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EPIDEMIOLOGIC APPROACHES TO CANCER ETIOLOGY[1]

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INTRODUCTION

Epidemiology has contributed substantially to knowledge about the causes of human cancer and provides the basis for preventive measures. The approach dates from 1700 when the occupational physician Bernadino Ramazzini reported that nuns were at high risk of breast cancer, and 1775 when the surgeon Percivall Pott found that chimney sweeps exposed to soot were prone to scrotal cancer (1). In more recent times the initial leads to epidemiologic investigations have continued to come from astute clinicians who noted an excessive number of patients with the same tumor and traced the "cluster" to a particular cultural, occupational, or iatrogenic exposure. New insights into cancer etiology are provided also by experimental approaches to detect carcinogens in laboratory animals or mutagens in short-term test assays, and to clarify basic mechanisms of carcinogenesis. In recent years the pace of epidemiologic and experimental research in cancer etiology has accelerated, including efforts to identify environmental determinants, which are generally held responsible for a large proportion of cancers in the general population (2).

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DEMOGRAPHIC PATTERNS

Cancer is second only to heart disease as a cause of death in the United States, and accounts for 20% of all deaths. It is estimated by the American Cancer Society that in 1981 about 815,000 Americans will develop cancer, excluding in situ carcinomas and nonmelanoma skin cancer, and that about 420,000 will die from this disease (3). The most common cancers arise from the lung in males, the breast in females, and the colon and rectum in both sexes combined. These three sites account for over 40% of cancer cases and deaths in the United States. The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute has recently published detailed information on the incidence and mortality from cancer during the first five years of operation, 1973–1977 (4). The 11 areas participating in the Program represent over 10% of the US population, and permit analyses according to a variety of demographic variables, including ethnic groups and geographic areas, that provide important clues for epidemiologic investigation.

It has been widely reported that 80% or more of all cancer is attributed to environmental influences, particularly those related to life style practices, and that this fraction of cancer is potentially preventable (5). These estimates are derived from the substantial international variation in cancer incidence, in which rates for the lowest risk countries are subtracted from the rates prevailing in the United States. The resulting difference is attributed to extrinsic causes, and the lowest risk is assumed to represent the baseline level for tumors that may be difficult or impossible to avoid. Around the world the reported age-adjusted incidence rates for total cancer vary by a factor of about three, while the range of rates for certain anatomic sites, particularly the esophagus and liver, is greater than 100-fold (6). The risks for the more common tumors in developed countries differ by factors of about 8 to 40, with substantial differences in rates apparent even when the analyses are confined to European countries (7). Although some of the global variation may be influenced by a genetic component or by reporting practices in different parts of the world, the major contribution of environmental factors is indicated by the patterns of risk among migrant populations, such as the Japanese who moved to Hawaii and California (8). Generally, as migrant groups adopt customs of the new land, their risk of various cancers shifts away from the rate prevailing in the country of origin to approximate that of the host country. The change in incidence for some cancers, notably the colon, is evident within two to three decades of migration, whereas the change for other cancers, notably the breast, requires more than one generation. Although variations within countries are not as great as those seen internationally, the mapping of mortality statistics at the county level in the United States, China, and other countries has revealed geographic peculiarities and clustering that provide starting points for etiologic studies (9, 10).

Variations in cancer incidence and mortality over time may also reflect environmental factors, although some fluctuations can be explained by changing medical practices and reporting procedures (11). Most dramatic has been the increase in lung cancer rates in all countries that have adopted the practice of cigarette smoking. Upward trends have been noted also for thyroid cancer resulting from X-ray exposures to the head and neck during childhood, malignant melanoma from changing clothing habits and recreational exposures to sunlight, and endometrial cancer from the use of menopausal estrogens (12). The increases in prostatic cancer, multiple myeloma, and certain other neoplasms are at least partly due to improvements in diagnostic measures. In the black population of the United States, sharp increases over time have been reported for cancers of the lung, esophagus, prostate, and pancreas, and multiple myeloma, so that these tumors are now more common in blacks than whites. Several cancers have shown little change in whites or blacks, while some have displayed downward trends, notably cancers of the stomach, cervix, and liver.

CAUSES OF CANCER

Although much remains to be learned about the factors responsible for the geographic and temporal variations of cancer in the general population, several environmental exposures have been identified as carcinogenic in man (Table 1). The evidence is based primarily on case-control studies (comparing the past experience of persons with and without a particular cancer) or cohort studies (following up individuals whose experiences and characteristics are already defined). There is a growing recognition, however, that most cancers result from the combined effects of multiple exposures and susceptibility states. This is consistent with multistage models in which different risk factors accelerate the transition rates at various stages of carcinogenesis (13). Some affect early stages as initiators, others act at late stages as promoters, while still others influence both early and late stages. It is generally thought that cumulative environmental exposures, long latency periods, and multistage processes account for the increasing risk of most cancers with advancing age.

Tobacco

The principal carcinogenic hazard to man is tobacco smoking, which produces cancers of the lung, larynx, mouth, pharynx, esophagus, bladder, pancreas, and probably kidney. It is estimated that smoking, especially of

Table 1 Environmental causes of human cancer

Agent	Type of exposure	Site of cancer
Alkylating agents (melphalan, cyclophosphamide, chlorambucil)	Medication	Leukemia, bladder
Androgen-anabolic steroids	Medication	Liver
Alcohol	Drinking	Mouth, pharynx, esophagus, larynx, liver
Aromatic amines (benzidine, 2-naphthylamine, 4-aminobiphenyl)	Manufacturing of chemicals	Bladder
Arsenic (inorganic)	Mining and smelting of certain ores, pesticide manufacturing and application, medication and contaminated drinking water	Lung, skin, liver (angiosarcoma)
Asbestos	Manufacturing and application	Lung, pleura, peritoneum
Benzene	Leather, petroleum, and other industries	Leukemia
Bis(chloromethyl)ether	Manufacturing of ion exchange resins	Lung
Chlornaphazine	Medication	Bladder
Chromium compounds	Manufacturing	Lung
Estrogens	Medication	
Synthetic (DES)		Vagina (adenocarcinoma)
Conjugated (Premarin)		Endometrium
Steroid contraceptives		Liver (benign)
Immunosuppressants (azathioprine, cyclosporin)	Medication	Lymphoma (histiocytic), skin (squamous carcinoma), soft tissue sarcoma
Ionizing radiation	Atomic blasts, treatment and diagnosis, radium dial painting, uranium and metal mining	Nearly all sites
Isopropyl alcohol production	Manufacturing by strong acid process	Nasal sinuses
Mustard gas	Manufacturing	Lung, larynx, nasal sinuses
Nickel dust	Refining	Lung, nasal sinuses
Phenacetin-containing analgesics	Medication	Renal pelvis
Polycyclic hydrocarbons	Coal carbonization products and some mineral oils	Lung, skin (squamous carcinoma)
Tobacco chews and powder	Snuff dipping and chewing of tobacco, betel, lime	Mouth
Tobacco smoke	Smoking, especially cigarettes	Lung, larynx, mouth, pharynx, esophagus, bladder, pancreas, kidney
Ultraviolet radiation	Sunlight	Skin, including melanoma
Vinyl chloride	Manufacturing of polyvinyl chloride	Liver (angiosarcoma)
Wood dusts	Furniture manufacturing	Nasal sinuses

cigarettes, contributes to about 25 to 35% of all cancer deaths in men and 5 to 10% in women (14). The greatest impact is on lung cancer, with the risk for male smokers of two or more packs per day being about 20 times that of nonsmokers, based on an evaluation of the three largest cohort studies (15). However, the rates for lung cancer are now rising more sharply in women than in men, reflecting the growing popularity of cigarettes among women in the past 20 to 30 years. Recent studies indicate that smokers of filter-tipped cigarettes with reduced levels of tar and nicotine have lower risks of lung and larynx cancers than do smokers of nonfilter cigarettes, but an even greater reduction of risk comes from cessation of smoking (16). The risks from cigar and pipe smoking resemble those of cigarette smoking for cancers of the mouth, pharynx, larynx, and esophagus, but the lung cancer risks are not greatly elevated over those of nonsmokers, presumably because cigar and pipe smoke is more irritating than cigarette smoke and less conducive to inhalation (17). Smokeless tobacco products are also of concern, since oral cancer has been linked with snuff dipping, a common practice in rural southern areas of the United States (18). In parts of Asia, oral cancer is very common in people exposed to various tobacco chews, which are often mixed with betel, lime, and other agents that may enhance the risks.

Alcohol

Consumption of alcoholic beverages has been shown to multiply the carcinogenic effects of tobacco smoking on cancers of the mouth, pharynx, larynx, and esophagus, but no such effect has been shown on the lung (19). For heavy drinkers who do not smoke, the risks appear only slightly elevated, so that the effects are strongly dependent upon smoking habits. Heavy drinking also increases the risk of liver cancer, particularly among cirrhotic patients. Based on these relationships, it is estimated that alcohol contributes to about 3% of all cancer deaths (20). Although some studies suggest that the carcinogenic effect is greatest following consumption of spirits, the bulk of evidence indicates that the influence of alcohol is independent of the type of beverage. Since pure alcohol is not carcinogenic in laboratory animals, the mechanism by which alcohol promotes carcinogenesis is not clear. Under suspicion are nutritional deficiencies associated with heavy drinking, the effects of congeners or contaminants (e.g., nitrosamines, hydrocarbons) in alcoholic drinks, and the capacity of alcohol to solubilize carcinogens or enhance their penetration into tissues lining the upper digestive and respiratory tract (21). Some recent studies have suggested that beer consumption may be related to cancer of the large bowel, particularly the rectum, although this association has not been confirmed (22).

Sunlight

The dominant risk factor for nonmelanoma skin cancer (squamous and basal cell carcinomas) and for malignant melanoma is ultraviolet (UV) radiation from the sun (23). The evidence is based on the tendency for skin cancers to arise on sun-exposed surfaces, the high rates among outdoor workers, the inverse correlation between skin cancer incidence and distance from the equator, the predisposition of light-skinned and especially fair-complexioned populations who sunburn easily, the resistance of dark-skinned populations with protective melanin pigment, the exceptional risks of skin cancer among persons with genetic diseases exacerbated by sunlight (e.g. xeroderma pigmentosum, albinism), and the capacity of UV radiation in repeated doses to induce skin cancer in experimental animals, particularly in the UV-B spectral range (290–320 nm) that causes delayed erythema in human skin (24). The intensity of UV-B exposure on the earth's surface is limited by the ozone layer in the stratosphere, but there is concern that this protective barrier may be impaired by certain atmospheric pollutants, especially the continued release of chlorofluorocarbons used in aerosol propellants, refrigerators, and air conditioners. Based on recent surveys of skin cancer in the United States, it is estimated that the relative impact of ozone depletion would be greater for squamous cell carcinoma, which shows a steeper gradient with UV-B exposure than does basal cell carcinoma (25). The relationship of melanoma to sunlight exposure is less clear cut, but the recent recognition of the dysplastic nevus syndrome as a precursor state has provided a better understanding of host susceptibility to this tumor (26).

Radiation

Although ionizing radiation probably accounts for less than 3% of all cancer deaths, it appears that virtually no site of the body is spared from its carcinogenic effects (27). It is difficult to measure directly the effects of low doses of sparsely ionizing radiation, such as X or gamma rays, and debate continues about the precise nature of the dose-response relationship at low doses. However, extrapolations are possible by studying populations who have been exposed to high and moderate doses for medical, occupational, or military reasons (28). These studies also provide insight into the basic principles of cancer induction. In general, the breast, thyroid, and bone marrow are the most radiosensitive organs (29). Radiogenic leukemia shows a wave-like pattern with the excess risks starting about 2–4 years after exposure, peaking at 6–8 years, and declining to normal within 25 years. In contrast, radiogenic carcinomas of various sites have a minimum latent period of 5 years, and a temporal distribution that closely resembles the natural incidence curve and suggests that age-dependent cofactors influence tumor expression. Except for dose of radiation, the age at exposure may be the most critical determinant of risk, with the vulnerable age groups varying with the type of cancer.

Surveys of medically irradiated populations have revealed excess risks of the following (29): (*a*) leukemia and other cancers in the radiation field among patients treated for ankylosing spondylitis, metropathia hemorrhagica, and various neoplasms; (*b*) breast cancer among women treated for postpartum mastitis or who received pneumothorax fluoroscopies for tuberculosis; (*c*) thyroid cancer among children treated for thymus enlargement, benign head and neck disease, or tinea capitis; and (*d*) cancers at the deposit sites of radioactive compounds (osteosarcoma with radium-224, leukemia with phosphorus-32, and leukemia and liver angiosarcoma with thorotrast). It is generally felt that significant lowering of the radiation burden to the population can be attained mainly from reduced exposure to X rays in medical and dental practice (27). This will require measures to improve the efficiency of x-ray equipment, and judicious weighing of the benefits versus the risks of radiation when diagnostic procedures and therapy are under consideration.

Occupation

Occupational exposures are usually reported to account for about 5% of all cancer deaths (2). However, the percentage varies according to the type of neoplasm and the geographic location, and is likely to change as new hazards are recognized or as protective measures are instituted. Since the present state of knowledge of occupational cancer is so limited, it has been difficult to resolve controversies over the proportion of cancer that may be attributed now or in the future to occupational exposures. The wide range of percentages suggested by various investigators has resulted usually from the kinds of assumptions that are made (e.g. extrapolating from animal studies, estimating effects of low doses when human data are available only for high exposure levels). In spite of this uncertainty, it is clear that no other approach has identified so many human carcinogens as the study of occupational groups (30). Usually the initial leads have come from clinical and epidemiologic observations, with subsequent confirmation by laboratory studies. Although benzene and inorganic arsenic have not been conclusively shown to be carcinogens in animals, an experimental study of benzene suggests a carcinogenic effect in rats (31), and epidemiologic analyses of lung cancer risk among smelter workers indicate that the effect of arsenic may be on a late stage in the manner of a promoting agent (32). In the case of mustard gas and vinyl chloride, the risks were detected in man after the substances had been shown to induce tumors in laboratory animals, although little attention was given to the experimental studies when first

reported. The effects of some carcinogens, particularly asbestos and radon, are greatly potentiated by cigarette smoking, so that programs to reduce either the workplace exposure or smoking would substantially lower but not eliminate the occupational risk. It is noteworthy that a number of manufacturing industries (e.g. furniture, leather, rubber) are associated with cancer risk, but specific carcinogens remain to be identified (30). Industrial hazards and their detection have important implications beyond the workforce, since most agents are not confined to the plant but ultimately become part of the general environment to which large segments of the population may be inadvertently exposed.

Pollution

Pollutants in the urban air have long been suspected in the etiology of lung cancer, with fossil fuel combustion products, especially polycyclic hydrocarbons, being of special concern (33). In several studies the rates for lung cancer have shown correlations with measurements of benzo(*a*)pyrene in the ambient air, yet the available evidence suggests that the urban excess of lung cancer is due mainly to cigarette smoking and partly to occupational exposures. In the large-scale survey of the American Cancer Society, age- and smoking-standardized rates for lung cancer were computed among men not occupationally exposed to dust, fumes, or vapors (34). No major differences in mortality were seen between urban and rural areas, or between cities characterized by indices of pollution. Another approach has been to extrapolate from studies of workers heavily exposed to hydrocarbons; the results have suggested only small effects from urban air pollutants, on the order of 10 cases of lung cancer per year per 100,000 men with average smoking habits (35). In some studies the effects of smoking a particular amount were greater in urban than rural areas, suggesting that tobacco smoke may interact with carcinogens in the ambient atmosphere (36).

Asbestos bodies and calcified pleural plaques have been reported in large segments of the urban population, but the effects on lung cancer following nonoccupational exposures are uncertain. It is clear, however, that mesotheliomas may result from neighborhood exposure to asbestos industries and from household contact with asbestos dust, particularly through laundering of work clothing (37). Another hazard may result from airborne levels of arsenic, since high mortality rates for lung cancer have been reported among male and female residents in communities with arsenic-emitting smelters (38).

Recently interest has centered on contaminants in drinking water, since several halogenated organic compounds (trihalomethanes) produced during chlorination are carcinogenic or mutagenic in laboratory tests. Levels of these compounds in drinking water have shown geographic correlations with the rates for cancers of the bladder and large bowel (39). Although it is difficult to evaluate causal relationships, efforts are being made through case-control studies that assess lifelong exposures to drinking waters of varying quality (40).

Medications

A valuable source of leads to carcinogens comes from studies of patients exposed to medicinal agents, which may presently account for about 1 to 2% of all cancers (41). This approach probably ranks second to occupational studies as a means of discovering substances that are carcinogenic in man. Although some drugs that cause cancer have been withdrawn from clinical practice, others are retained since risk-benefit considerations may warrant their use in certain conditions. A major impetus to research in this area was the discovery in 1971 that synthetic estrogens given during pregnancy produced adenocarcinomas of the vagina and cervix several years later in daughters exposed in utero (42). This was the first demonstration of transplacental carcinogenesis in humans, and also heightened concern about the hazards of exogenous estrogens given at any time. Subsequently, a series of studies firmly linked endometrial cancer to the use of conjugated estrogens for menopausal symptoms and then suggested that breast cancer may also occur excessively in exposed women (43). These findings are consistent with epidemiologic and experimental observations on breast and endometrial cancer indicating that the risks depend upon menopausal and ovarian status, and appear mediated by the metabolism of endogenous estrogens (44, 45). The hazards of oral contraceptives are less clear, but there are relationships to liver adenomas, to endometrial cancer among users of the sequential type of contraceptives, and possibly to breast cancer among high-risk women (e.g. with benign breast disease or familial predisposition) (41).

An excess risk of acute nonlymphocytic leukemia, and perhaps other cancers, has been seen among patients receiving alkylating agents, especially melphalan, cyclophosphamide, and chlorambucil (46). These risks may be acceptable when treating conditions with a poor prognosis such as metastatic cancer, but for conditions with a favorable long-term prognosis the benefits of treatment should be carefully balanced against the risks. These drugs may exert their action in part by breaking chromosomes, since other leukemogens (radiation, benzene) have a similar effect.

Immunosuppressive agents have been assessed primarily by studies of renal transplant recipients, most of whom have had azathioprine and corticosteroids (47). The risk of histiocytic lymphoma is very high, and first appears within months of transplantation. This explosive onset has suggested that a latent oncogenic virus may be activated by immunologic

mechanisms. For all other cancer combined, the excess risk is about two-fold and first becomes evident about two years after transplantation. It has not affected all forms of cancer as might be predicted by the hypothesis of "immunologic surveillance," but increased risks have been noted for cancers of the liver, biliary system, and bladder, and for soft-tissue sarcomas (including Kaposi's sarcoma), adenocarcinoma of the lung, squamous carcinoma of the skin, and malignant melanoma (48). Recently, other groups of patients receiving immunosuppressants have shown an excess of lymphomas, squamous carcinoma of the skin, and soft-tissue sarcomas, but at lower rates than those seen in transplant patients (49). It is noteworthy that the predominance of lymphomas with drug-induced immunosuppression is seen also among patients with heritable immunodeficiency syndromes (50).

Infection

Viruses have not been linked with certainty to the origins of any human cancer, although several candidate agents are under scrutiny (51). The epidemiologic patterns of cervical cancer have long suggested venereal transmission of an infectious agent, with herpes simplex virus type 2 being a chief suspect. The Epstein-Barr virus (EBV) is related to nasopharyngeal cancer and Burkitt's lymphoma, particularly in areas of the world where these tumors are highly prevalent. Hepatitis-B infection is related to hepatocellular carcinoma, especially in endemic regions of Africa and Asia. There is little evidence that any form of cancer is transmitted from one case to another, and reports of time-space clustering of leukemia and lymphoma have not been confirmed (52). A viral origin for Hodgkin's disease in young adults, however, is suggested by the association with childhood environments, such as small family size, that tend to reduce or delay early life exposures to infections, in a manner resembling paralytic poliomyelitis (53). In some cases EBV may be involved, since antibody titers appear elevated and an increased risk of Hodgkin's disease has been reported among persons with infectious mononucleosis.

Two new developments have expanded the opportunities for work in this area. Kaposi's sarcoma shows a geographic concentration in Africa resembling that of Burkitt's lymphoma and has been related to infection by cytomegalovirus (54). Recently, in the United States, clusters of this usually rare tumor have been identified in homosexual men, often in association with opportunistic infections and immunosuppression of unknown cause (55). Another discovery has been the isolation of a retrovirus from T cell leukemias in the United States and in the southwestern part of Japan where elevated rates have been reported (56).

If viruses are oncogenic in humans, it seems likely that predisposing factors are operating (12). Thus, EBV may interact with certain histocompatibility antigens to produce the high rate of nasopharyngeal cancer in Chinese populations, with persistent immunostimulation from malarial infections to induce African Burkitt's lymphoma, or with a genetic immunodeficiency trait to cause family clusters of lymphoma. Hepatitis-B infection may combine with dietary aflatoxin and other cofactors to produce liver cancer in endemic regions. In animal models the production of immunodeficiency enhances viral carcinogenesis, so that the comparatively narrow range of tumors complicating immunodeficiency states of man suggests that viruses play only a limited role in human cancer.

Parasitic infections affect the risk of cancer in certain developing areas of the world (57). In Africa and Papua New Guinea the geographic patterns of malaria and Burkitt's lymphoma are closely correlated; in the Middle East and north Africa schistosomiasis produces squamous carcinoma of the bladder; and in parts of Asia infestation with liver flukes (clonorchiasis and opisthorchiasis) predispose to cholangiocarcinoma.

Nutrition

International correlations and migrant studies have suggested that certain features of the affluent Western diet contribute to a large but uncertain proportion of all cancers (58). Various nutritional hypotheses are under study by epidemiologic and experimental investigations, although the mechanisms appear complex and difficult to unravel. The role of dietary fat in colon cancer has been suggested in some studies (59), and may act by increasing the concentration of bile acids in the bowel, which are then metabolized by bacterial flora into carcinogens or co-carcinogens (60). Dietary fat may also alter the risk of breast cancer (61), perhaps by increasing estrogen production or prolactin release (62). It has been suggested that dietary fat and caloric excess may contribute to endometrial cancer, including its associations with obesity, diabetes, and hypertension (45). Obesity is also associated with gallbladder cancer, which is consistent with its effect on gallstones, the major risk factor for biliary cancer (63).

However, there is evidence that a low intake of certain food classes may predispose to cancer. Several studies indicate that the risk of colon cancer is inversely related to the consumption of fiber, which may protect against intestinal carcinogens or precursors by dilutional or other effects (64). Micronutrients may also have a protective influence, since cancers of the lung and several other sites have been associated with a low intake of vitamin A and β-carotene (65). The risk of stomach cancer has been related to a deficiency of fruits and vegetables, especially those containing vitamin C, which may act by inhibiting the formation of carcinogenic nitrosamines in the stomach (66). In one study of colon cancer, patients ingested comparatively small amounts of cruciferous vegetables (e.g. cabbage, brussels sprouts, cauliflower), which contain indole compounds with the potential to inhibit carcinogenesis in laboratory animals (67). In a recent study of

esophageal cancer in the United States, the high rate among black men was attributed to heavy alcohol consumption and a complex nutritional deficiency state that could not be narrowed down to any particular food class or nutrient (68).

A variety of other dietary factors, including additives and contaminants, have fallen under suspicion (58). The consumption of aflatoxin, a carcinogenic metabolite of the fungus *Aspergillus flavus*, correlates closely with the distribution of liver cancer in high-risk areas such as Africa. Coffee intake has been associated with bladder cancer and recently with pancreatic cancer (69), but causal relationships have not been established. The artificial sweeteners, saccharin and cyclamate, are weak bladder carcinogens or co-carcinogens in laboratory animals, but a large-scale study of bladder cancer indicates that the risk in man is very small if present at all (70). Cooking practices may release hydrocarbons and other carcinogens in food, although there are no epidemiologic indications that consumption of various cooked foods is related to gastric or other forms of cancer.

Genetic Factors

Compared to environmental factors in cancer, genetic determinants are less conspicuous and more difficult to identify by clinical and epidemiologic means (71). Although the racial and ethnic differentials for most cancers appear largely modulated by environmental influences, genetic factors appear to contribute to some high rates (e.g. nasopharyngeal cancer among Chinese and gallbladder cancer among American Indians and certain Hispanic groups) and some low rates (e.g. testicular cancer and Ewing's sarcoma among blacks in Africa and the United States). Genetic susceptibility is most evident for skin cancer, since ethnic variations correspond to the degree of protective skin pigmentation.

Although only a small percentage of cancer is inherited in a Mendelian fashion, over 200 single-gene disorders have been linked to neoplasia (72). Some tumors seem to arise directly as an inherited trait (e.g. bilateral retinoblastoma, familial polyposis coli), while others occur as a complication of inherited precursor states (e.g. neurofibromatosis, xeroderma pigmentosum, chromosome instability, and immunodeficiency syndromes). In certain heritable syndromes, environmental factors contribute to the development of cancer, and provide valuable insights into genetic-environmental interactions and multistage models of carcinogenesis. Neoplasms of a hereditary nature tend to occur earlier in life than do nonfamilial occurrences of the same tumor, and usually arise from multiple foci within the affected organ.

In contrast to the hereditary syndromes, the common human cancers show small familial risks, on the order of two- to three-fold (73). However,

like the hereditary syndromes, the familial risks for breast and colon cancers may be as high as 20 to 30-fold among subgroups of patients with early onset and bilateral or multifocal origin (74). Familial susceptibility also appears to enhance the effects of environmental exposures, such as smoking in lung cancer, estrogenic compounds in breast cancer, and sunlight exposure in melanomas derived from dysplastic nevi. In some families there are remarkable aggregations of cancer consistent with an autosomal dominant mode of inheritance. These "cancer families" may display either a single type of cancer or a constellation of multiple cancers, especially adenocarcinomas of the colon and endometrium, or the breast and ovary. Other families are prone to diverse cell types of childhood and adult cancers, particularly soft-tissue and bone sarcomas, breast carcinoma, brain tumors, adrenocortical neoplasms, and leukemia (75). The delineation of genetic and familial syndromes is helpful in applying laboratory probes to clarify the heritable component of carcinogenesis, and in targeting screening and prevention programs designed to protect high-risk individuals.

CONCLUSIONS

Despite the large gaps in present knowledge of cancer epidemiology and etiology, the wide international variation in cancer incidence has suggested that the bulk of human cancer is related to environmental factors and is not an inevitable consequence of the aging process (2). This notion has provided a great stimulus to etiologic research by indicating that cancer is in principle a preventable disease. Although the established risk factors still appear to account for a minority of cancer cases, leads to nutritional factors seem especially promising in resolving key etiologic questions for several common cancers (76). Most cancers appear to result from the cumulative effects of multiple factors, including susceptibility states, and initiating and promoting agents acting at various stages of carcinogenesis. Even when specific causes are related to a particular tumor, further work should be encouraged to identify other factors that contribute to the multistage process that eventuates in cancer.

The overall impact of genetic factors is difficult to gauge at present, but should not be downplayed as a residual category after subtracting the environmental component. Genetic-environmental interactions may account for a sizable proportion of cancer, so that the delineation of susceptibility mechanisms is likely to have far-reaching implications to the ultimate prevention of cancer. Although experimental research is the approach required for a full understanding of mechanisms, epidemiologic observations may provide valuable guidance in clarifying, for example, the role of immunosurveillance in cancer etiology.

The initial leads to cancer causation may come from many different sources, including alert clinicians, experimentalists, or epidemiologists. It is important to encourage multidisciplinary interaction to ensure that these leads are evaluated and pursued to the fullest. The traditional observational approaches of epidemiology may have nearly reached their limits in attempting to elucidate a number of carcinogenic hazards, including nutritional and metabolic factors, oncogenic viruses, environmental pollutants, and genetic susceptibility. Some of these factors may elude the usual strategies of epidemiology, and may act through complex and subtle mechanisms that will require innovative approaches combining the best efforts of epidemiologists and laboratory investigators.

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CONTROL OF CIGARETTE SMOKING FROM A PSYCHOLOGICAL PERSPECTIVE[1]

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Cigarette smoking has sociological, physiological, and psychological determinants related to the initiation and maintenance of the behavior as well as important medical and economic implications. The interrelationship of all of these must be understood in order to control the behavior.

Epidemiological studies have proven repeatedly that acute myocardial infarction, sudden death, lung cancer, and other disease processes are strongly associated with cigarette smoking (1–4). Nevertheless, 30 billion packages of cigarettes are sold in the United States each year. Helping people to stop smoking cigarettes presents one of the greatest challenges facing public health and preventive medicine in the United States and other industrialized countries today.

The strongest case for a causal relationship between tobacco and any specific disease is for lung cancer. Before 1930, lung cancer was a rare disease, ten times less common than stomach cancer; five times less common than colon and rectal cancers (5). Since then, the age-adjusted death rates for lung cancer have increased almost 20-fold in males.

An encouraging epidemiologic finding has been that former smokers have coronary heart disease (CHD) mortality rates well below the rates of cur-

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