

# GOING BY THE NUMBERS

BY KAREN WRIGHT

"WHAT I WANT TO TALK TO YOU ABOUT today are trends in cancer in industrial countries." So begins the lecture that Devra Lee Davis has delivered in dozens of formal appearances and extemporaneous discussions this year, a monologue she recites for anyone who wants to listen and for a good many who don't.

"Our data draws on mortality statistics for six countries, provided through the World Health Organization and checked for quality," she says. Translation: I am not pulling numbers out of thin air.

"This is truly an international collaborative effort," she adds, naming colleagues from three countries. Translation: I am not the lone evangelist I appear to be.

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"May I have the first slide, please." Up in the top tier of the auditorium at the University of California at San Francisco in April, Davis's 11-year-old daughter, Lea, flicks on the projector. Lea has heard her mother's disquisition so many times that she once fell asleep at the table when the subject came up over dinner.

Davis's message has the opposite effect on just about everyone else. As a specialist in public health policy and scholar in residence at the National Research Council of the National Academy of Sciences, a prestigious position she was appointed to in 1989, Davis has compiled one of the few systematic comparisons of recent changes in deaths from cancer. Culling information from millions of death certificates, Davis has shown that deaths from breast cancer, brain cancer, kidney cancer, myeloma, melanoma and non-Hodgkin's lymphoma have climbed since the late 1960's, particularly among the elderly.

That claim in itself is enough to make headlines — and enemies. There are big money, big prizes

and big reputations at stake in cancer research and there are more than half a million lives a year to be saved in this country alone. But assertions about lack of progress in the so-called war against cancer are never greeted warmly by the cancer establishment. And consensus among epidemiologists, the fractious corp of medical scientists who study the distribution of diseases and hope of discovering causes, is rare even when stakes are low.

But Davis goes further, suggesting that many of those cancers may be caused by preventable factors like exposure to chemicals in the workplace and changes in exercise and dietary habits. Her studies aren't detailed enough to point the finger at any one culprit, but Davis suspects causes are there because the increases have occurred so suddenly and because cancer rates are significantly lower in some countries than they are in others.

And then she ups the ante by using her conclusions to argue that the United States is not putting enough money into research on cancer

A resident scholar at the prestigious National Academy of Sciences, Davis recites her statistics to anyone who wants to listen (and many who don't). Here, she advises two lawyers who do — they are working on a case involving public health issues.





Left: Davis chats with Marvin A. Schneiderman, a former associate director of the National Cancer Institute, while Albert Einstein eavesdrops outside the National Academy of Sciences offices in Washington.

Below: Mother and daughter, Lea, await a routine doctor's appointment.

prevention. With death rates rising from unidentified causes, she says, research on treatment — currently the lion's share of the Government's \$2 billion annual cancer program — seems a feeble palliative. Care for cancer patients already costs nearly \$30 billion a year. Ultimately, Davis maintains, the only way to get cancer under control is by naming and eliminating its causes.

In some ways, her timing couldn't be better. On the 20th anniversary of the signing of the National Cancer Act, the country's cancer effort has been skewered between new developments and new disappointments. Though basic research programs have made spectacular advances in the understanding of cancer biology, those advances have not revolutionized treatments for the most common cancers.

The National Cancer Institute's 1982 goal of reducing cancer deaths 50 percent by the end of the century looks ludicrous today. The mortality rate is actually higher than it was when the war on cancer began, even though death rates for some cancers, like those that afflict children, have gone way down and even though at least 30 percent of all cancer deaths are due to a fully preventable cause, smoking.

But Davis's scrutiny is not welcome. Whether through manner or material, she has managed to alienate two of the world's leading experts on cancer statistics: the redoubtable Oxford physician Sir Richard Doll, who with A. Bradford Hill helped establish the link between smoking and lung cancer in the 1950's, and his notoriously feisty protégé, Richard Peto. Doll explained to Davis years ago that he thought her ideas were both wrong and unoriginal; he hasn't changed his mind since. And Peto's feelings, after much subterranean rumbling, finally erupted in print in November 1990 when he and Doll told the journal *Science* that Davis's work was "uninteresting," "uninformative," "boring" and "old junk."

"I do not know what explains these trends that I've shown you today," Davis says at the conclusion of her San Francisco lecture. "But I think we need to find out. What we learn may allow us ultimately to come up with strategies to prevent



thousands of millions of deaths." Your average scientist might try to tone down her rhetoric. Devra Lee Davis is not your average scientist.

ALBERT EINSTEIN SITS IN A GARDEN OUTSIDE the entrance to the building that houses the august National Academy of Sciences in Washington. His granite dais has a view across Constitution Avenue to the Mall, the memorials, the cherry blossoms, the tourists. But Einstein — in bronze, larger than life — never lifts his eyes from the stainless-steel map of the constellations at his feet. "The right to search for truth implies also a duty," he says in a marble exhortation. "One must not conceal any part of what one has recognized to be true."

In an office a hundred yards away sits Davis, the antidote to the statue's sobriety. She talks a lot, wears bright red and stands 5 feet 8 inches tall, not counting the corona of thick brown curls that envel-

op her head. Photos of her husband and children, Lea and Aaron, fill the walls where she could have hung her master's degree (in public health from Johns Hopkins) and her Ph.D. (in "science studies" from the University of Chicago). Davis does aerobics, speaks Russian, studies Torah, plays the cello, coaches her children's soccer teams, is host for international meetings, rescues stray dogs and is evasive about her age (she's 45). With little more than a decade of work on cancer trends under her belt, she is an upstart of the most fearful kind: earnest, outspoken, indefatigable. And, perhaps significantly, female: a bejeweled brunette amid gray heads and bow ties.

"A tremendous decline in cancer deaths has occurred in people under age 45 in the United States," Davis begins. "A tremendous decline. Due largely to improvements in treatment for childhood cancers. But in the age groups over 45, there is an increase." It is most (Continued on page 77)

announced in people more than 64 years old, who account for about two-thirds of all cancer mortalities.

"Now, we're not talking about small increases here," he says. "Some of these cancers have increased 25 percent to more than 200 percent" in the past two decades. When something increases rapidly over such a short period of time, that strongly suggests there may be a preventable cause behind it."

Last year, in a paper published in the British medical journal *Lancet*, Davis and her colleagues reported similar rises in England and Wales, West Germany, France, Italy and Japan. "All forms of cancer are increasing in persons over age 54 except lung and stomach," she wrote. "The ranges ... are so great and rapid that it would be imprudent not to investigate their causes aggressively."

That conclusion put Davis in network television and in national newspapers. It also put her in the doghouse as far as some of her peers were concerned. Critics saw the *Lancet* report as the most sensational in a series Davis and various co-authors had given in the late 1970's, when Davis worked as a policy analyst and science director at the Environmental Law Institute in Washington. Between articles on risk assessment, acid rain and asbestos, Davis began looking at occupational exposure to cancer-causing chemicals. She pointed out that chemical production had increased dramatically in his country since the 1960's and that because of the latency periods typical of such carcinogens the potential effect of the increase on cancer mortality would probably not be evident for another decade or so — not until, say, the 1990's.

But, as Davis concedes, with cancers associated with industrial exposures amounting to only about 6 percent of all cases, increases due to greater chemical production would be difficult to detect. So she began to examine deaths from particular types of cancer in people 65 and over, people who were likely to have longer histories of exposure.

That's when she crossed Doll and Peto the first time. In their classic 1981 treatise on the causes of cancer, the Oxford duo had maintained that the data on cancer vic-

tims older than 64 was too unreliable to be used in evaluations of cancer trends. Apparent increases in mortality in the elderly, they said, may have resulted from greater access to medical care and improvements in diagnosis — influences that statisticians call artifacts. So Doll and Peto limited their appraisal to those 64 and under, and found no cause for alarm. In a conference report from the early 1980's, Peto took a side-long dig at Davis with his assertion that "opposite conclusions by other commentators appear to derive chiefly from methodological oversights."

Davis was unpersuaded. Doll and Peto's calculus discounted more than 60 percent of all cancer deaths. She did agree that advances in diagnostic equipment and techniques and the start-up of Medicare in the mid-1960's could have introduced artifacts in the data of the time period — from 1933 to 1977 — that Doll and Peto had chosen to study. Her solution was to consider the data only from 1968 on. There hadn't been much change in access to medical care after that date. It is true that CAT scans and magnetic resonance imaging machines brought major improvements in diagnosing cancer. But in the mid-80's, after she'd moved to the academy, Davis did a number of studies to show that improved diagnosis alone couldn't explain the increase in cancer deaths in the elderly. One was an analysis of deaths between 1968 and 1978 from senility, cancer of unspecified type and "unspecified" causes. If the apparent increase in cancer mortality was simply the result of better diagnosis, Davis reasoned, then deaths in these "default" categories should drop, reflecting the detection of previously unrecognized tumors. But they had risen as well.

The more she looked at the statistics, the more alarmed Davis became. At first, she confined her interests to brain, lung and bone cancer (myeloma), because those were among the cancers more likely to be caused by occupational exposure to carcinogens. But the larger question of cancer trends in older populations led her to include other kinds of cancer, and to exclude lung and stomach cancer, whose causes are fairly well known. Her *Lancet* paper drew attention to in-

creases in brain and breast cancers and in myeloma, melanoma and non-Hodgkin's lymphoma. It also showed that rates of those cancers are relatively low in some industrialized countries, most notably Japan. The fact that Japanese immigrants to this country quickly develop cancer rates similar to those of the natives further indicates that there may be avoidable causes of those cancers.

Davis's analyses do not attempt to name what those causes might be; it takes epidemiologists years to arrive at a cause, even in obvious cases like the link between asbestos and cancer of the respiratory tract. She likes to call her work "hypothesis generating" — meaning it raises more questions than it answers. Why has brain cancer doubled in people over age 65 since 1968? Why do Japanese women have lower rates of breast cancer than women in the Western industrialized nations? Why do black men have a 50 percent higher death rate from lung cancer than white men, even though they start smoking later in life? Why is the death rate from melanoma increasing almost 5 percent a year among fair-skinned older people?

Some observers have explained trends in the elderly by evoking what's known as the "competing causes of death" argument: that fewer people are dying of heart disease and other maladies, so more die of cancer. But that fact shouldn't change the rate of cancer mortality in specific age groups, Davis points out. If more people live to be 75, then the total number of 75-year-olds who die from cancer will go up, but the proportion of 75-year-olds should stay the same. It may be that the miracles of modern medicine are saving people who are more likely than their naturally resilient contemporaries to develop cancer. "But even if that's part of the answer, it still means we have something to prevent," she says.

The dissonance between the Doll and Davis camps reached a crescendo of sorts at a September 1990 meeting on the origins of human cancer held at the Cold Spring Harbor Laboratory on Long Island. In an opening night address, Samuel Broder, director of the National Cancer Institute, mentioned that "those over 65 have disproportionate high rates of can-

cer mortality." Davis took it as an implicit endorsement of her position and couldn't resist asking a rival what he thought of Broder's remark. Being Davis, she asked a fairly illustrious rival — Prof. Bruce N. Ames of the University of California at Berkeley, who pioneered the testing of potential carcinogens. Being Davis, she confronted Ames while dozens of colleagues looked on.

And being Davis, she wound up in an argument with Peto, when Ames deferred the question to him.

Scientific disputes are rarely so public. The enmity over Davis's position seems obsessive at times, degenerating into what she calls "ad feminam" attacks. Ames, who says cancer statistics are not a cause for alarm, keeps a file on Davis because "she's always coming out with something I disagree with." He says Davis's interpretations present ambiguous trends in the worst possible light.

"She's out for publicity," he says. "I think she's wrong on everything. Well, not everything — she's not that reliable." Anyway, says Ames, "the world's leading epidemiologists don't agree with her." He means Doll and Peto.

"Let me tell you something," says Davis. "There's nobody who'd be happier to learn that there's some great artifact here. But I don't think it's doing anybody any good to assume that all of these increases, in men and women everywhere, are just some fluke that seems to be afflicting medical statistics worldwide."

**I'M NOT ANXIOUS** to be joined in any controversy with Dr. Davis," says Sir Richard Doll, who is speaking — ever so cautiously — on the record. His partner, Peto has decided to decline that privilege.

"Nobody argues about the mortality in many developed countries in people over 65 going up," says Doll. "The question is, Is it of any particular importance with respect to causes?" Doll maintains that when you look at the trends for each type of cancer, they seem much less formidable. Increases in lung cancer, for example, are clearly due to smoking. Deaths from stomach cancer have plummeted, probably because of

changes in diet. Doll believes the increases in brain cancer are almost certainly the result of better diagnosis. (Davis maintains, with some corroboration from recent independent studies, that these alone cannot account for all the increases.)

"I'm not saying there are no new hazards," Doll says. But if there were unidentified risk factors, he says, they would show up as increasing cancers in younger people as well as the elderly. That's one of the reasons he and Peto felt safe in excluding cancer deaths in people over 64 from their 1981 monograph: "There's no example of any cancer that requires longer than 15 or 20 years to reach a fairly high incidence as a result of exposure to a carcinogen. You're not going to have an epidemic occurring 30 years after first exposure."

And even if some cancers are rising mysteriously, he maintains, Davis isn't the first person to notice it. The increases in melanoma, myeloma and non-Hodgkin's lymphoma are probably legitimate, he says, and are still inexplicable. But "these have been a matter of scientific knowledge for a long time before Devra Davis drew attention to them."

So is Davis wrong, or just unoriginal? "Both," says Doll. "Both."

Given his tepid opinion of her work, Doll might be surprised to learn that Davis ends her lectures with an homage to his efforts. In fact, he's the figure she seems to identify with most — not the esteemed Sir Richard of the present but the young, modest, methodical researcher who antagonized the medical establishment in the late 1940's and early '50's with his insistence that there was a sinister correlation between the prevalence of cigarette smoking and the sharp rise in lung cancer. "I don't think you can imagine the respect and awe with which most of us regard Richard Doll," she says. In an adroit display of tautology, pathologists had argued that smoking couldn't cause cancer because they knew of no mechanism by which the chemicals in cigarette smoke could cause cancer. The increase might just reflect the fact that doctors were getting better at distinguishing between lung cancer and tuberculosis, they said. It wasn't until 1964 that the United States Sur-

on General formally acknowledged the smoking and lung cancer connection. The moral of the story, according to Davis, is that a new era in science rarely gets a warm reception. "At first, people say it's ridiculous," he says. "Then they say, 'Well, it might be true, but it's not important.' Then they say, 'Well, actually, I discovered it myself.'" Davis unabashedly applies this moral to her own situation.

But it's not clear what chapter of the story she's in now. It seems, at times, that Davis cannot count even on the support of her collaborators. Alan D. Lopez, a statistician for the World Health Organization in Geneva, now claims he was "surprised" to see himself listed as a co-author of the *Lancet* article that pushed Davis to the spotlight. His office provided the data for the paper and he sent Davis complimentary comments on it; he admits he noticed that his name was on several drafts, but he says the paper was published before he had a chance to tell Davis to take it.

Davis thinks Lopez's denial is the result of pressure from Doll and Peto. Lopez says he had to re-ingratiate himself with the cancer establishment after the *Lancet* article came out — the establishment being Doll and Peto, with whom he has been working since 1989 and who, Lopez admits, had "a few sharp words" for him.

"That's a sad comment on the politics of the issue," Davis says. "For some reason, Doll and Peto are exercised about this far beyond what is merited. And I really can't figure out why."

Lopez offers one explanation when he says Davis's work "is dangerous in the sense that it draws the principal public health concern away from cigarettes." Or it may be that statistical interpretation is a kind of esthetic and that scientists become wedded to their personal visions. "Doll and Peto stuck their necks out before," says Thomas C. Chalmers of the Harvard University School of Public Health, referring to the conclusions of their 1981 report, which Davis's work contests. "And they're unwilling to admit they were wrong."

"It would be hard to insure that Devra, too, wasn't blinded by a desire to make a contribution. But I think

she's going about it the right way, by just gathering data and presenting it. You can draw your own conclusions."

DEVRA LEE DAVIS GREW up in Donora, Pa., a small town south of Pittsburgh that's famous for two things: the baseball Hall of Famer Stan Musial and the country's worst air-pollution disaster.

In October 1948, when Davis was 2 years old, a high-pressure condition swept toxic fumes from a nearby steel mill into the horseshoe-shaped valley the Monongahela River cut around Donora. The hills that surround the town trapped the killer smog for five days. Twenty people died of heart and lung trauma; all told, almost half of the town's residents were affected. A decade later, death rates among Donorians who had been affected were still higher than average.

Davis was "completely unaware" of the smog. "The sky was always dark. It did not strike me as unusual." For a child, chronic pollution afforded novel opportunities for adventure, including sliding down hills conveniently denuded of vegetation.

Davis says it's just coincidence that she ended up in public health, doing the kind of work that eventually cleaned up her hometown. Her undergraduate career at the University of Pittsburgh was an amorphous collage of science courses, civil rights activism and German philosophy; after she got her Ph.D. from the University of Chicago, she wrote scholarly articles on acupuncture, door-to-door interviewing in urban neighborhoods and the psychological effects of overcrowding in cities. It was her postdoctoral adviser at Johns Hopkins University, the late Abraham M. Lilienfeld, who encouraged her to read William Farr and John Snow, the English patriarchs of epidemiology. The story of how Snow stemmed a London cholera epidemic by deducing its connection to the water supply is heady reading, even 140 years after the fact. "We need people like Snow — people who think about the big picture," Lilienfeld told her.

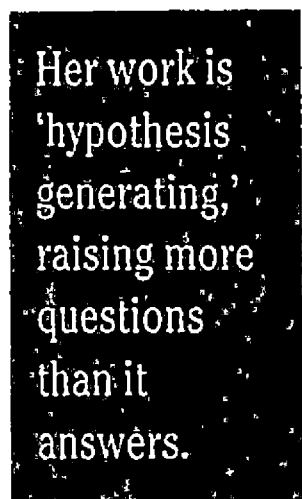
In 1979, a year after Devra Davis wrote her first paper on cancer trends, her father was told he had myeloma. A former machinist at U.S. Steel, he was 55 and a successful businessman at the time. He died in 1984. Soon

after, Davis, who had been hired at the National Academy of Sciences the year before, decided to devote herself to cancer research. She says her father's illness had no effect on her decision to pursue her studies of cancer trends: "I don't want my own story to detract from the major concern I have, which is that there are preventable causes of cancer out there and we don't know what they are."

A few years later, she began a 16-month sabbatical from her staff position at the National Academy of Sciences to travel in Europe and collect the data that eventually went into her *Lancet* paper. As head of the board on environmental studies and toxicology at the academy, she had had three personal assistants and 45 staffers, coordinated hundreds of experts in 30 cities and presided over consensus reports like the one that led to the ban on smoking on most domestic airline flights. But when the sabbatical was over, in 1989, Davis resigned from her directorship to pursue cancer research full time. Now, as a scholar in residence, she works alone and without the academy's imprimatur.

In her argument that more money and effort should go into research on prevention as the rational weapon against cancer, she has the weight of history behind her. The scourges of the recent past — malaria, tuberculosis, typhus, cholera and others — have been controlled primarily through prevention, not treatment. On economic grounds alone, it's unreasonable to expect any other strategy to work against cancer. The direct and indirect cost of cancer now amounts to nearly 2 percent of the United States gross national product. "Even if we could cure every single case of cancer, we can't afford to," says Davis. John Cairns of the Harvard University School of Public Health made a similar argument in a 1985 article in *Scientific American*: "To put most of the effort into treatment," he wrote, "is to deny all precedent."

About a third of the National Cancer Institute's \$2 billion annual budget goes to prevention research. But those are "rubber numbers," says McGill University's John C. Bailar 3d, a 35-year veteran of cancer-trend research. Bailar himself antagonized the cancer



institute in 1986, when he published a heretical critique of the American cancer effort. Most of the institute's so-called prevention research money, he says, is going into basic etiology — the cellular mechanisms of cancer development — rather than epidemiological studies and prevention trials. "The prevention of cancer on a big scale is going to require that we change our habits, change our life styles, clean up the workplace, clean up the environment, change the consumer products that contain hazardous materials," says Bailar. "It's going to mean a whole new approach to everyday living."

"If we had good treatments, they would probably be far less expensive and disruptive than prevention. The problem with that approach is that it hasn't worked. Cancer death rates are higher now than they were when we started 50 years ago. At some point, I think somebody has to step back and ask whether we're going about this the wrong way."

There's no shortage of defenders of the way the National Cancer Institute spends its appropriations. Though Sam Broder, the institute's director, declined to discuss the country's cancer effort with me, Vincent T. DeVita of the Memorial Sloan-Kettering Cancer Center, who headed the institute from 1980 to 1988, says the basic research has "paid off handsomely." The discovery of specific genes for predispositions to cancer "will give us the tools, finally, to define at-risk populations," he says. "It's the first time that there's a clarity to the idea of preventing cancer."

But even DeVita admits that without epidemiology to

define risk factors, doctors won't know how to advise individuals to avoid getting cancer. "The real danger is that we're going to be able to tell people they're at risk before we know enough about it to prevent it."

The problem is that the most obvious — and potent — causes of cancer have already been discovered. Carcinogens like radiation and asbestos, for example, were relatively simple to identify because they caused spikes in cancer rates in select populations. All an epidemiologist had to do to pinpoint a cause was examine how the habits of those afflicted differed from the habits of the population as a whole. But the new generation of cancer causes, which specialists prefer to call risk factors, are less potent and more diffuse — like fat in the diet.

The tobacco or asbestos models do not apply. "That's not the way breast cancer develops," says Edward Sondik, deputy director of the cancer institute's division of cancer prevention and control. "That's not the way colon cancer develops. Do you think we're going to find that there's a particular cause of melanoma at this point in time? Do you think we're going to find that there's a particular cause of colorectal cancer, when it's as widespread as it is?"

John Cairns maintains that there are "huge financial incentives" for governments to do nothing about cancer prevention. Sales and excise taxes on cigarettes, for example, provide about \$14 billion in annual revenue. And smoking saves billions more every year on Social Security payments because smokers on average die sooner than non-smokers.

There might be disincentives for the private sector, as well. "When you treat cancer, profits are made through drugs or surgery," Davis points out. "But when cancer is prevented, nobody makes any money." She claims the impetus from the public isn't there, either. "Where's the constituency for cancer research?" she says. "It comes often from the families of cancer victims, who are deeply moved and want to do something about treatment. There is almost no constituency for cancer prevention."

Perhaps Davis knows better than anyone how hard building that constituency will be. ■