Experts Clash Over Cancer Data

While new studies sound an alarm about increasing cancer rates, Oxford epidemiologists Doll and Peto report there are no surprises

CANCER IS A MORE SERIOUS PROBLEM IN the industrial world now than it was 20 years ago, according to Devra Lee Davis, scholar in residence at the National Academy of Sciences. The United States has spent tens of billions of dollars developing treatments for the disease, yet—if Davis is right—the picture is still getting darker.

Not everyone agrees with this bleak assessment. Soon after an article by Davis and three colleagues appeared in *The Lancet* last August, objections erupted from a handful of renowned scientists. The first skirmish took place during a meeting at the Cold Spring Harbor Laboratory on 4 September when Bruce Ames, a biologist at the University of California, Berkeley, confronted Davis and questioned her work before an audience of cancer experts. This has rekindled a debate among the world's top epidemiologists about how to interpret cancer trends.

Davis isn't alone in raising this concern: Her coauthors include the head of Britain's census, John Fox, the acting chief of the U.S. National Institute for Environmental Health Sciences, David Hoel, and the World Health Organization's chief biostatistician, Alan Lopez. But the names on the opposite side are, perhaps, better known. They include Sir Richard Doll, the 78-year-old Oxford University epidemiologist who established the link between smoking and lung cancer, and his protégé, Richard Peto, who is also at Oxford. Doll and Peto dismiss the *Lancet* report as trivial.

Though the arguments revolve around narrow points in the statistics, the implications are broad: Just how much benefit has the "War on Cancer" brought? And is it being fought on the right fronts? Davis thinks the government should allocate more funding to research on the causes of cancer. Like John Bailar, a McGill University biostatistician and MacArthur grant winner who has argued this point for years, Davis says only a small fraction (7%) of the National Cancer Institute research budget goes for epidemiology and that it should be increased. Ultimately, this debate is about how much effort the nation should put into "doctoring" cancer versus investigating its causes and attacking them. The answer hinges in part on whether you think the war on cancer is going well or not.

The mainstream view was summarized by National Cancer Institute director Samuel Broder at the Cold Spring Harbor meeting. The commander-in-chief of the war on cancer sought to give a balanced picture of the long-term trends, saying there was "both good news and bad news." The good news, Broder said, involves younger people, among whom the death rates for testicular, stomach, blood, and colorectal cancer have been declining. The bad news is that death rates are climbing for the over-65 population. And for blacks, the situation is worse. Said Broder: "Poverty is a carcinogen."

But Davis had already reached a far more grim conclusion: Cancer is on the rise in the United States and five other industrial countries. The *Lancet* article described what the authors call "remarkable shifts in patterns of cancer," concluding that the increases "are so great and rapid that it would be imprudent not to investigate their causes aggressively." Deaths from brain cancer in all countries, they found, nearly doubled among people over 65, and deaths from all types of cancer (except lung and stomach) increased in people over 54. In a forthcoming paper, Davis and another group of colleagues report that the incidence of brain cancer for people over age 45 in the United States has been increasing by 2% a year since 1973.

Susan Bascomb/USA Today

The alarmist view. *Devra Lee Davis sees discouraging trends in cancer incidence.*

Ames, who has become a public scourge of cancer alarmism, challenged the validity of these conclusions at the Cold Spring Harbor meeting, and he got strong support from Peto. Peto said people put too much emphasis on rising trends in certain types of cancer. He told *Science* later in a telephone interview that there's no reason to get excited because the big pattern has not changed dramatically in 15 years. Peto and Doll seemed overcome with ennui about this subject when *Science* contacted them at their Oxford University lab. They found the Davis article "uninteresting," "quite uninformative," "boring," "old junk," and "well known for years."

Yet, for a non-event, the publication of Davis's paper has stirred a lot of activity. It made headlines in the *New York Times,* the *Washington Post*, and even in Beijing, says Davis. And it has prompted marathon transatlantic phone calls between the Davis and Doll-Peto groups, at least three sharply worded letters to the editor of *The Lancet*, and extensive backstage lobbying of peers by the protagonists. Indeed, if it were politicians doing this rather than scientists, you might say they were engaged in spin control.

Professional rivalry plays a part in the debate, too. The "nothing new" position adopted by Peto and Doll is the same one they held 10 years ago during a similar debate with Davis, then at the Environmental Law Institute in Washington, D.C. Back then, the Oxford epidemiologists attacked the popular view that environmental factors—often interpreted to mean chemicals—could be blamed for causing most cancers. As Peto wrote, one reason this idea took hold in the 1970s is that some people "positively *wish* to believe ill of the modern world."

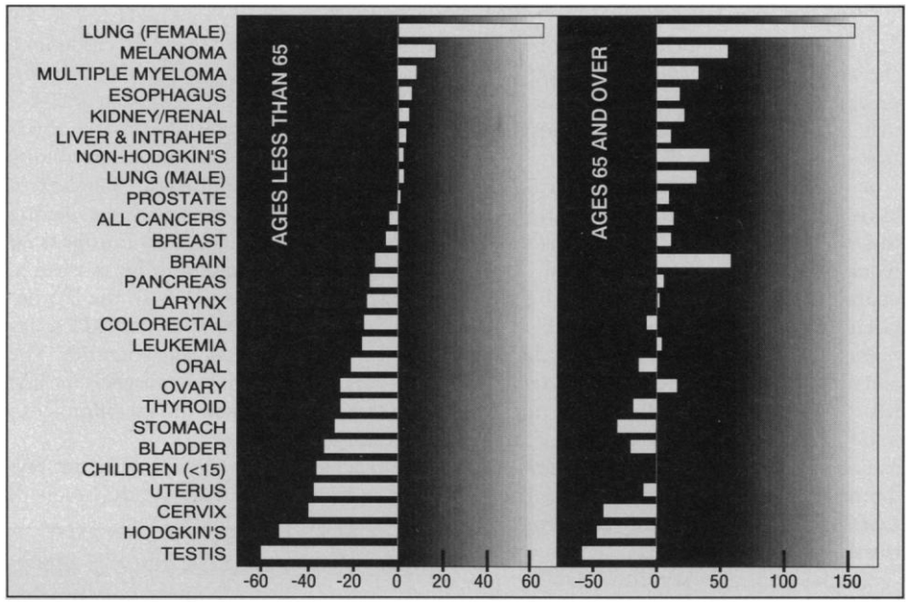
As is often the case when technical debates get personal, the two sides differ not on the data themselves but on how to interpret them. One side (Davis's) gives a lot of weight to the reported rise in brain tumor deaths among the elderly and to a rising incidence of several types of cancer among the middle aged. The other sees these changes as un-

important—a reflection of better diagnosis and increased longevity rather than a cancer epidemic. Skeptics like Peto also think data on incidence (as opposed to mortality) offer a shaky foundation for generalities because the war on cancer has been encouraging everyone to find tumors at an earlier stage. The predictable result is that more are being found.

In addition, the big picture (see chart, p. 902) may be skewed by the types of cancer that are included or left out. Peto leaves out the increase in lung cancer, the single biggest killer, because it "swamps" all the other data, and the causes (mainly tobacco smoking) are well known. So in his analysis, tobacco-related deaths are set aside as a special category. This approach makes sense, but a chart based on it yields a picture tinged with questionable optimism. Despite the encouraging trend lines, people are still dying of lung cancer in droves, and doctors must care for them.

While Davis and colleagues agree that tobacco deaths should be set aside for analytical purposes, they use similar arguments to omit stomach cancer as well. The 60-year decline in stomach cancer is one of the few genuine pieces of good news. In the United States, for example, it dropped at an annual rate of 2.6% from 1973 to 1987. While no one knows precisely why this is happening, Davis suggests it may be due to improved diet, better food storage, and less use of salt and nitrate preservatives. The rationale for leaving stomach cancer out of the picture is to ignore dietary changes and focus on other problems, but doing so makes the scene grow dark. Davis *et al.* report that (leaving aside lung and stomach cancer) total cancer mortality has been rising since the early 1970s for people over age 54 in the United States, England and Wales, France, Italy, Japan, and West Germany. Davis says a new paper will report soon that cancer mortality is increasing in 18 developed nations.

The *Lancet* report has found a sympathetic audience in some parts of the medical research world. Thomas Chalmers of Harvard University, a pioneer in the use of clinical trials, says he was "impressed" with it and agrees that cancer rates "are going up." Edward Sondik, deputy director of the National Cancer Institute's division of cancer prevention and control, says there is reason for concern. "While mortality has been declining generally for those under age 65, incidence has been rising both for those under and over 65." He adds that, "We need to find out what's causing this," and he thinks recent reports "reinforce the need for prevention efforts." And Philip Landrigan, a well-known specialist in occupational health at the Mount Sinai Medical Center, says: "Doll and Peto are correct in that this isn't new. These trends have been 10 years in the making. But the recognition of this upward trend is a new thing. The finding is real and I think [Davis] deserves credit for bringing it to everyone's attention."



The conventional wisdom. *Changes (by percent) in cancer death rates from 1973 to 1987 are good news for the young (left) and bad news for their elders.*

John Bailar, the biostatistician, is a stalwart champion of Davis's point of view. He not only agrees that her "overall picture is correct: cancer incidence is going up," but he also argues that Peto is "flat wrong" to discount older people. Such data may be unreliable in developing countries, says Bailar, "but this is not an important consideration in the United States."

But Peto's camp also has broad support. For example, Catherine Hill, an epidemiologist at the French national health agency (INSERM) and coauthor of a 1989 book on cancer rates, sent a letter to the *Lancet* editor blasting its conclusions as "completely unwarranted by the data presented and...essentially wrong, at least for France." She writes that between 1950 and 1987 there has been a small 1.2% annual growth in male cancer deaths, "mostly due to increases for sites associated with tobacco and alcohol." The rate for women has actually declined by 0.4% a year, mainly because cervix and stomach cancer deaths have dropped off more rapidly than breast cancer has increased.

Walter Willett, a specialist on breast cancer at Harvard University, told *Science* he had found nothing new in the *Lancet* article. And Brian Henderson, epidemiologist and head of the University of Southern California's cancer center, said in a telephone interview: "Cancer mortality in general has been relatively stable [in the United States], or actually declining, if you eliminate lung cancer."

As this dissection of methods reveals, the heart of the argument is in the data on specific types of cancer. To weigh the merits of the generalized overview, it helps to know something about the details. Davis and her colleagues base their alarm on what they perceive as dramatic increases in the number of brain tumors and several other forms of cancer, notably breast cancer, melanoma (lethal skin cancer), multiple myeloma (a blood disease), and non-Hodgkin's lymphoma (lymph cancer). Except for breast cancer, these are not big killers in the United States. But the rates are increasing, particularly among older people, and experts differ on each type of disease and on the age of patients to focus on.

■ **Old or young people?** Many of the strongest changes reported in the *Lancet* paper appear in the population over age 65. "We really should be looking with great attention to what happens in old age," because older people get two-thirds of all the cancers, says Lorenzo Tomatis, director of the International Association of Cancer Research in Lyon, France. Furthermore, as Davis points out, doctors and public health planners must cope with patients no matter what their age.

But Peto argues strongly that trend analysis should focus on younger people—particularly on death rates among people in their twenties to early sixties. He prefers to look at this age group because the treatment of older patients has changed so much more. "It's normal for old people to die," he says, and, until very recently, no great effort was made to find the precise cause of death among the elderly. Now that effort is being made, so recent trends are more likely to reflect social rather than biological changes.

And Peto distrusts incidence data because the war on cancer has put such an emphasis on early detection that aggressive doctoring may have influenced the records more than true disease rates.

■ **Brain tumors.** The *Lancet* article reports that since the late 1960s deaths from this type of cancer have "nearly doubled" or worse for people over age 65 in all six countries examined. Another article by Nigel Greig of the National Institute on Aging examines this problem in the United States and finds that the occurrence of brain tumors has "increased dramatically...by up to fivefold" since 1973 in people over age 75. "Irrespective of causes," Greig concludes, "the dramatic rise in incidence rates indicates that these tumors are a greater concern than hitherto recognized."

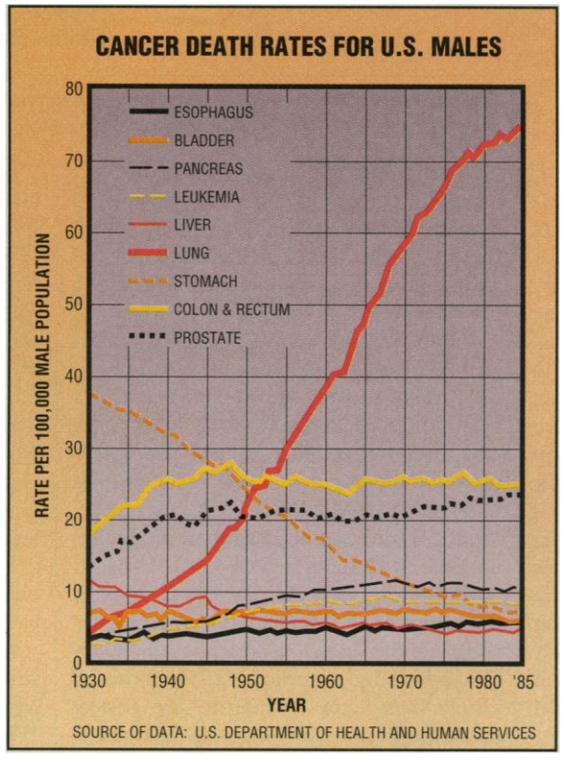
To the contrary, say Peto, Doll, and Hill, everyone knows that doctors test old people more accurately now than they did 15 years ago. New technology in this period—x-ray computed tomography (the CAT scan) and nuclear magnetic resonance imaging—make it safer and easier to examine brain lesions. With Medicare picking up the tab, there is no economic barrier to getting a complete diagnosis either. The skeptics argue that old people who in the past might have been diagnosed as "senile" or "demented" are now being given detailed examinations. As a result the records list more brain tumors.

Leonard Kurland, a specialist in epidemiology of brain diseases at the Mayo Clinic in Rochester, Minnesota, also thinks that the "diagnostic effect" may be contributing more to the database than an actual increase in tumors. His evidence comes from his own community. "We showed these high rates [for brain tumors]—and rates continuing to go up with age—as early as 1958, long before these people [Davis *et al.*] noticed it."

In response, Davis says she recognizes that part of the increase reflects better doctoring, but not all of it. In an analysis of 60,000 cancer cases reported to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database, Davis and her colleagues checked the quality of diagnosis. They found that in each of three periods between 1973 and 1987 brain tumors were confirmed with hard evidence—by microscopic examination of tissue or a CAT scan—more than 96% of the time. This suggests the recorded increases are real. Furthermore, Davis says, brain tumors began to increase before the deployment of new diagnostic machinery, and they are still increasing even now. "It strains credulity," she says, to argue that a simultaneous increase in six countries is purely an artifact.

■ **Breast cancer.** After lung cancer, this is the leading cause of cancer death among women in the industrial world. The *Lancet* authors report that the incidence among women in North America and Europe is 30 times greater than among those in western Africa and Central America. In the last decade, mortality rates have continued a long-term rising trend in affluent countries. The causes are not clear, but the suspects include excess fat in the diet and the use of prescription estrogens.

Peto acknowledges the increase, but says the rise in incidence may be the result of



The big picture. *For U.S. men, lung cancer death rates (age-adjusted to 1970) have gone up, while stomach cancer has gone down.*

efforts to detect the problem earlier and a greater willingness to discuss it. He adds however, that there is some good news: Early screening may save as many as 10,000 lives a year worldwide.

■ **Melanoma.** This lethal form of skin cancer is increasing rapidly among fair-skinned people throughout the world. Although the overall U.S. mortality rate is not high (2.2 per 100,000), the rate of incidence is rising steeply, especially among whites (4.4% a year). Although the *Lancet* article includes this as one of the more alarming cancers, Peto and Doll argue that there's nothing surprising about it. Says Doll: The problem of melanoma "has been known for a long time," and it's probably due in the main to overexposure to the sun as a child.

■ **Multiple myeloma.** This form of blood cancer is occurring more frequently as well, but the rate of increase is smaller than for melanoma, and the causes are less clear. The *Lancet* authors found a consistent pattern throughout six industrial countries of generally increasing mortality since the 1960s for men older than 55. The death rate rises with age in both sexes. Doll again views this as an "old problem," though not a well-understood one. He and Peto suggested in 1981 that the reported increases in multiple myeloma, as with brain tumors, may be the result of increasing skill and attention devoted to the care of older patients.

■ **Non-Hodgkin's lymphoma.** This is the one cancer that seems to puzzle everyone. Doll says, "It has been increasing in most countries, and it is a bit of a problem." Although some researchers have sought to link it to herbicide exposure, according to Doll, the disease is not markedly on the rise in Australia, where herbicides are widely used. Its share of cancer mortality in the United States in 1987 was small (3%), but its incidence has been increasing steadily at 3.2% a year and its mortality at 1.7% a year. Says Brian Henderson: "We really do not understand it. We have looked at the epidemiology of over 1000 cases," and it remains "mysterious."

All these details add up to an apparent increase in cancer incidence and mortality for some categories. But even in the face of these trends, Peto and Doll remain optimistic. The surge in reported cases and deaths, they say with confidence, is not a measure of failure but of success. Doctors are now doing their job better, and their increased productivity is reflected in the data.

The argument makes sense. But it has a flaw according to Bailar: It's weak on evidence. "I have not seen any data from Peto or Doll," Bailar says, to support the view that the boom in cancer diagnosis itself is responsible for these increases. He believes the burden of proof is on those who doubt that the increases are real. "We need a broad statistical analysis of earlier misdiagnosis and of what the real trends are," he concludes.

As they stand now, the statistics seem to support either an optimistic or a pessimistic reading of the trends. And perhaps this is the most significant aspect of the debate: Fully two decades after the war on cancer began, it's not immediately clear that public health programs have gained more ground than they have lost. ■ ELIOT MARSHALL