social forces that led to restrictive legislation on public smoking, raised taxation, and revealed the deceptive marketing strategies of the tobacco industry (81). The recently published reports of the Surgeon General on the benefits of smoking cessation and the consequences of nicotine addiction are new landmarks in cancer prevention (82, 83). An outstanding example of the contribution of behavioral scientists is the improved technology to maintain adherence to cancer prevention programs (84). A tangible impact of the benefits of prevention are the screening and early detection programs that have contributed substantially to reducing the lethality of cervical and breast cancers (85, 86).
Epilogue
The recent expansion of knowledge and technology relevant to cancer etiology mandates interdisciplinary collaboration in its research. It no longer seems possible for one scientist, à la Leonardo, to master sufficient knowledge and techniques to advance the field alone. Scientists in many fields have made important contributions to epidemiology. Many prominent epidemiologists have come from other disciplines, such as statistics and clinical medicine. More than ever, laboratory scientists working with human material are contributing to cancer epidemiology. The key to progress in the future may be in the collaborative work between scientists from several disciplines, forming teams in which epidemiological thinking and methodology play coordinating roles.

Following the advice of Susser, such teams could bring to cancer epidemiology a new depth by taking advantage of the exciting recent advances in biology, and expanded breadth by utilizing more fully the concepts and techniques of the social sciences.

References
7. Stern, R. Fatti statistiche relativi alla malattie cancerose. Giornale per Ia Leonardo, to master sufficient knowledge and techniques to advance the field alone. Scientists in many fields have made important contributions to epidemiology. Many prominent epidemiologists have come from other disciplines, such as statistics and clinical medicine. More than ever, laboratory scientists working with human material are contributing to cancer epidemiology. The key to progress in the future may be in the collaborative work between scientists from several disciplines, forming teams in which epidemiological thinking and methodology play coordinating roles.

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