What Causes Cancer?

The top two causes—tobacco and diet—account for almost two thirds of all cancer deaths and are among the most correctable

by Dimitrios Trichopoulos, Frederick P. Li and David J. Hunter

Cancer, a major killer throughout human history, changed its grasp as humankind advanced industrially and technologically. Although the risk of a few types of cancer has declined dramatically in developed countries in this century, the incidence of the most significant forms of the disease has increased. Cancers of the lung, breast, prostate and colon and rectum have all become more frequent in countries where risk factors such as cigarette smoking, unhealthful dietary habits and exposure to dangerous chemicals at work or in the environment are now more common.

As industrialization has proliferated, so, too, have the suspected causes of cancer. In recent years, news accounts have been full of warnings about all manner of modern conveniences, from pharmaceuticals to cellular telephones. Meanwhile the pace of technological advance makes it more vital than ever to single out definitive causes of cancer from an ever expanding array of possibilities.

For this daunting task, researchers rely heavily on epidemiology. Epidemiologists identify factors that are common to cancer victims' history and way of life and evaluate them in the context of current biological understanding. Ultimately, the evidence may persuade researchers that one or more of these factors or characteristics "cause" the disease—that is to say, exposure to them significantly increases the odds of the illness developing.

Over the past half century, epidemiology has enabled researchers not only to ferret out many of the environmental (that is, noninherited) causes of cancer but also to estimate how many annual cancer deaths can be attributed to each one. Although the work cannot be used to predict what will happen to any one individual, it nonetheless provides broadly useful information for people seeking to minimize their exposure to known cancer-causing agents, or carcinogens.

Cancer seems to arise from the effects of two different kinds of carcinogens. One of these categories comprises agents that damage genes involved in controlling cell proliferation and migration. Cancer arises when a single cell accumulates a number of these mutations, usually over many years, and finally escapes from most restraints on proliferation. The mutations allow the cell and its descendants to develop additional alterations and to accumulate in increasingly large numbers, forming a tumor that consists mostly of these abnormal cells. Another category includes agents that do not damage genes but instead selectively enhance the growth of tumor cells or their precursors. The primary danger of malignancies is that they can metastasize, allowing some of their cells to migrate and thus carry the disease to other parts of the body. Finally, the illness can reach and disrupt one of the body's vital organs [see "How Cancer Arises," by Robert A. Weinberg, page 62].

Hardly any researchers doubt that repeatedly exposing parts of the body to, for example, chemicals in tobacco smoke, may eventually bring about the cellular damage that can lead to cancer. But the details of how most exposures give rise to such damage remain elusive. One long-standing theory holds that many environmental stressors, as well as aging and other life processes, play a role by increasing the generation in the body of so-called free radicals—chemically reactive fragments of molecules. By reacting with a gene's DNA, these fragments can damage and permanently mutate the gene. Other cancer-causing agents, such as some viruses, seem to act differently, by accelerating the rate of cell division.

Of course, the genes people inherit from their parents also influence cancer development. Some are born with mutations that directly promote excessive growth of certain cells or the formation of more mutations. Evolutionary pressure, however, assures that such mutations are rare; they are responsible for the development of fewer than 5 percent of fatal cancer cases. (Known genes linked to inherited human cancers are listed in the table on page 87.)

On the other hand, more general inherited physiological traits, in contrast to mutations in genes that regulate cell growth, contribute in some way to the vast majority of cancers. For example, inheriting fair skin makes a person more prone to skin cancer. But although fair-skinned people are more susceptible, they develop the disease only after extensive exposure to sunlight, an environmental carcinogen. Further, if someone inherits a normal genetic variant that causes the body to eliminate certain carcinogens relatively inefficiently, that person, after repeated exposure to the carcinogen, will be more likely to acquire the cancer than will a person who has a more efficient form of this gene.

One common question about cancer concerns the number of cases that would be expected to arise naturally in otherwise healthy, genetically normal individuals who somehow had managed to avoid all environmental carcinogens. Only a rough estimate is available, arrived at by comparing populations with very different cancer patterns. Perhaps a quarter of all cancers are "hard core"—in other words, they would develop even in a world free of external influences, simply because of the production of carcinogens within the body and the occurrence of unrepaired genetic mistakes.

Epidemiologists have shown, however, that in most cases, the environment (including lifestyle factors) plays a profound role. How strong are these data? The weak link in cancer epidemiology is the inability to conduct trials in which groups of people, selected at random, are exposed to potential carcinogens or even to potential cancer-preventing compounds. Randomized studies of carcinogens are obviously unacceptable for ethical reasons; unfortunately, lack of

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FATTY FOODS such as these being consumed in a New York City restaurant can contribute to a variety of cancers.

such studies can seriously complicate the interpretation of the evidence.

Consequently, we can consider epidemiologic studies to have identified a cause of the disease only when people who have a given type of cancer are consistently found to have a history of unusually high exposure to a particular agent. Alternatively, a link can be declared when a weak relation between an agent and a form of cancer is consistently reported in a variety of circumstances and backed by persuasive biological plausibility.

Accordingly, we have based our assessment of the evidence for what causes cancer either on overwhelming epidemiologic data for which the precise biological mechanisms remain speculative or on weak but consistent epidemiologic findings that are also biologically credible. The role of vegetables and fruits in cancer prevention, for example, tends to be in the former category, whereas the carcinogenic potential of secondhand smoke fits into the latter: relatively few people are afflicted with lung cancer after exposure to secondhand smoke alone, but the connection has been documented consistently and credibly explained.

We have culled the data presented here from hundreds of studies, and the views we offer are shared by many, if not most, researchers and health professionals. In keeping with the standard practice in cancer epidemiology, our focus is on fatal rather than all cancer cases, to avoid distortions introduced by common cancers that only rarely become lethal. All the results we discuss apply to the U.S. and to other industrial nations unless we indicate otherwise. The data for developed countries do not necessarily apply to developing countries, in which cancer-causing infections and, increasingly, some occupational carcinogens tend to be more prevalent.

Tobacco Smoke Is Top Carcinogen

More than half the cancer deaths in the U.S.—perhaps even 60 percent—can be attributed to tobacco smoke and diet. Smoking causes 30 percent of cancer deaths, making tobacco smoke the single most lethal carcinogen in the U.S. Apart from smoking and diet, other environmental factors each contribute to only a few percent of total deaths.

Smoking, mainly of cigarettes, causes cancer of the lung, upper respiratory tract, esophagus, bladder and pancreas and probably of the stomach, liver and kidney. Smoking is implicated in chronic myelocytic leukemia and may also cause cancer of the colon and rectum and other organs. Whether smoking will result in malignancy depends on several factors, including the frequency of smoking, the cigarettes' tar content and—most important—the duration of the habit. Taking up the habit while very young substantially amplifies the risk. The risks vary from one type of cancer to another; thus, on average, smokers are twice as likely to be afflicted with cancer of the bladder but eight times more likely to contract cancer of the lung.

Passive smoking, or inhalation of tobacco smoke in the environment, causes much less lung cancer than active smok-

ing does. Nevertheless, a few thousand people die every year in the U.S. from cancers attributable mainly to secondhand smoke. Thus, passive smoking is as much a killer as general outdoor air pollution or household exposure to the radioactive gas radon (which is emitted naturally from the earth in some areas).

Eat Right, Live Longer

Only diet rivals tobacco smoke as a cause of cancer in the U.S., accounting for a comparable number of fatalities each year. Animal (saturated) fat in general and red meat in particular are associated with several cancers; both are strongly linked to malignancies of the colon and rectum; saturated fats have been implicated in prostate cancer as well.

A few issues concerning dietary fat still puzzle researchers. Investigations with animals have indicated that under specific conditions certain types of polyunsaturated fat increase the risk for cancer at some bodily sites, but we have little supportive human evidence. Also, rigorous epidemiologic studies have not supported some of the early and still popular hypotheses concerning dietary fat and cancer. For example, high intake of fats (typically, animal fat) in adults has not been shown to increase risk for breast cancer in most investigations that have followed large groups of women for up to a dozen years.

Among nonnutrient food additives, only salt appears to be a significant contributor to cancer. Studies of populations outside the U.S. suggest that high intake can lead to stomach cancer. Also, in Southeast Asia, very young children who eat a great deal of salty fish tend to have excessive rates of cancer of the nasopharynx (the upper part of the pharynx, which reaches the nasal passages). Similarly, drinking beverages while they are very hot, including maté, a South American tea-like drink, has been shown to increase the risk of esophageal cancer.

In contrast, most investigations of coffee (with or without caffeine) have not linked it to human cancer. Moreover, it does not seem to matter how the beverage is sweetened: there is ample evidence that artificial sweeteners, in reasonable quantities, do not cause cancer.

The links between diet and cancer, however, may have as much to do with what is *not* in a diet as with what is. Skimping on vegetables and fruits can be a significant contributor to many different kinds of cancer, for reasons that are not fully known. The protective effects of these foods may derive from specific constituents that block the carcinogenic activities of substances made in our own bodies. For instance, antioxidants in foods are believed to neutralize free radicals. Other chemicals in healthful foods, it has been suggested, block the signals that such steroids as estrogen send—signals that cause cells in the breast and elsewhere to proliferate. Yet foods contain thousands of chemicals, and investigators remain unsure of which ones, and which combinations, are most potent as cancer blockers.

Diet can exert its effects not only through the type of calories consumed but also through their quantity. Researchers believe that taking in more energy than is expended can be harmful throughout life, probably through different mechanisms at different ages. Children who overeat and exercise too little often grow more and seem to be at a higher risk of acquiring certain cancers.

SLIM FILMS

These findings have been most striking for breast cancer. Excessive childhood growth, as reflected in attained height and weight, seems to push girls into menstruating when they are relatively young, and early menstruation is a major risk factor for breast cancer (it may contribute to other cancers as well). Such early-life factors as excessive growth caused by overeating and insufficient exercise could be a component cause in perhaps 5 percent of cancers of the breast and prostate, which become fatal relatively frequently.

Obesity in adult life is an important cause of cancer of the endometrium (the lining of the uterus) and an established but relatively weak cause of postmenopausal breast cancer. For unknown reasons, obesity also appears to increase the risk for cancers of the colon, kidney and gallbladder.

Consumption of large quantities of alcoholic beverages, particularly by smok-

Microbes That Cause Cancer

More than 100 years ago researchers began considering the possibility that cancerous tumors were caused by viruses and other infectious agents. In the decades that followed, though, their attempts to verify this theory failed. Introduction of various infections into animals usually did not yield cancer. Gradually, the theory fell out of favor.

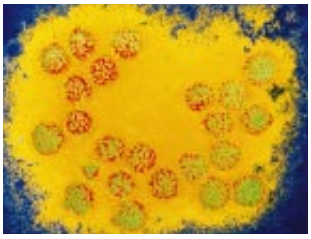
Over the past 20 years, however, investigators have not only proved that many different types of cancer indeed stem from viruses, bacteria or parasites, they have also learned that perhaps as many as 15 percent of the world's cancer deaths can be traced to them. The vast majority of these cases occur in developing countries, where communicable diseases are much more prevalent. Yet even in such developed countries as the U.S., about 5 percent of cancer fatalities result from diseases brought on by infections. Determining exact numbers has been difficult because it often takes several decades for an infection to lead to cancer.

The most common cancer-causing pathogens are the DNA viruses, which propagate by invading the living cells of a host and using the cells' DNA-synthesizing and protein-making machinery to generate copies of themselves. Of these carcinogenic agents, the two most important are the human papillomaviruses types 16 and 18, which are sexually transmitted, and the hepatitis B virus. The papillomaviruses can lead to cancer of the cervix, among other types of cancer, and the hepatitis B virus can cause liver cancer.

Although papillomavirus types 16 and 18 are responsible for 70 to 80 percent of the world's cases of cancer of the genitals and anus, as many as 30 other papillomavirus types may be involved in these cancers, which affect women far more often than men. And in certain places—notably Japan—the hepatitis C virus causes almost as many cases of liver cancer as hepatitis B does. All told, viral infec-

tions, mainly hepatitis, cause as many as 80 percent of liver cancer cases around the globe.

Several other viruses have also been found to cause various kinds of cancer, some of which are fairly rare. For instance, Epstein-Barr virus, which is best known for producing mononucleosis, at times becomes carcinogenic as well. It is believed to contribute worldwide to approximately half the cancers of the upper pharynx, as well as to more than 30 percent of all cases of Hodgkin's disease, 10 percent of non-Hodgkin's lymphoma and some gastric cancers. The human immunodeficiency virus (HIV) can cause the soft-tissue cancer known as Kaposi's sarcoma and also lymphoma, a type of cancer characterized by an abnormal proliferation of lymphoid tissue.



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PAPILLOMAVIRUS is a significant cause of cancer.

Helicobacter pylori, the only bacterium linked to cancer, apparently gives rise to the disease in part by causing stomach ulcers [see "The Bacteria behind Ulcers," by Martin J. Blaser; SCIENTIFIC AMERICAN, February]. *H. pylori* is strongly associated with the occurrence of stomach cancer, although the proportion of cases attributable to the bacterium remains to be determined.

Researchers are now trying to understand why these pathogens give rise to cancer in some infected people but not in others. Lately experimental evidence has pointed to secondary occurrences in the body, which can interfere with the host's immune system before an infection becomes cancerous. More knowledge about the details of this chain of events may lead to such new preventive measures as vaccines that block the secondary events, prohibiting a disease from becoming cancerous.

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ers, increases the risk of cancer of the upper respiratory and digestive tracts, and alcoholic cirrhosis frequently leads to liver cancer. Although modest drinking does seem to reduce the risk of heart disease, converging data suggest that intake of as few as one or two drinks a day may contribute to breast and perhaps colon and rectal cancer.

Alcoholic beverages have been estimated to contribute to about 3 percent (beyond the 30 percent attributed to diet) of total cancer mortality in the developed world. A sedentary way of life contributes to an additional 3 percent. And food additives, mainly salt, may contribute to another 1 percent.

Radiation and You

Unlike smoking and the dietary practices we have discussed, many other threats, albeit less consequential ones, are rather difficult to avoid. Various forms of radiation—from the sun, electric power lines, household appliances, cellular telephones and naturally occurring, radioactive radon gas—are the most highly publicized of the threats that have been proposed. Radiation causes perhaps 2 percent of all cancer deaths. Most of these fatalities result from natural sources of radiation—the majority can be attributed to melanoma skin cancer triggered by the sun's ultraviolet rays.

Within the ultraviolet spectrum that reaches the earth's surface, the most troubling component consists of the higher-frequency ultraviolet B rays, which can damage DNA. Ultraviolet B rays alone cause more than 90 percent of skin cancers, including melanomas, which are much more frequently fatal than all other forms of skin cancer [see "Sunlight and Skin Cancer," by David J. Leffell and Douglas E. Brash; SCIENTIFIC AMERICAN, July]. Many researchers now believe that the frequency of sunburns during childhood, rather than the cumulative exposure to sunlight, is the key factor in bringing about melanoma. People who tan but do not burn, therefore, are at much less risk.

Another natural source of radiation is radon, a colorless, odorless and radioactive gas that is emitted from the earth in some regions. It can seep into buildings and collect in ground-floor or basement areas. Prolonged breathing of the gas at very high levels, found mostly in underground mines, has been tied to increased incidence of lung cancer. This is not a significant cause of cancer in the general population, however, and radon levels are usually lowered by improving the ventilation of a building or mine.

The electric and magnetic fields generated by power lines and electric household appliances, which oscillate at 60 cycles per second in the U.S., are known as extremely low frequency fields. They have been intensively studied for possible cancer-causing effects. So far the collective evidence is confusing, selectively propagated and generally incorrectly perceived. Too often these accounts sow fear by discounting basic science. A cancer-causing genetic mutation cannot be induced by radiation, as far as anyone can discern, unless molecules in the body become charged by gaining or losing one or more electrons—in other words, unless they become ionized. And the photons associated with extremely low frequency fields would have to be a million times more energetic before they could ionize molecules.

Epidemiologic studies have indicated, however, that these fields may somehow increase to a marginal degree the risk of childhood leukemia; the evidence for other cancers is considerably weaker. It is not possible to discount completely the possibility that power lines contribute to some forms of cancer, but the evidence, in our view, is scant. Even for childhood leukemia, the collective evidence is so thin that it can be interpreted either way—as showing a genuine link with the disease or merely as reflecting flaws in the epidemiologic data.

The fear of extremely low frequency fields seems to have several underlying causes. One is the incorrect association made between such fields and other forms of radiation. Another is the wide publicity that has been given to relatively small and preliminary studies.

Radio-frequency electromagnetic radiation, which is emitted by cellular telephones, microwave and other wireless systems and even living creatures, is quite distinct from extremely low frequency fields. Even at the much higher radio frequencies, though, photon energy is still several orders of magnitude below the level required to ionize a molecule. In urban settings, where radio-frequency fields are strongest, ambient energy levels are less than one one-hundredth of those emitted by a human be-

Carcinogens in the Workplace

Chemical/ Physical Agent	Cancer Type	Exposure of General Population	Examples of Workers Frequently Exposed or Exposure Sources
Arsenic	Lung, skin	Rare	Insecticide and herbicide sprayers; tanners; oil refinery workers
Asbestos	Mesothelioma, lung	Uncommon	Brake-lining, shipyard, insulation and demolition workers
Benzene	Myelogenous leukemia	Common	Painters; distillers and petrochemical workers; dye users; furniture finishers; rubber workers
Diesel exhaust	Lung	Common	Railroad and bus-garage workers; truck operators; miners
Formaldehyde	Nose, nasopharynx	Rare	Hospital and laboratory workers; manufacture of wood products, paper, textiles, garments and metal products
Man-made mineral fibers	Lung	Uncommon	Wall and pipe insulation; duct wrapping
Hair dyes	Bladder	Uncommon	Hairdressers and barbers (inadequate evidence for customers)
Ionizing radiation	Bone marrow, several others	Common	Nuclear materials; medicinal products and procedures
Mineral oils	Skin	Common	Metal machining
Nonarsenical pesticides	Lung	Common	Sprayers; agricultural workers
Painting materials	Lung	Uncommon	Professional painters
Polychlorinated biphenyls	Liver, skin	Uncommon	Heat-transfer and hydraulic fluids and lubricants; inks; adhesives; insecticides
Radon (alpha particles)	Lung	Uncommon	Mines; underground structures
Soot	Skin	Uncommon	Chimney sweeps and cleaners; bricklayers; insulators; firefighters; heating-unit service workers

MARIA SUTTON

ing. Investigators are currently studying the radio emanations associated with cellular telephones for a possible link to brain cancer, but so far no empirical evidence supports such a connection. (The only major study so far did not establish a connection.)

On the other hand, the radiation that comes from nuclear materials and reactions is sufficiently energetic to ionize molecules and is unquestionably carcinogenic. But, again, the general public tends to overestimate the risk posed by low levels of radiation. Among Japanese residents of Hiroshima and Nagasaki who survived longer than approximately one year after the atomic bomb blasts—and who were exposed to radiation levels far higher than most people will ever encounter—only 1 percent have died from cancers known to be related to radiation. Epidemiologic studies have failed to validate claims that the incidence of leukemia is higher among those living near nuclear plants and among children of nuclear reactor workers.

Of Work, Medications and Microbes

A number of substances now known to be carcinogenic, including asbestos, benzene, formaldehyde, diesel exhaust and radon, were initially revealed to be dangerous in unfortunate "natural experiments" involving exposures to very high concentrations in the workplace [*see table at left*]. In recent years, however, the control of such occupational carcinogens, at least in the developed world, has brought about a little known success story in public health.

Strict control measures in the workplace over the past 50 years have shrunk the proportion of fatal cancer cases caused by occupational exposures to perhaps less than 5 percent. Before 1950 the proportion may have been twice as great. Unfortunately, though, occupation-associated cancers, which occur mostly in the lung, skin, bladder and the blood-forming (hematopoietic) system, are likely to increase in developing countries as they rapidly industrialize.

Medical treatment, like workplace exposure, has generated unintended insights into cancer causation, as some procedures or medications have turned out to have carcinogenic effects. Ironic as it may seem, medical products and procedures may be responsible for about 1 percent of all cancers. Still, their overall clinical usefulness far outweighs the risks. This is true of many cancer therapies, including radiation and chemotherapy. Some effective drugs or combinations of such drugs used to treat cancers such as Hodgkin's disease can cause acute leukemia in about 5 percent of survivors and, in rare cases, bladder cancer.

Immunosuppressive drugs can also be carcinogenic, causing certain types of lymphomas; supplemental estrogens taken to offset menopausal symptoms have been linked to endometrial and breast cancer. And steroids used for treatment of aplastic anemia have been associated with rare cases of liver cancer.

Early reports indicated that tamoxifen, an experimental breast cancer drug, could occasionally cause endometrial cancer, although recent studies are more equivocal. Fertility drugs that mimic the effects of gonadotropins, including Pergonal, are suspected of increasing the risk of ovarian cancer. Growth hor-

mones administered to children might elevate their risk of leukemia. Some diuretics could increase the risk of kidney cancer, and some cholesterol-lowering drugs may heighten the risk of colon and rectal cancer, but for these, too, the evidence is very tenuous.

Oral contraceptives slightly increase the risk of some types of liver tumors and, under certain conditions, of premenopausal breast cancer. Yet birth-control pills also reduce the risk of ovarian and endometrial cancer and perhaps that of colon and rectal cancer as well.

Viruses and other infectious agents, overlooked as causes of cancer only 30 years ago, may contribute to about 5 percent of all fatal cases in developed countries [*see box on pages 82 and 83*].

Pollution's Share

Environmental pollution in the air, water and soil plays an infrequent and difficult-to-document role in human cancer. Harmful effects are hard to verify because they generally result from exposure to several carcinogens at very low levels. Nevertheless, it is reasonable to assume that pollutants could contribute to about 2 percent of fatal cancers, mainly of the lung and bladder.

Ecological studies, which are similar to epidemiologic ones but with less specificity and detail, indicate that lung cancer rates in polluted cities exceed those in rural areas. And, in fact, data do suggest that urban smokers are more likely to develop lung cancer than rural smokers—even after accounting for smoking behavior (how heavily a person smokes, what kind of cigarettes are smoked and so on). Yet urban nonsmokers do not appear to be at increased risk for lung cancer.

SLIM FILMS

Taken together, such studies, emission inventories and chemical analyses of air samples from urban areas suggest that long-term exposure to high levels of air pollution could increase lung cancer risk by about 50 percent, especially among smokers. (Although this figure may seem like a great increase in risk, heavy smoking, by itself, increases risk by about 2,000 percent.) Diesel exhaust, which is probably more carcinogenic than nondiesel exhaust, has been proposed as a likely carcinogenic factor.

Some researchers maintain that organic compounds whose molecules contain chlorine and ring-shaped components increase the risk of breast cancer and, perhaps, other malignancies related to the female hormone estrogen. Among these compounds are ones produced when certain pesticides, such as DDT, have been altered in the body. The underlying hypothesis is that these substances, called xenoestrogens, mimic the body's own (endogenous) estrogens and thus stimulate cell division in the breast and other reproductive organs. The empirical evidence in humans is scant, however, and the estrogenic potency of xenoestrogens is much weaker than that of endogenous estrogens.

Proximity to hazardous-waste sites or contaminated wells may have health effects, but it has not been shown to impart a measurable excess risk for cancer. It is not certain whether the lack of association is genuine or a reflection of the limited capacity of statistical methods to document a very weak correlation.

A few studies have suggested—without convincingly demonstrating—a tenuous positive association between water chlorination and cancer of the bladder. All over the world, but especially in developed countries, chlorination is used to kill germs in drinking water. Even if

Why Community Cancer Clusters Are Often Ignored

The 10-foot-long map of Lorraine Pace's Long Island community of West Islip is spread out on her dining-room table. Pace, a 55-year-old breast cancer survivor and the 20th of her neighbors to be diagnosed with the disease, points out patches of yellow-highlighted squares scattered across the map. "These are the breast cancer cases," she explains. Within days of undergoing a lumpectomy in 1992, Pace had galvanized some of the women represented by these squares, and the group—the West Islip Breast Cancer Coalition—spent the next year and a half mapping breast cancer cases in an effort to pinpoint "hot spots" of the disease. They hoped these spots could be correlated with potential environmental threats—and their illness linked to a cause.

At first glance, such community cancer clusters would appear to be the perfect vehicle for identifying cancer-causing agents: by tracing factors to which all the individuals were exposed, investigators should in theory be able to spot a culprit. And the public certainly views clusters that way. State health departments in the U.S. received about 1,500 requests for cancer cluster investigations in 1989, according to a survey by Daniel Wartenberg of the Robert Wood Johnson Medical School in New Jersey, and that number has continued to increase.

But most cancer clusters appear to happen by chance. It is largely for this reason that health officials these days are usually reluctant to investigate reports of localized excesses in cancer incidence—even the Centers for Disease Control and Prevention gave up routinely investigating cancer clusters in 1990 because they required such intensive resources and yielded so little information in return.

Indeed, although several known carcinogens have been discovered through occupational or medical clusters (for instance, vinyl chloride's link to angiosarcoma in workers who make polyvinyl chloride or the connection of diethylstilbestrol, or DES, to gynecologic cancers in daughters of women who took the drug during pregnancy), only one community cancer cluster has ever been traced to an environmental cause. In that case, researchers linked an epidemic of a rare respiratory cancer called mesothelioma in a Turkish village to an asbestoslike mineral, erionite, that was abundant in the soil.

Among the reasons for which health officials may discount a community's suspicion of common cause is that local groups often lump together different types of cancers (which are unlikely to be triggered by the same carcinogen). These citizens tend to include cases that were diagnosed before the afflicted individuals moved into the neighborhood, or they conduct what the epidemiologist Robert W. Miller of the National Cancer Institute calls epidemiologic gerrymandering: "They find the cas-

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chlorination did present an extremely small cancer risk—which is by no means certain—the danger would be more than outweighed by chlorine's capacity to prevent the spread of such waterborne diseases as cholera, dysentery and typhoid fever. Investigations of water fluoridation have been reassuring.

Reproductive and Gynecologic Factors

Among the body's natural processes, those related to reproduction are most closely linked, epidemiologically, to cancer. For women, early age at menarche, late age at first pregnancy and late age at menopause tend to increase the risk for breast cancer; the more offspring a woman has had, the less likely she is to develop cancer of the endometrium, ovary or breast.

Physiological rationales for these observations are elusive, for the most part. No one knows exactly why, for example, early menarche and late menopause are associated with breast cancer. Both may simply extend the period in a woman's life when she is exposed to her own sex hormones, especially estrogen.

The protective effects of having children early in life, on the other hand, may accrue by causing breast cells to become more differentiated. Differentiation restricts the ability of a cell to grow abnormally, change its type and survive in other types of tissue. A first pregnancy at a young age may differentiate breast cells early in life, after which they would be much less susceptible to carcinogens.

In developed countries, reproductive behavior is determined mainly by social and economic forces. Thus, for educational, career-related and other reasons, millions of women in these countries are putting off childbearing and are also having fewer children, in general, than their mothers and grandmothers did. Unfortunately, such life decisions will lead to higher rates of breast and ovarian cancer. The postponing of first pregnancies by younger women in the U.S. that has already occurred will increase their breast cancer rates by about 5 to 10 percent within the next 25 years.

Induced abortions have been associated in some studies with a slight increase in breast cancer risk, but the data are not conclusive. Several other associations between cancers of the reproductive tract and certain conditions or behaviors have been noted, but they, too, are not conclusive, are of marginal importance or are thought to be surrogates for actual causes. For example, having multiple sexual partners was once believed to increase a woman's risk of acquiring cancer of the cervix. Instead the increased risk probably reflects greater exposure to sexually transmitted, and potentially carcinogenic, human viruses.

Taking all these considerations into account, we might attribute around 4 percent of cancer deaths to reproduction-related factors.

Socioeconomic Differences

Differences in cancer rates among socioeconomic groups can usually be attributed to differences in lifestyle. Underprivileged people have higher rates of cancers of the mouth, stomach, lung, cervix and liver and of a type of esophageal cancer (squamous cell cancer). Pov-

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es, draw boundaries around the cases, and say, 'Aha, we've found a cluster.'"

Even when such assemblages are ruled out, most clustered cases that initially appear to be statistically significant turn out to be simply naturally occurring spikes in cancer incidence. According to Raymond R. Neutra of the California Department of Health Services, probability theory suggests that 17 percent of the 29,000 towns or census tracts in the U.S. will have at least one of the 80 recognized types of cancer elevated in any given decade, producing 4,930 chance clusters. This high false positive rate is further compounded by the problem of statistical legitimacy—most reported cancer clusters are too small (often fewer than 10 cases) to be judged conclusively.

ADAM J. FERNANDEZ

LORRAINE PACE mapped a Long Island breast cancer cluster.

Even when there is a potential cause in the environment—and a biologically plausible hypothesis of how it might contribute to cancer—trying to trace cancer cases to a specific cause still poses unique challenges. "Cancer cases are clinically nonspecific—you can't look at a leukemia case clinically and say, 'Ah, this is radiation-caused leukemia,'" explains Clark W. Heath of the American Cancer Society. This problem is exacerbated by cancer's latency. Unlike outbreaks of infectious diseases, which can be linked to some recent exposure, a cluster of cancer cases might have its roots in an exposure that occurred 10 to 20 years earlier.

"Reconstructing a person's exposure history is a tremendous scientific challenge," says G. Iris Obrams of the NCI. "For one thing, none of us can reliably recall all the things we've been exposed to. And the further back we go, the more uncertain we are about the accuracy of exposure information and the more likely it is that measurement techniques have changed as well." Obrams also notes that one has to take into account many known cancer risk factors when trying to assess the impact of environmental agents, in part because the disease may be triggered by a combination of environmental, genetic and other factors.

In conducting its own crude version of a cancer cluster investigation, the West Islip Breast Cancer Coalition could never have overcome all these obstacles. But together with many other reports of breast cancer clusters on Long Island, the West Islip situation managed to point epidemiologists in the right direction. Subsequent studies revealed that Long Island did indeed have higher than expected rates of breast cancer incidence and mortality and was, in fact, part of a broad breast cancer cluster extending all the way to Philadelphia. They also helped to establish Long Island as the setting for the largest epidemiologic study ever to be conducted on the link between environmental contaminants and breast cancer.

"We tend to move beyond cluster analysis as quickly as we can," says Obrams, explaining public health officials' decision not to follow up on every reported cluster in Long Island. "We get whatever information we can about clusters to see if there is any lead that we can develop for scientific study, but we know we can get more conclusive data from a larger, well-designed scientific project."

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erty may be thought of as the underlying cause, because it is almost universally associated with higher rates of tobacco smoking, alcohol consumption, poor nutrition and exposure to certain infectious agents—which, together, can explain most of the cancer-risk propensities listed above.

In contrast, for reasons that remain largely unknown, cancers of the breast, prostate and some other sites are more common among higher socioeconomic groups. Some scientists have speculated that excessive growth in early life, presumably because of reduced physical activity and abundant nourishment, may in some way increase the risk of these cancers. But this hypothesis has not been evaluated rigorously.

Most of the differences in cancer incidence between races, too, can be attributed to socioeconomic factors. Some of the differences between races might have a genetic basis, but genetic variability is higher within than between races. In general, most differences among blacks, whites and Asians can be traced to diet, way of life and environmental exposure. For example, Japanese women in Japan have 25 percent of the risk for breast cancer that white women in the U.S. have. Yet third-generation Japanese-American women contract breast cancer almost as frequently as other American women do.

Genes and Cancer Risk

Inherited mutations in these genes confer a very high cancer risk. Red type indicates cancer most often associated with mutation in the listed gene.

Gene	Tumor Type	Gene Class
Breast cancer		
BRCA1	Breast, ovary	Tumor suppressor
BRCA2	Breast (both sexes)	Tumor suppressor
p53	Breast, sarcoma	Tumor suppressor
Colon cancer		
MSH2	Colon, endometrium, other	Mismatch repair
MLH1	Colon, endometrium, other	Mismatch repair
PMS1,2	Colon, other	Mismatch repair
APC	Colon	Tumor suppressor
Melanoma		
MTS1 (CDKN2)	Skin, pancreas	Tumor suppressor
CDK4	Skin	Tumor suppressor
Neuroendocrine cancer		
NF-1	Brain, other	Tumor suppressor
NF-2	Brain, other	Tumor suppressor
RET	Thyroid, other	Oncogene
Kidney cancer		
WT1	Wilms' tumor	Tumor suppressor
VHL	Kidney, other	Tumor suppressor
Retinoblastoma		
RB	Retinoblastoma, sarcoma, other	Tumor suppressor

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Elusive Mechanisms

Although many of the specific physiological and genetic mechanisms by which environmental carcinogens cause cancer remain elusive, scientists now have a good sense of the extent to which various categories of agents contribute to lethal cancers. By and large, in industrial nations tobacco consumption and dietary habits are the dominant cancer-causing behaviors. In developing nations, cancer cases stemming from infectious agents are more common. But the rapid worldwide spread of the tobacco habit promises to push smoking to the forefront of causes of cancer deaths in these regions, too.

Useful though they are for establishing preventive guidelines and setting health policy objectives, epidemiologic data on the relative significance of environmental carcinogens cannot predict the fate of any given individual. A heavy smoker might avoid lung cancer, a long-term carrier of hepatitis B virus may remain free from liver cancer, and many healthy elderly people have lived long lives on terrible diets. For many of the other factors considered in this article, such as ionizing radiation or some occupational factors, only extreme exposures (or carrying mutant genes) put an individual at substantial risk. This is because multiple, interacting factors are almost always necessary for cancer to develop.

At present, we have a very limited understanding of how these interactions allow potential carcinogens to cause cancer. But in time, research may reveal this crucial link, giving us a more complete picture of what cancer is—and how it can be stopped. SA

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Further Reading

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