Is the War on Cancer Being Won?

Critics point out that cancer mortality rates have been increasing; others argue that the numbers game obscures real treatment successes

President Reagan is doing for colon cancer what Betty Ford did for breast cancer. Millions of Americans now know the warning signs of colon cancer and are requesting tests for blood in the stool and sigmoidoscopic examinations. But, so far, there is no direct evidence that colon cancer screening reduces mortality and, in fact, there is disagreement within the medical community over whether mass screening of asymptomatic individuals for colon cancer should even be recommended.

The colon cancer dilemma is part of a larger discussion about cancer survival data in general and early detection in particular. The optimists like to point out that 5-year survival data for cancer patients look better and better. Colon cancer, like several others, can be detected and treated early. The war on cancer is being won. But the other side of this picture, as statisticians are only too aware, is that survival data and other indices of cancer treatment success can be quite misleading and that early diagnosis may not actually prolong life. For the major cancers, the war is at a stalemate, some critics say.

It is a dispute over points of view. The critics tend to emphasize the failure of the anticancer program to reduce overall mortality from cancer. For example, the age-adjusted cancer mortality rate in the U.S. in 1962 was 170.2 per 100,000. In 1982, it was 185.1 per 100,000. "That shows why we're worried," says John Bailar of Harvard School of Public Health. "Overall cancer mortality is going up." But no one is arguing against cancer treatments. "The fundamental problem is not that cancer treatment is ineffective but that it is not getting better," Bailar emphasizes.

Those who counter this argument do not dispute the critics. Instead, they say that there is more than one way to look at the data and that death rates do not begin to describe major advances in treatment, even for cancers that cannot be cured. "Everybody's right," says Edward Sondik, who is chief of surveillance and operations research at the National Cancer Institute (NCI). "That's what's difficult about this area."

No one disputes one success story—the astonishing cure rates for certain rare cancers, including childhood leukemia and Hodgkin's disease. The NCI reports that the 5-year relative survival rate for children with leukemia, for example, has increased from 5 percent in the 1950's to 65 percent in the period ranging from 1976 to 1981. Hodgkin's disease was almost invariably fatal 30 years ago. Now almost all patients are cured.

But success in treating these cancers does not extend to success in treating the common cancers. Vincent DeVita, head of the NCI, notes that, "50 percent of all cures through chemotherapy occur in 10 percent of all cancer patients." That 10 percent consists mostly of children and patients with Hodgkin's disease.

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It is the data on the other 90 percent of patients that worry some statisticans and epidemiologists. Some are quite adamant in their concern. Bailar, for example, says, "the overall picture is really pretty grim." John Cairns, also at the Harvard School of Public Health, states that there have been no significant gains in survival from any of the major cancers since the 1950's and that the cancer data are so discouraging that it is difficult to discuss them in public. "That's why this dispute has been carried on in a gentlemanly way," he says. "People do get cancer and they have to be given encouragement. Research has to go on." (Cairns argues his case in detail in the upcoming November issue of *Scientific American*.)

Yet in its most recent *Annual Cancer Statistics Review*, the NCI published graphs showing increases in the 5-year relative survival rates for all cancers, including a slight increase in survival rates for lung cancer patients. This review, which, DeVita says, "keeps all the critics in business," demonstrates, once again, how tricky it is to interpret cancer data.

The problems with the naive interpretation of cancer survival data are twofold, says physician and statistician Bailar. First, there is the lead-time effect. Suppose you can diagnose a type of cancer earlier but you can do nothing to alter the course of the disease. If a patient normally would have died within 6 months after diagnosis but now you can diagnose his cancer 1 year earlier, his survival time, defined as the time he lives after his cancer is diagnosed, has been extended to 18 months. But he is no better off than before.

Yet recognizing that the lead-time effect can be a problem and actually demonstrating that it is are two different things. To show conclusively that early diagnosis improves—or does not improve—survival, a randomized controlled clinical trial must be done. The idea is to establish two groups of persons at high risk for the cancer in question. Monitor one group with early diagnosis and leave the other group alone. Then, if the monitored group lives longer, you will have proved that early diagnosis really does improve survival.

Lead-time bias has been examined in two clinical trials. A major study of breast cancer showed that early diagnosis does seem to help women aged 50 and over, but not younger women; and a study of early diagnosis of lung cancer showed, according to most interpreters, that early diagnosis for that cancer is useless. The Pap smear, perhaps the most widely used early diagnostic test, has never been studied with a randomized controlled trial. (Most observers are convinced nonetheless that the Pap smear is useful.)

The breast cancer study began 20 years ago and involved 62,000 women aged 40 to 64 covered by the Health Insurance Plan of Greater New York. Half the women were offered free annual mammograms and physical examinations of their breasts and the others were not. Those over age 50 in the group offered the exams had significantly fewer deaths during the follow-up period.

The lung cancer study was an immense disappointment. Although it was only recently completed, recruitment of volunteers began in the late 1960's when investigators at the Mayo Clinic, Johns Hopkins University, and Memorial Sloan-Kettering Cancer Center initiated independent clinical trials, which were coordinated and sponsored by the NCI. The three trials had slightly different designs, but asked the same crucial ques-

tion. If a group of middle-aged men who are heavy smokers are monitored regularly for the early appearance of lung cancer, will their subsequent mortality from this disease decline?

Each medical center enrolled 10,000 men in the study. The Mayo Clinic screened half the men several times a year with sputum cytology—"essentially a Pap smear of the bronchial tree," explains Ralph Buncher of the University of Cincinnati—and chest x-rays. The other centers offered regular chest x-rays to all the men and sputum tests to only half of them.

Bailar describes what happened: "They found a series of interesting differences [between the tested and control groups]. The screened group had a lot more lung cancer. Everybody got excited. The lung cancers were at early stages and the patients had excellent survival rates. Everyone got really excited. It was all fine down until the bottom line: The numbers of men in the two groups who died of lung cancer were virtually identical."

As a result of these trials and additional corroborating evidence, the American Cancer Society dropped its recommendation that heavy smokers have annual chest x-rays. "We simply do not have good evidence that lung cancer screening reduces mortality," says David Eddy, a physician and mathematican at Duke University who was the author of the Cancer Society's report. The lung cancer studies are, in Eddy's opinion, the best example yet of the real hazards of lead-time bias.

The lung cancer studies also illustrate a second potential problem with the interpretation of early diagnosis results. It is entirely possible that many things that look like early cancers under the microscope are not, in fact, cancers. Eddy, Bailar, and others suspect that this "overdiagnosis" occurred in the lung cancer study and quite a number of investigators believe it is occurring with other cancers, such as those of the breast and prostate, as well.

So should asymptomatic people forget about early diagnosis except for breast cancer and, perhaps, cervical cancer? Policy-makers are finding themselves doing a difficult balancing act. The ACS, for example, does not recommend a massive screening program to detect colon cancer in the general population. But it does recommend regular stool occult blood tests and sigmoidoscopic examinations for people over the age of 50. "The ACS's purpose is not to launch a nationwide screening program," says Eddy. "Rather, its purpose is to assist physicians in the management of patients on a day-to-day, person-to-person basis."

Robert Fontana of the Mayo Clinic further explains this philosophy. "As far as I'm concerned, there is an essential difference in scope, management, and philosophy of individual health counseling and public health recommendations. To make a test on a person in a one-to-one clinical setting requires judgment. Yes, I would get a chest x-ray and a sputum sample on a patient at high risk for lung cancer. That requires an exercise of judgment. A decision to screen the population requires evidence of a reduction in mortality."

The problems of interpreting survival data and deciding on early diagnosis are not the only ones to plague interpreters of cancer data. There is also what statisticians call the staging effect. Suppose you have a better way of detecting cancer so that you can not only find it earlier but can more precisely determine whether it has spread and the extent of its spreading. Then several things will happen to your data. First, you will have patients with milder disease in your stage I group because you are picking up patients that you would not have included previously. These patients will live longer than the other stage I patients whose disease is more advanced, so your group of stage I patients will do, on the whole, better. Since you can also better detect metastases, you will exclude some patients from stage I who would otherwise have been included. These patients with very early metastases will now be placed in stage II. Their absence from stage I will further improve that group's survival rate since their metastases tend to be quite early—they would not have been found in previous years—and their presence in stage II will make that group do better too.

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Feinstein calls this staging problem "the Will Rogers phenomenon" after a remark attributed to Rogers. Apparently, Rogers quipped that when the Okies went from Oklahoma to California, they raised the average IQ of both states. Feinstein recently showed that this Will Rogers phenomenon actually occurs—as everyone suspected it did—by analyzing a group of lung cancer patients whose disease is now detected with new diagnostic imaging procedures such as abdominal ultrasound and CT scans.* Without taking into account the effects of these imaging procedures, it looked as though patients treated in 1977 did significantly better than a similar group treated during the period between 1953 and 1964. But when Feinstein and his colleagues Daniel Sosin and Carolyn Wells corrected for the Will Rogers phenomenon, they found no significant differences in the stage-specific survivals of the earlier, as compared to the more recent, patients.

Sondik agrees that the staging problem complicates analyses but remarks that in all the discussions of cancer survival data, no one seems to address the question of how much progress can be made, on the basis of clinical trials of new treatments, and then to assess the progress that occurs. If survival in stage II breast cancer patients is prolonged a few years, on average, from improved treatments, how will that affect overall breast cancer survival and how long will it take for the effect to show up in mortality data? "We are doing that kind of analysis now," Sondik says. "We are developing a large number of models of different cancers in different stages to give us a handle on what we can expect." Without such information, Sondik argues, it is hard to say that the war on cancer is being lost.

DeVita, too, believes the critics paint too bleak a picture. First, researchers and clinicians have established that certain cancers, such as those of the breast and testes, can be treated with drugs. "That was an extremely important finding," DeVita says. "It means cancer is not king."

In addition, DeVita notes, even cancer patients who do not live longer than they would have a decade or two ago frequently have vastly improved qualities of life. Breast cancer treatment has gone from radical mastectomies to lumpectomies. Osteosarcoma patients no longer routinely have their cancerous limbs removed. More patients with anal-rectal cancer can avoid colostomies.

"When I came into the field, there was no good treatment for leukemia or Hodgkins disease," DeVita says. "I remember little kids with leukemia and all we had was steroids. They died horrible deaths. Now we cure 56 percent of childhood leukemias on average and even when we fail, the end is nowhere near as miserable. I think that's lost in the numbers game."—GINA KOLATA

*A. R. Feinstein, D. M. Sosin, C. K. Wells, *N. Engl. J. Med.* **312**, 1604 (1983).