PREVENTION • DETECTION • NEW THERAPIES • LIVING WITH CANCER

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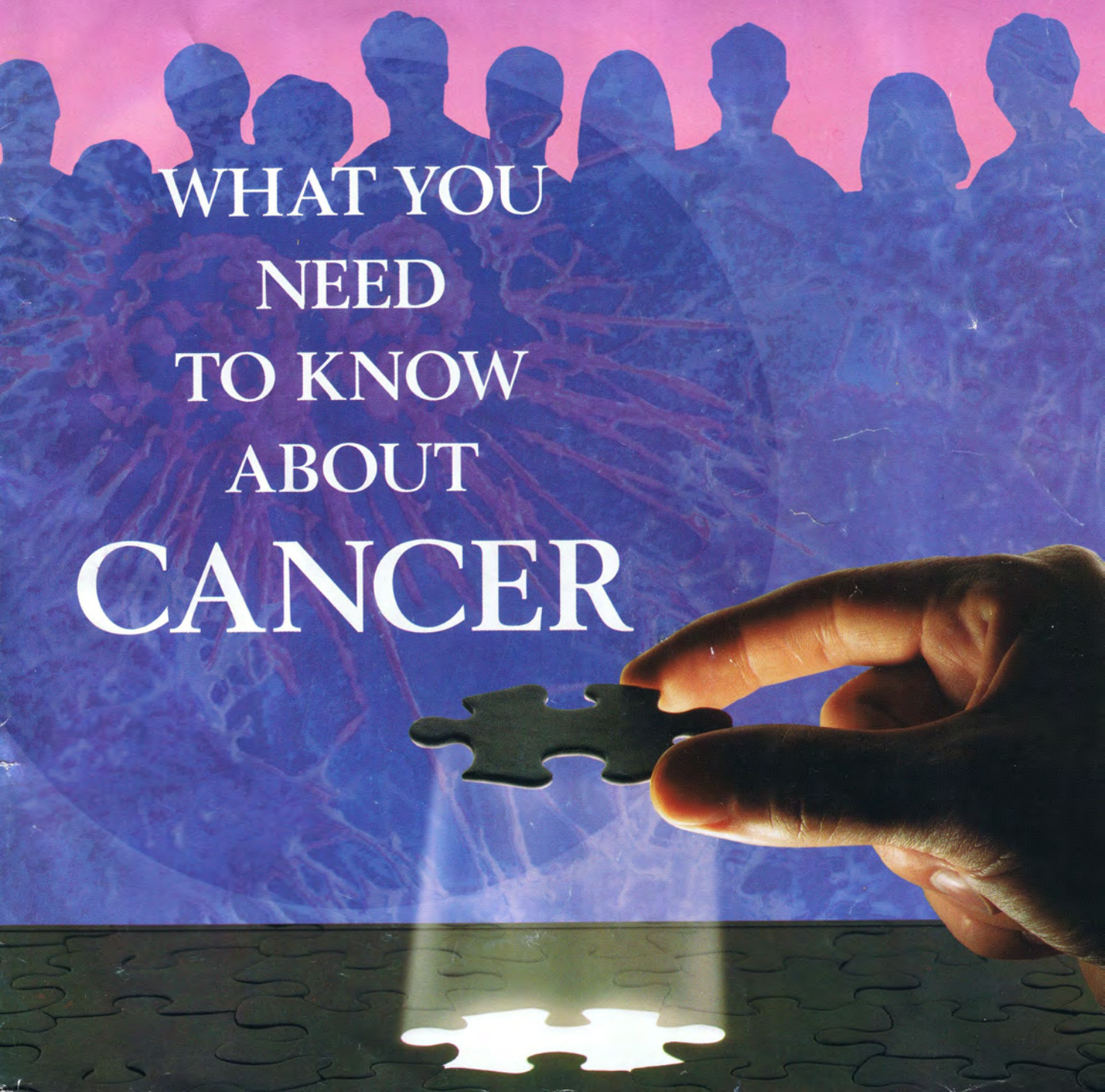

WHAT YOU NEED TO KNOW ABOUT CANCER

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.

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."

—Lori Miller Kase is a science and health writer based in Virginia.

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

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.

The Authors

DIMITRIOS TRICHOPOULOS, FREDERICK P. LI and DAVID J. HUNTER are colleagues at Harvard University. Trichopoulos is director of the Harvard Center for Cancer Prevention at the School of Public Health, professor of epidemiology and the Vincent L. Gregory Professor of Cancer Prevention. He was born in Athens, Greece. Li, who was born in China, is professor of medicine at Harvard Medical School and professor of clinical cancer epidemiology at the School of Public Health. Hunter, a native of Australia, is associate professor of epidemiology at the School of Public Health and executive director of the Center for Cancer Prevention.

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Further Reading

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