

Sounding Board

GRAPPLING WITH CANCER — DEFEATISM VERSUS THE REALITY OF PROGRESS

When you come to a fork in the road, take it.
— Yogi Berra

A RECENT article by Bailar and Gornik¹ in the *Journal* pointed out the obvious — that cancer, a collection of diseases that will claim more than 560,000 lives in our country this year,² is “undefeated.”¹ Extrapolating from trends in mortality from cancer, the authors conclude that the nation’s investment in cancer research is doomed to fail because it is based on impossible dreams of cure, when prevention is far more likely to rid us of the scourge of cancer. Bailar and Gornik agree with previously published data that for the first time since the passage of the National Cancer Act of 1971, overall mortality from cancer has declined, beginning in 1991, and the decline is projected to continue.³ But having pointed out that a corner has been turned in our efforts to decrease such mortality, they assert that the National Cancer Institute has reached a fork in the road and taken the wrong path: toward treatment and away from prevention.

Bailar and Gornik base their conclusions on three faulty premises. First, they maintain that current research strategies will fail because they have historically done so; that is, the future is simply epilogue to the past. Second, they consider the current strategies to be lopsided and taking us on a narrow path, aimed for the most part at treatment. Finally, they assume that cancer is homogeneous enough to respond to strategies focused primarily on prevention and early detection. Each of these premises warrants scrutiny.

IS THE FUTURE EPILOGUE TO THE PAST?

There are far more good historians than there are good prophets. It is extraordinarily difficult to predict scientific discovery, which is often propelled by seminal insights coming from unexpected directions. The classic example — Fleming’s discovery of penicillin on moldy bread and the monumental impact of that accidental finding — could not easily have been predicted, nor could the sudden demise of iron-lung technology when evolving techniques in virology allowed the growth of poliovirus and the preparation of vaccine. Any extrapolation of history into the future presupposes an environment of static discovery — an oxymoron.

Although cancer remains undefeated, defeatism is

simply not supported by recent research, which provides abundant evidence of unanticipated breakthroughs. Tamoxifen was first investigated as a fertility pill and rapidly dropped. However, when tested in women with metastatic breast cancer, it was discovered to be one of the most effective anticancer agents in the therapeutic armamentarium. It has subsequently been proved effective in treating progressively earlier stages of the disease. Because it can demonstrably decrease the risk of second cancers (in the contralateral breast) in the adjuvant setting, tamoxifen is now being evaluated in randomized, prospective trials for the prevention of primary breast cancer. Likewise, the discovery of the biologic activity of cisplatin started with the accidental finding that electrolysis products from a platinum electrode inhibited cellular division in cultures of *Escherichia coli*.⁴ From this observation came the single most important agent responsible for the cure of advanced germ-cell cancers.

Nevertheless, the ultimate effect of major insights and interventions takes time and patience. The prevalence of tobacco smoking in the United States began to drop among men soon after the first Surgeon General’s report on the harmful effects of smoking appeared in 1964, and it dropped among women by the mid-1970s. But the decreasing mortality from lung cancer that Bailar and Gornik correctly point to as a successful result of prevention was delayed by more than three decades. Likewise, the therapeutic benefits of tamoxifen were demonstrated in the 1970s. The logical and necessary sequence of research that led from therapy to prevention took a quarter-century.

Insights are emerging from basic mechanistic studies that seem likely to lead to the next generation of progress in cancer prevention. Inhibitors of specific cyclooxygenase pathways have recently given justification for studies of colorectal-cancer prevention. The identification of the human papillomavirus as the major carcinogen responsible for uterine cervical cancer and of *Helicobacter pylori* as a cause of gastric cancer opens the door to studies of vaccines and preventive antimicrobial interventions. These developments, plus the linkage of hepatitis B and C viruses with hepatocellular carcinoma, have prompted the National Cancer Institute to plan a unit specifically devoted to preventing cancers of infectious cause. Finally, recent insights into nicotine addiction are leading to pharmacologic strategies for the enhancement of behavioral approaches to tobacco control.

ARE CURRENT RESEARCH EFFORTS LOPSIDED?

Given that scientific progress is unpredictable, depending on discoveries from many directions, the National Cancer Institute has a responsibility, in its role as the centerpiece of the National Cancer Pro-

gram, to maintain a broad portfolio of research. Funding must be directed down multiple pathways as insights and leads emerge. Table 1 indicates some of the dynamic adjustments we have made to suit the discovery process. One's view of the proportion of the institute's budget that is devoted to prevention hinges, of course, on one's definition of prevention. When this definition is most restricted — to interventional studies with a preventive focus — prevention accounts for about 10 percent of the 1997 budget. But prevention is impossible without some understanding of the risk factors for cancer. If we therefore add the portion of the budget that is devoted to epidemiology, causation, and carcinogenesis, the proportion allocated to prevention comes to about 38 percent. By comparison, treatment-oriented research amounts to about 35 percent of the current budget. The most striking number in the table, however, is the relative increase in the allocations for prevention and control interventions — an increase of 121 percent from 1993 to 1997. As more insights into prevention have surfaced, the institute has redistributed its budget to pursue them.

It is important to assess the research enterprise continually, in a way that includes external feedback on opportunities for future investment. Priorities cannot be set without a continuing dialogue with the multidisciplinary research community. The National Cancer Institute has asked a series of panels of outside experts for advice on directions for research. Two such panels are the Cancer Prevention Progress Review Group and the Cancer Control Progress Review Group. They are submitting formal reports that summarize the results of systematic reviews that began nearly a year ago. (Other such panels are examining the cancer centers and the process and infrastructures associated with clinical trials.)

Finally, the director of the National Cancer Institute consistently champions the need for increased funding for research. Paths in cancer prevention are opening, and more funding would help us to speed along them. We agree fully with Bailar and Gornik that more funding for prevention is needed, but it should not come at the expense of other areas. Prevention, detection, and treatment all depend on fundamental research into cancer causation, cancer risks, and cancer biology.

IS CANCER HOMOGENEOUS ENOUGH FOR US TO TAKE A SINGLE PATH AT THE FORK IN THE ROAD?

Figure 1 shows overall trends in cancer mortality as a function of age. For all age groups, the picture in the 1991–1995 period is better than it was in the previous 18-year period. Mortality rates for people under 55 have fallen dramatically. We need a better understanding of the slower rate of improvement among older Americans, but multiple factors are probably involved: birth-cohort effects due to changes in risk factors, less tolerance of therapy by older persons, and patterns of medical practice that may entail the undertreatment of older patients. The heterogeneity of trends according to age and type of disease demonstrates that cancer is immensely complex, whatever the strategy used to combat it.

Figure 2 shows the estimated annual percent changes in mortality from the most common types of cancer during the same two periods, 1973–1990 and 1991–1995. For most types of cancer there was improvement in the later period as compared with the earlier one, but there are clear differences in both the magnitude and the direction of the changes. This heterogeneity among cancer types has been noted previously.⁵ "Cancer" is, in truth, a variety of

TABLE 1. PROGRAM ALLOCATIONS IN THE CURRENT BUDGET OF THE NATIONAL CANCER INSTITUTE, AS COMPARED WITH THOSE IN 1993.

TYPE OF PROGRAM	1993 BUDGET	1997 BUDGET		INCREASE, 1993 TO 1997 (%)	
		AMOUNT ESTIMATED	PERCENT OF TOTAL		
	thousands of \$				
Research on epidemiology, causation, and carcinogenesis	550,981	661,922	28	20	
Studies of prevention and control	112,579	248,715	10	121	
<i>Subtotal</i>	<i>663,560</i>	<i>910,637</i>	<i>38</i>	<i>37</i>	
Treatment-oriented research	770,212	844,694	35	10	
Studies of biology and basic research	326,411	375,187	16	15	
Other (cancer centers, training, and construction)	218,157	250,631	11	15	
<i>Total</i>	<i>1,978,340</i>	<i>2,381,149</i>	<i>100</i>	<i>20</i>	

All ages
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15–24
25–34
35–44
45–54
55–64
65–74
75–84
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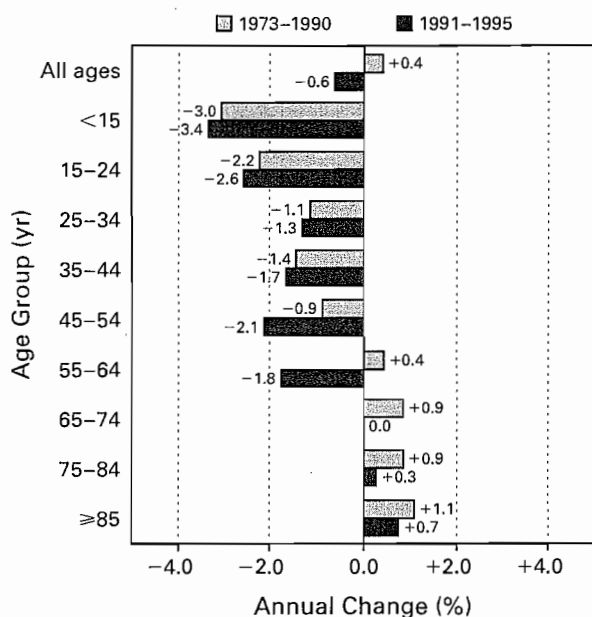


Figure 1. Estimated Annual Percent Changes in Mortality from All Types of Cancer in the United States over Two Periods, 1973-1990 and 1991-1995, According to Age Group.

Data are from tapes in public use compiled by the National Center for Health Statistics. Preliminary data were used for 1995.

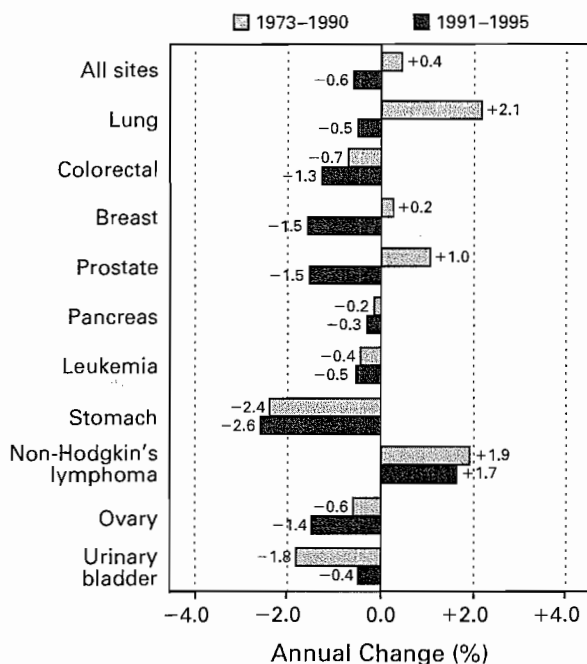


Figure 2. Estimated Annual Percent Changes in Mortality from Cancer Overall and at Specific Sites over Two Periods, 1973-1990 and 1991-1995, in the United States.

Data are from tapes in public use compiled by the National Center for Health Statistics. Preliminary data were used for 1995. Data on breast and ovarian cancers are for women only. Data on prostate cancer are for men only.

diseases. Viewing it as a single disease that will yield to a single approach is no more logical than viewing neuropsychiatric disease as a single entity that will respond to one strategy. It is unlikely that we will soon see a "magic bullet" for the treatment of cancer. But it is just as unlikely that there will be a magic bullet of prevention or early detection that will knock out the full spectrum of cancers. Furthermore, although prevention is immensely attractive, implementing it successfully may be just as complex and frustrating as providing treatment.

If we are to learn what accounts for the clear changes in cancer mortality, we must move away from lumping all cancers together to examining each form separately and carefully in each segment of the population. A full analysis is beyond the scope of this article, but areas in which there has been substantial success firmly reinforce the need to pursue multiple strategies. Certainly, treatment has played the dominant part in breakthroughs involving cancers affecting younger patients, such as acute leukemia in childhood, Hodgkin's disease, and testicular cancers. Preventive strategies are not likely to supplant therapeutic approaches for such cancers. In other cases, such as cervical cancer, screening is emerging as the most successful approach. Research into vaccines may eventually reduce the incidence of cervical cancer greatly. Lung cancer, which has been quite resistant to screening and therapeutic approaches, is responding to preventive measures. For breast and colorectal cancers, multiple strategies are proving effective, with decreases in mortality associated with both adjuvant therapy and screening.

OTHER MEASURES OF PROGRESS

Although reductions in mortality from cancer are arguably the most important and objective measure of success, they are not the only one. Other measures of progress include the possibilities of limb-sparing surgery for patients with sarcomas, laryngeal (and voice) preservation for those with squamous-cell cancers of the head and neck, anal-sphincter preservation for rectal cancer, and breast conservation for breast cancer — all at no sacrifice in the probability of disease control. Such advances, not reflected in the mortality statistics, could have emerged only with careful therapeutic studies. Research on pain control is an additional active and important part of the research portfolio of the National Cancer Institute. Perhaps a less tangible measure of success has been the increased funding for research on the long-term health, psychosocial and physiologic, of survivors of cancer and on strategies to prevent second cancers among patients successfully treated for an initial cancer. The past 25 years have seen improvements in the quality of life of cancer survivors that have benefited millions and that cannot be dismissed.

IMPLICATIONS

We are making progress. Although we also have a long way to go, it is facile to claim that the pace of favorable trends in mortality reflects poor policies or mistaken priorities. One fact remains clear — cancer is a varied and complex set of diseases with many causes, risks, and characteristics. It remains an extremely difficult problem, and this, more than anything, limits progress. We will probably not learn to prevent cancer if we do not identify its many causes and test preventive interventions carefully. We at the National Cancer Institute fully agree on the urgent need for preventive measures. But this year more than 1.3 million Americans will receive a cancer diagnosis. Although some substantial fraction of these cases represents failures of prevention, even if all tobacco use stopped today and even if we all adopted “perfect” diets overnight (recognizing that we don’t know for sure the preventive value of changing one’s diet), we would still be confronted with an enormous number of people who have cancer. These people cannot be forgotten because we have chosen a single path. Our broad-based approach is working; it would be unwise to abandon it.

As a multidisciplinary research agency and the central force in the National Cancer Program, the National Cancer Institute must invest broadly in re-

search and in the application of new discoveries. We must invest not only in prevention, early detection, and epidemiology, but also in treatment, supportive care, the care of survivors, and the basic research that is the underpinning of all interventions. As we come to each fork in the road, we must take it.

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This commentary represents the opinions of the authors and does not necessarily represent the official opinion of the Department of Health and Human Services.

REFERENCES

1. Bailar JC III, Gornik HL. Cancer undefeated. *N Engl J Med* 1997;336:1569-74.
2. Cancer facts and figures, 1997. New York: American Cancer Society, 1997.
3. Cole P, Rodu B. Declining cancer mortality in the United States. *Cancer* 1996;78:2045-8.
4. Rosenberg B, Van Camp L, Krigas T. Inhibition of cell division in *Escherichia coli* by electrolysis products from a platinum electrode. *Nature* 1965;205:698-9.
5. Devesa SS, Blot WJ, Stone BJ, Miller BA, Tarone RE, Fraumeni JF Jr. Recent cancer trends in the United States. *J Natl Cancer Inst* 1995;87:175-82.

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