Europe: As Many Cancers as Cuisines

The Old World has more epidemiological puzzles per square kilometer than any other place on Earth, providing a feast for researchers trying to understand the causes of cancer

Paris—FOR THE CANCER EPIDEMIOLOGIST, Europe is a land of opportunity waiting to be explored. Between the Urals and the Atlantic, the continent is home to more than two dozen nations, each with its own unique cuisine, customs, and climate. Just about every known or suspected risk factor for cancer—including smoking, diet, exposure to sunlight, industrial pollution, reproductive behavior, and genetic makeup—varies from country to country and from region to region. And so do the cancer rates.

"We have wonderful differences in the rates of all sorts of cancers," says Lenore Kohlmeier, head of the department of epidemiology of health risks at the German Federal Health Office in Berlin. But until recently, Kohlmeier says, there had not been much concerted effort to capture the information on risk factors and use it to understand the various types of cancers. Now that situation is beginning to change, in part because the fall of the Iron Curtain has offered an unparalleled opportunity to see how life-styles affect cancer rates, but also because European epidemiologists have generally stepped up their efforts to exploit the Europe-wide differences in cancer incidence.

Emerging from these studies are some very broad—but sometimes baffling—geographic trends, as can be seen in the wealth of information being gathered into Europe's biggest epidemiological database, maintained at the International Agency for Research on Cancer (IARC) in Lyons, France. Rodolfo Saracci, IARC's chief of analytical epidemiology, points out that the death rate for all cancers combined (excluding non-melanoma skin cancers) tends to be higher in northern European countries such as Belgium, the Netherlands, the United Kingdom, and France, and lower in the southern European nations of Spain, Greece, and Portugal. This south-to-north gradient is also reflected in the higher incidences of many of the common cancers, including lung, breast and colon, in the northern countries. In contrast, the relatively rare cancers of the larynx, liver, esophagus, and buccal cavity are more frequent in the south.

Tracking cancer. *Epidemiologist Kohlmeier.*

One big surprise from the IARC database is the overall trend for malignant melanoma, a particularly dangerous form of skin cancer, which is increasing in Europe at the epidemic rate of 3% per year. Common sense dictates that this cancer should be more common in the sunny Mediterranean than in the chilly northern European countries such as the United Kingdom, Germany, and Denmark. But exactly the opposite is true (see color map), with the incidence among males in Denmark, for example, six times greater than in Portugal. The highest skin cancer rates of all are seen in places like the northern Scottish isles of Orkney—noted for their long hours of heavy rainfall, not bright sunshine.

Many epidemiologists believe that the explanation may lie with the "Costa Brava effect," the increasing fashion for northerners to take vacations in the south. "People work 11 months of the year without getting sun, and then comes vacation time, and they go to Spain or the south of France," says Maurice Tubiana, retired director of the Institute Gustave Roussy, a cancer research center in Villejuif, near Paris, and current president of the scientific advisory committee to the European Community's Europe Against Cancer campaign. "These people are at much higher risk than the fishermen or other people who are out in the sun every day of the year," Tubiana says.

Other trends are consistent with what cancer researchers already know about risk factors. The IARC data show, for example, that breast cancer strikes women at almost twice the rate in the United Kingdom as in Spain. "A vast proportion of these differences will be explained by differences in reproductive behavior," says Kohlmeier. "Earlier childbirth, as well as the number of children, is clearly and strongly associated with a lower risk, and in Mediterranean countries people have their children younger."

But if the north-south difference in breast cancer incidence is more or less what epidemiologists would have predicted, new studies are revealing an intriguing discrepancy between the east-west rates. The reunification of Germany has given Kohlmeier and her colleagues a rare opportunity to study the effects of life-style on breast cancer, she says. "We are looking at the differences between East and West Germany, where you had a formerly homogeneous population artificially separated by the wall. This is a natural experiment, which is very exciting for epidemiologists." And the results so far have been the opposite of what was expected.

Although direct comparisons are tricky because the data were not collected the same way in the two Germanies, preliminary work indicates that West German women have a 15% higher incidence of breast cancer, and a 30% higher death rate from the disease. "This is a bit of a surprise, because East Germany has, overall, a greater mortality and shorter life expectancy than the west," Kohlmeier says. "I can only speculate at this point, but we are looking closely at several factors." These include differences in the relative intake of dietary substances, such as vitamin C and indoles, which some researchers think might protect against cancer. "Cabbage, for example, is a rich source of indoles in the diet, and it was a major staple in Eastern Europe," Kohlmeier says. She also believes that differences in the consumption of alcohol, which is a known risk factor for a number of different cancer types, may play a role. Although Germans east and west love their beer, some surveys indicate that East

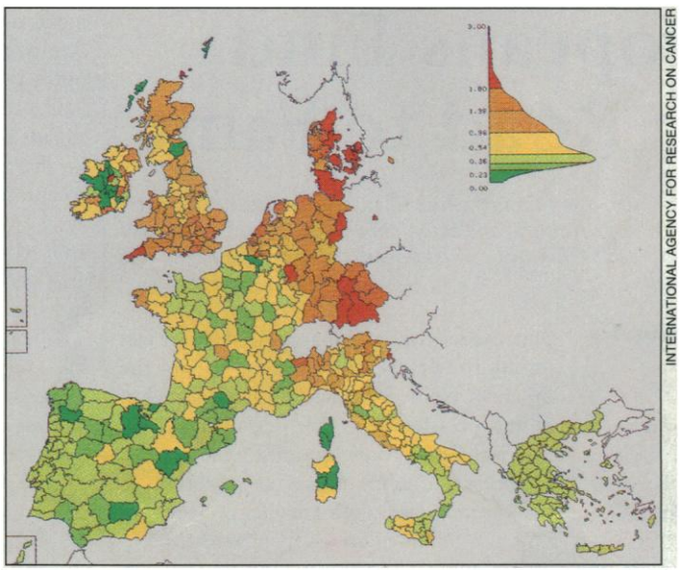
Special Report on Cancer

Cancer research is a highly international endeavor, as the articles on pages 1131 to 1177 make clear, but a little regional variety still enlivens the subject. The following six pages celebrate cancer research in Europe's big three biomedical research nations, England, France, and Germany. Read on to find out why epidemiologists should vacation in Europe, how to get to the top with style, and why some of Europe's cancer researchers owe everything to some dedicated volunteers.

German women drink less.

The fall of the Iron Curtain has also brought a whole host of possible links between cancer and industrial pollution within epidemiological reach, for the simple reason that pollution in the East has reached levels unknown in the West. One of the most affected regions is Central Silesia, home to some 4 million people and much of Poland's heavy industry, including steel mills, chemical plants, and coke factories.

"We have polluted everything —air, water, and soil," says Mieczyslaw Chorazy, head of the department of tumor biology in the Gliwice laboratories of the Warsaw-based Institute of Oncology. "Until very recently, we were able to measure a deposit of large particulate material at a rate of 1.5 kilograms per square meter each year. It's been dropping lately, but this is probably due to the fact that our industries are not working very efficiently at the moment."



A shade of difference. *This map illustrates how melanoma rates tend to increase from southern to northern Europe. (The rates for Spain and Portugal are estimated.)*

Chorazy and his colleagues are analyzing samples of small particulate material collected by epidemiologists in Silesia, and have so far identified about 200 different organic substances, including carcinogens such as the polyaromatic hydrocarbons. "We know that this material contains enormously high mutagenic activity, as measured by the Ames salmonella test and a number of other techniques," Chorazy says. In collaboration with scientists in Finland and the United States, Chorazy's group has also found that people from the most highly contaminated areas have suffered a much greater burden of genetic damage compared to controls from unpolluted areas.

Chorazy and his colleagues have not gone far enough in their work yet to know if there is any correlation between the genetic damage they see and increased cancer mortality. But there is reason to think that there might be. Chorazy says that preliminary studies indicate a significant amount of "clustering" of cancer cases in the most industrialized regions. "There is a striking correlation. This is a very obvious effect and is much above the level quoted for Western countries. And I am pretty sure that these clusters cannot be correlated with smoking," he says.

Although the existence of cancer clusters in a place as polluted as Silesia may not be surprising, their appearance in Western countries often leads to a prolonged search for a persuasive cause. The well-known Sellafield affair is a case in point: In the early 1980s, an increased incidence of leukemia and non-Hodgkin's lymphoma was found among children who live near the Sellafield nuclear reprocessing plant in the Cumbria district of England. After years of detective work, a group of scientists, led by Martin Gardner of the British Medical Research Council's Environmental Epidemiology Unit at the University of Southampton, found a link between the leukemias and the occupational radiation exposures of the children's fathers: Those who worked at the Sellafield plant and had the higher exposures, although still within the occupational limits, were more likely to have children who developed one of the two cancers (also see *Science*, 6 April 1990, p. 24).

That story was hard for epidemiologists to swallow, as there seemed no simple way the fathers' radiation exposures could cause cancer in the children. And indeed, it flew in the face of the 40-year study of the Hiroshima and Nagasaki atom bomb survivors, which has turned up no increased incidence of leukemias and other cancers, or of genetic defects, in the survivors' children. Nevertheless, no one to date has been able to find serious flaws in the study.

A newer study, released in late September by the United Kingdom's Office of Population Censuses and Surveys, may, however, help explain why some clusters of childhood leukemia occur, although it apparently doesn't shed any light on the Sellafield cluster. A survey of nearly 10,000 cases of childhood leukemia and non-Hodgkin's lymphoma by workers at Oxford University's Childhood Cancer Research Group and their colleagues has found that children of more affluent families are at greater risk for developing leukemia. "Childhood leukemia, almost uniquely among childhood diseases, is actually a disease of the higher social classes," says epidemiologist Gerald Draper, director of the group.

The correlation between childhood leukemia risk and affluence is highly significant statistically. "If we divide the population into five equal groups and compare the highest and lowest social strata," Draper says, "childhood leukemia rates are 10% to 15% higher in the top group than in the lowest." He notes that while these results cannot explain away the cluster of leukemia cases found at Sellafield, they may account for higher rates of the disease found at certain other nuclear plants in England, such as those at Aldermaston and Burghfield, which are located in relatively affluent areas.

Exactly what the connection between affluence and childhood leukemia might be is still a mystery. But one hypothesis, advanced by Melvyn Greaves of the Institute of Cancer Research in London, has recently been getting a lot of attention. Greaves thinks that children of more affluent families may be exposed to viral infections somewhat later in life than those whose parents are less well off. That means that such children might have more time to accumulate potentially carcinogenic mutations in their white blood cells before these cells become exposed to cancer-inducing viruses.

In an effort to test this idea, a committee of leading British epidemiologists, gathered together by Ray Cartwright at the University of Leeds and chaired by Richard Doll of Oxford University, will launch a case control study in England and Wales, beginning in January, which will compare the infectious disease histories of childhood cancer victims with those who do not get cancer. A parallel study is already under way in Scotland.

The hypothesis advanced by Greaves is plainly speculative, and the fact that Great Britain's top epidemiologists are gathering together to try to test it and other possible explanations of the link between parental wealth and childhood leukemia says something about the growing spirit of confidence among European epidemiologists. "We are in a good place at a good time," Kohlmeier says. "Things are beginning to happen."

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