Cancer Prevention Strategies for the Future: Risk Identification and Preventive Intervention

GRAHAM A. COLDITZ and
STEVEN L. GORTMAKER

Harvard University

ADULT CANCER MORTALITY IN INDUSTRIAL COUNtries (Davis et al. 1990) has not undergone the significant decline that has been recorded for cardiovascular mortality over the past three decades. Greater understanding of the important scientific factors in cancer prevention is now required, as are the development and implementation of preventive interventions. In this analysis, we describe a multifaceted strategy for cancer prevention in the United States.

The scientific basis for cancer prevention rests on two fundamental components: First, knowledge of biological processes and epidemiology forms the basis for our understanding of the causes of cancers. This knowledge base can lead to the identification of modifiable risks that are biological, behavioral, or environmental in nature. Some of these risks are proximate to the cancer—genetic predisposition or behaviors like smoking—whereas others are more distant, as in the case of worksite rules that allow individuals to be exposed to the smoking of others.

This article was prepared as a report of the Cancer Prevention Working Group. Members of the group are listed at the end of the article.

The Milbank Quarterly, Vol. 73, No. 4, 1995

Second, prevention science is grounded in our knowledge of the effectiveness of interventions to prevent cancer by changing modifiable risks. Interventions are generated from the social, behavioral, and economic sciences, and are evaluated in terms of cost-effectiveness, cost–benefit, and efficiency (Cochrane 1972). Interventions can focus on environmental, behavioral, or biological risks, and can be categorized into two types: those focused on individuals at risk, which we term *clinical interventions*, or those focused on populations, which we term *public health interventions*. Clinical interventions include programs like smoking cessation counseling or chemoprevention strategies, which target persons at high risk. Public health interventions, in contrast, are designed to alter the population distribution of risks. Effective interventions that change this distribution will also decrease risk among individuals at high risk (Rose 1985). Examples of population-focused interventions are comprehensive health education of schoolchildren, taxation of cigarettes, worksite and public facility restrictions on smoking, regulation of vitamin supplements in food, and mass media messages to change norms and increase consumption of fruits and vegetables.

A public health approach, aimed at the most important modifiable risks, is critical to an effective population prevention strategy. Approaches that concentrate on small numbers of individuals at high risk, however successful for the individuals, cannot influence the majority of deaths in the whole population (Rose 1982). Risks attributable to exposures that are widespread in the population have more impact on total cancer mortality than do large increases in risks that are experienced by only a few. For example, the relative risk of hepatic angiosarcoma among cleaners of vinyl chloride polymerization kettles is approximately 400 compared to the nonexposed population. However, the total number of such tumors reported in the world literature is less than 100 (Muir 1990). Occupational risks, although large for exposed workers, can account for only a moderate proportion of total cancer mortality (Doll and Peto 1981). Thus, although reducing occupational exposures (including benzene, aromatic amines, arsenic, hexavalent chromium, vinyl chloride, radon, asbestos, and talc, which contains asbestiform fibers) constitutes one important approach to prevention (Doll and Peto 1981; Muir 1990), its potential for reducing total population cancer incidence and mortality is limited.

Prevention science often comes into conflict with economic and political forces: examples would be the economic interests of corporations pro-

moting the sale of tobacco to minors and the federal government's support for tobacco agriculture. Hence, the issues of social strategies and political will (Richmond and Kotelchuck 1984) are significant components of the scientific study of interventions to prevent cancer. The disciplines that bear on each component are summarized in figure 1.

Further complicating prospects for effective intervention, major behavioral cancer risks like smoking, diet, and physical activity are embedded within lifestyles that are not often amenable to simple, single-component interventions because they involve complex behaviors within widely varying social and cultural contexts. In addition, the complex effects of lifestyle and behavioral alteration require documentation of comorbidity associated with prevention interventions. One current controversial example of the difficulties posed by comorbidity concerns alcohol: if moderate alcohol intake among women is identified as a risk for breast cancer and a protective factor for heart disease, it is clear that both outcomes need to be included in calculations of intervention effectiveness.

In this analysis, because our focus is on cancer prevention, we do not examine in detail the efficacy or effectiveness of screening. Screening does not generally prevent cancer onset, but rather aims to reduce cancer mortality through early diagnosis either of premalignant conditions that respond to therapy or of malignancies that show greater response when

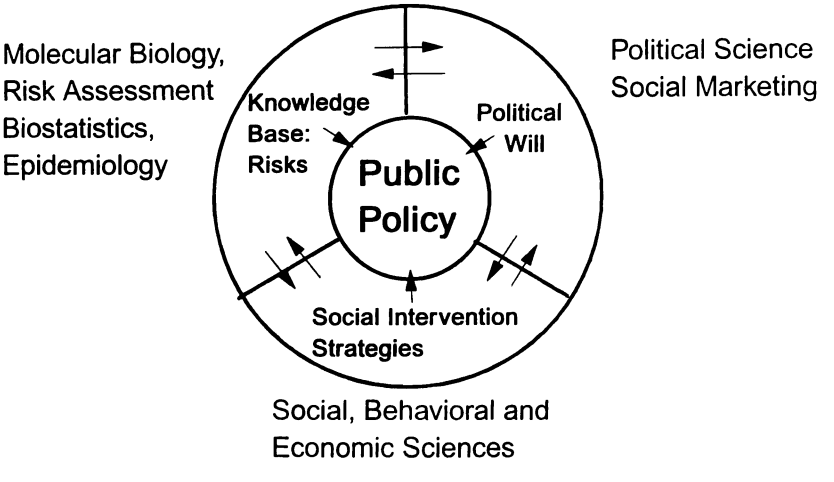

FIG. 1. Components of cancer prevention leading to public policy, and the major disciplines that bear on these components (adapted from Richmond and Kotelchuck 1984).

treated at an earlier stage. As an approach to prevention, this is very limited, because one must screen for each disease individually, and usually repeatedly, thus leading to issues both of compliance to achieve effectiveness and of the cost of frequent clinical procedures. Although screening traditionally is designed to advance the diagnosis of cancer, some screening approaches focus on precursor lesions whose treatment prevents the development of invasive disease. Examples here include Pap tests for cervical cancer and screening for colon polyps. Using this approach, many more precursor lesions are treated than will progress to invasive cancer. When screening for premalignant conditions, such as cervical dysplasia, it is possible to reduce the rates of invasive cervical cancer by as much as 60 percent through a national mass screening program (Tomatis 1990, 276–9). To achieve this level of efficacy, however, a program must reach all eligible women. Fiscal year 1991 marked the first appropriation by Congress: $29.3 million to increase low-income women's access to mammography and Pap smear screening and to facilitate appropriate treatment referral. This appropriation also designated funds for developing public education programs.[1]

At the extreme of screening are genetic markers either of predisposition for future disease or of early disease. Hundreds of genetic aberrations are detectable in early cancer of the head and neck, making screening for cancer in this one region of the body an enormous task. We do not review the benefits of screening programs, which have been extensively documented in the report that was published by the U.S. Preventive Services Task Force (1989). We also do not discuss the implications of genetic screening. Although this approach could enhance prevention for a sector of the population, and may prevent some cancer incidence, it may lead to stigma and fear among others, and in the worst-case scenario, to lack of access to adequate health and life insurance coverage and to employment discrimination. The report of the Institute of Medicine on Genetic Testing indicated that population screening for predisposition to late-onset monogenic disease should only be considered for treatable conditions of relatively high frequency. Further, it notes that when the lag between testing and effective treatment is long, then the nonmedical benefits and harms, as well as the ethical considerations, dominate decisions about whether testing should be undertaken, both for individuals and for society (Andrews et al. 1994).

[1] H.R. 4790.S.2283. 1990: Breast and Cervical Cancer Mortality Prevention Act.

In this article, we address the possible new directions that policy and research on cancer prevention may take and suggest a broad strategy to speed the development, implementation, and evaluation of effective methods for the primary prevention of cancer. We briefly review the distribution of cancer deaths, their known causes, and evidence that interventions can reduce mortality, morbidity, and risk factors. We focus on the most prevalent cancers for men and women: tobacco-related cancers; cancers of the breast, colon, and prostate; and malignant melanoma. Our analysis indicates that the main modifiable risks for these cancers have one common behavioral pathway, as they all involve substances that people put in their mouths: cigarettes, smoking pipes, chewing tobacco, and food. Two other clearly modifiable risks are lack of physical activity and ultraviolet light exposure as it relates to the risk of melanoma (and other skin cancers). Our analysis also, however, highlights our extremely limited knowledge concerning modifiable risks for breast and prostatic cancer. These findings indicate the need to focus on two aspects of prevention: implementation and evaluation of intervention research for tobacco-related cancers and for colon and skin cancer; and a stronger focus on identification of new, modifiable risks for breast and prostate cancer.

The Evidence for Increasing Cancer Incidence and Mortality

During this century, stomach cancer mortality in the United States has declined annually by about 1 percent, and since the 1950s cervical cancer mortality has steadily declined as well. Several recent reports, based on data from the Surveillance, Epidemiology, and End Results (SEER) cancer registries that cover approximately 10 percent of the U.S. population, indicate that age-specific incidence of breast (White, Lee, and Kristal 1990; Glass and Hoover 1990; Liff et al. 1991), brain (Grieg et al. 1990), and prostate cancers (Potosky et al. 1990) are rising. Although more widespread use of medical technologies may account for some of the increase through greater detection (Boyle et al. 1990; Severson et al. 1990), they do not explain all of it.

During the interval from 1975 to 1987, the age-adjusted mortality from cancer among Americans under the age of 55 decreased, reflect-

ing the decline in lung cancer and the efficacy of treatment for leukemia and testicular cancer. However, the age-adjusted mortality from cancer among those over 65 years of age increased during this interval. Because lung cancer has a known cause (cigarette smoking) and is the leading cancer, some have argued that it should be treated separately in analyses that address cancer mortality. Even when lung cancer was excluded from the analysis, age-adjusted cancer mortality increased from 1975 to 1987 among men and women over 65 (Ries, Hankey, and Edwards 1990). In summary, age-adjusted cancer mortality continues to rise in the United States, a trend that must be countered by a renewed focus on prevention.

In 1994, the number of new cancers was estimated to exceed 1.2 million cases, and the number of deaths due to cancer exceeded 538,000. Lung, colorectal, and breast cancer each account for approximately 15 percent of new cancer cases, or, together, nearly half of all cases. Because these cancers lead to approximately half of all deaths, any national efforts to reduce the total cancer burden of the U.S. population must focus on these three sites.

Cancer frequency differs between men and women. In order of frequency, the commonest causes of cancer deaths in men are neoplasms of the lung, prostate, colon and rectum, pancreas, bladder, and lymphomas. Among women, lung, breast, colon and rectum, pancreas, and ovary are the most frequent sites of neoplasms leading to cancer death.

Men and women of African-American descent bear a disproportionate burden of cancer. Black mortality caused by cancer of the esophagus is 3.1 times that of whites; by cancer of the cervix uteri, 2.7 times that of white women; and by cancer of the prostate gland, 2.2 times that of white men. At ages 55 to 64, black males have a mortality rate due to prostate cancer four times that of white males. The 1986–90 age-adjusted cancer mortality for black men (315 per 100,000) is 48 percent higher than that for white males (213 per 100,000). Black women experience mortality rates that are 19 percent higher than those of white women (166 per 100,000, compared with 139 per 100,000) (Miller et al. 1993). Despite these marked differences in incidence and mortality recorded in national databases for decades, before the 1990s there was astonishingly little research attention focused on these ethnic differences, in terms of either causes (do biological processes differ or do risk factors differ?) or interventions at the individual or population level that are sensitive to cultural variation.

Measures of the Progress against Cancer

Measures of the progress against cancer may be divided into direct measures of how cancer affects people (mortality, incidence and survival, quality of life, economic costs) and of the risks that predispose toward cancer (e.g., smoking). Mortality remains the most important yardstick of progress against cancer because it is the ultimate measure of the impact of the disease on the population (Extramural Committee to Assess Measures of Progress against Cancer 1990). Interpretation of changes in mortality rates, however, can be complicated by changes in disease classification.

Because mortality rates do not give a picture of the amount of life lost to cancer, we briefly review the impact of cancer mortality as measured by years of life lost. For all cancer sites combined, the average years of life lost by those diagnosed with cancer is approximately 16 years. That is, based on age- and sex-specific life tables, these people would have been expected to live another 16 years, given that they had survived to the age at which they died from cancer. Children who die of cancer lose the highest number of years (68). Women diagnosed with breast cancer lose an average of 20 years of life; persons with lung cancer average a loss of 16 years, and those with prostate cancer average a loss of 10.

In sum, whether the measure is mortality or years of life lost, the burden of cancer continues to increase in the United States. The loss of productive life to cancer points to the potential impact of successful preventive interventions.

In addition to mortality, however, we also need to examine the implications of competing risks and benefits (Keyfitz 1982) for research into cause and evaluation of interventions. Postmenopausal hormones and moderate alcohol consumption are relevant examples: both are linked to the risk of breast cancer, and both can potentially protect against heart disease. These examples highlight the importance of a multidisciplinary prevention strategy and illustrate the inherent dangers of health policy being driven by advocacy groups whose special interests lead them to focus on single diseases rather than on broader measures of mortality, morbidity, or quality of life. Although a focus on cancer-related endpoints is crucial for advancing the understanding of cause and identification of risks, evaluation of intervention strategies demands an analysis of competing risks and quality of life.

Tobacco-Related Cancers: Evidence for Risk and Intervention

Just under 20 percent of all deaths in developed countries are attributable to tobacco (Peto et al. 1992). This mortality includes deaths from cancers attributable to tobacco, and also the comorbidity caused by this behavior, including coronary heart disease, peripheral vascular disease, and stroke. Smoking causes lung cancer, the leading cause of cancer mortality, responsible for an estimated 153,000 deaths in 1994. It is estimated that lung cancer was diagnosed in 100,000 males and 72,000 females in 1994. For males, lung cancer incidence is second only to prostate cancer, and for females, it is third to incidence of breast and colon cancer. Doll and Peto (1981) conclude that 30 percent of all U.S. cancers could be avoided if men and women did not smoke, primarily through reduced incidence and mortality from cancers of the lung; mouth, pharynx, larynx, or esophagus; bladder; pancreas and kidney.

Age-specific mortality rates from lung cancer have begun to decline among younger cohorts. Mortality from lung cancer peaked among men born in the 1920s and among women born in the 1930s (Devesa, Blot, and Fraumeni 1989). The declining rates among all sex–race groups under age 45 appear to reflect lower rates of initiation and greater rates of quitting than in older cohorts (Pierce et al. 1989). Furthermore, changes in tar and nicotine content of cigarettes resulted in larger decreases in tar-adjusted cigarette consumption among men under 45 years of age, compared with other age groups during the interval from 1965 to 1980 (Winkelstein 1985). Further efforts to reduce initiation and increase cessation of smoking are clear policy priorities. In addition to direct effects on those who smoke cigarettes, evidence from many studies suggests that those who live with cigarette smokers have a significant increase in risk of lung cancer, compared to those who live with nonsmokers (Wald et al. 1986; U.S. Department of Health and Human Services 1986a).

Interventions to reduce the impact of tobacco smoke on cancer incidence and mortality take many forms, ranging from clinical interventions focused on smoking cessation counseling to public health approaches emphasizing mass education, restrictions on smoking in public settings, and taxation (U.S. Department of Health and Human Services 1989). Interventions can focus on either preventing initiation or encouraging cessation, or both. Although increasing numbers of adults have stopped smoking cigarettes (Keyfitz 1982), initiation of the habit by adolescents

remains a major public health policy issue (they also constitute a major target for manufacturers and marketers of cigarettes). Recent data documents the continuing utilization of tobacco by U.S. adolescents: rates of smoking by youths aged 12 to 17 has changed little since 1980, and recent evidence indicates increased use of smokeless tobacco among adolescent males (rising, for example, from 1.5 percent in 1970 to 6.8 percent in California in 1992) (U.S. Department of Health and Human Services 1986b; Pierce et al. 1993). Rates of smoking by youths aged 18 to 24 are currently 28 percent, the same as the overall adult population (National Center for Health Statistics 1990). An analysis of rates of smoking by indicators of socioeconomic status reveals that reductions have been concentrated among the higher socioeconomic groups (Pierce et al. 1989), while rates increased among African Americans and women. National data indicate that smoking rates among high school seniors have changed little over the past decade, and there is evidence of increases among males since 1984 (Giovino et al. 1994) (fig. 2).

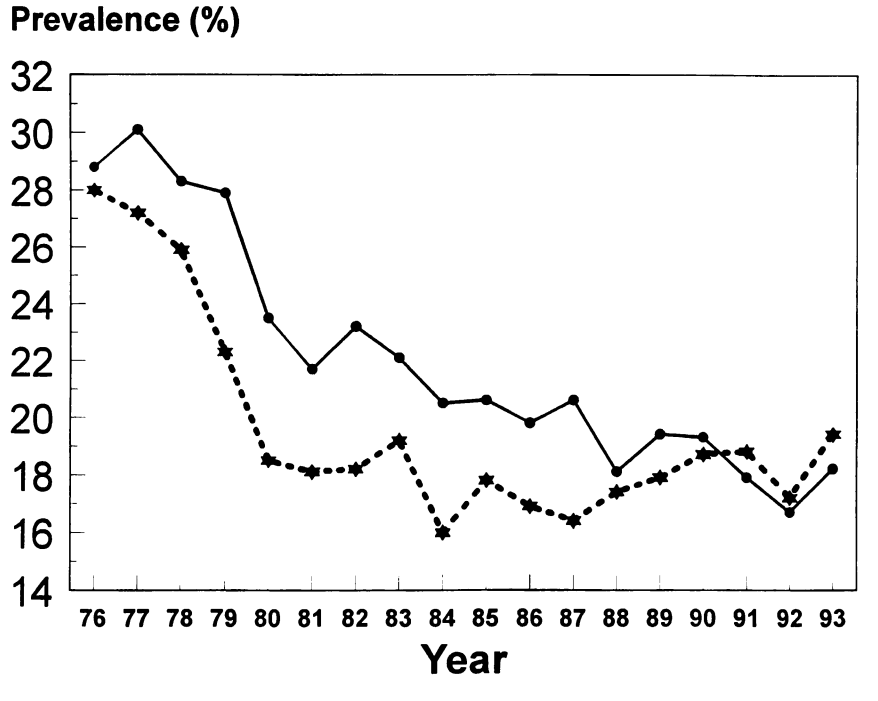

FIG. 2. Estimated prevalence of daily smoking among high school seniors, by sex, in the United States from 1976 to 1993 —●—, female; --★--, male (from Giovino et al. 1994).

> Factors that contributed to the leveling in smoking prevalence include the steady growth in market share of discount cigarettes and the recent 10.4% annual increase to an estimated $3.9 billion in domestic cigarette advertising promotional expenditures. (Centers for Disease Control and Prevention 1993)

A wide variety of clinical smoking cessation interventions have been shown to be partially effective, including interventions among special populations. Smoking cessation programs for pregnant women, for example, are cost-effective (Windsor et al. 1993), although they have not been widely implemented: insurance carriers and Medicaid do not generally pay for smoking cessation services. Research with adolescents now indicates that a program of appropriately structured, cohesive school health education can successfully increase knowledge of, and attitudes toward, health-related behaviors and reduce the prevalence of smoking as well as improve dietary habits (Connell, Turner, and Mason 1985; Walter et al. 1988; Killen et al. 1988; Bush et al. 1989; Errecart et al. 1991). When integrated into existing curricula, comprehensive school health education is less costly than a series of programs that are narrowly focused—for example, on smoking (Cleary et al. 1988)—and they provide clear mechanisms for education on cancer risk factors as new evidence becomes available. A promising strategy for the future would be group interventions segmented by age, socioeconomic states, and ethnic background.

Another effective public health intervention is taxation, which can significantly reduce cigarette consumption (Harris 1987), particularly by discouraging young people from starting to smoke (Lewitt, Coate, and Grossman 1981). A review of studies estimating this potential indicated that "a tax-induced price increase of, say, 10 percent would reduce adult cigarette consumption by 2.2 to 10 percent" (Manning et al. 1991). Furthermore, bans on advertising and sales (Warner, Goldenhar, and McLaughlin 1992), restriction of smoking in public places, and prohibiting sales of cigarettes to minors have all been shown to affect smoking rates significantly in the United States (U.S. Department of Health and Human Services 1989).

Remarkably, discussions of intervention approaches often ignore their relative costs. A dramatic example of this oversight is apparent when counseling by health care providers is compared with taxation in order to ascertain the relative costs to both smokers and nonsmokers. The costs of

counseling by health care professionals, a clinical intervention recommended as part of the Healthy People 2000 national prevention strategy (U.S. Department of Health and Human Services 1990b), are born by both groups. The costs of taxation, however, are born only by smokers, and serve to reallocate the financial burden associated with risk behaviors (Lewitt, Coate, and Grossman 1981).

Of this broad array of intervention options, from clinical smoking counseling, to population interventions such as taxation on cigarettes, only some strategies have received the major share of federal government research funding. Reasons for a limited focus may be that the interventions geared toward smoking prevention and cessation are based on the social and economic sciences, can involve political and economic conflict, and are often viewed by other scientific disciplines as less amenable to serious scientific study because of their political and economic contexts.

For example, the National Cancer Institute's Cancer Control Objectives for the Nation, 1985–2000, do not mention taxes as an effective intervention strategy. Suggested strategies include worksite or community smoking cessation programs, laws to prohibit smoking in enclosed public places, and separate smoking areas at work and in eating establishments (Greenwald and Sondik 1986, 2). Similarly, the Year 2000 objectives for tobacco use in the United States do not discuss taxation of cigarettes as a major strategy (counseling by health professionals is mentioned) (Warner, Goldenhar, and McLaughlin 1992). In a companion volume, *Healthy Communities 2000: Model Standards*, excise taxes are mentioned in the context of a suggestion to raise tax rates to an average level (American Public Health Association 1991). In fact, the real federal tax imposed on cigarettes has declined dramatically over the last 35 years. In 1951 the excise tax represented 42 percent of the purchase price of a package of cigarettes; in 1984 it was 17 percent (Lewitt, Coate, and Grossman 1981). In contrast to the lackadaisical approach by the federal government to exploring taxation strategies, some states—like California, Massachusetts, and Michigan—have very aggressively pursued them as a way of both decreasing use and funding other public health interventions.

The National Institutes of Health have traditionally funded smoking-related research that focuses on clinical interventions rather than on developing and evaluating public health interventions. More recently, however, the National Cancer Institute has initiated the Community Intervention Trial for smoking cessation (COMMIT), an eight-year, $45

million dollar program (COMMIT Research Group 1991). In collaboration with the American Cancer Society, NCI has funded the American Stop Smoking Intervention Study for cancer prevention (ASSIST) (U.S. Department of Health and Human Services 1991). Although no specific intervention approaches are being experimentally tested in the ASSIST program, the 17 participating states will carry out a very broad range of activities during the funded period, 1993 to 1998. These programs contrast with the $4 billion spent by the industry to advertise tobacco products, in addition to the government funds allocated to subsidize tobacco production.

Both the COMMIT and the ASSIST programs are focused upon the application of methods to control tobacco use via community intervention strategies, although the evidence of its effectiveness derived from prior community intervention trials in the United States is inconclusive (Lichtenstein, Wallard, and Pechacek 1990–91). Results of the COMMIT trial confirm the inconclusive results from prior community studies indicating no difference between intervention and control communities for cessation among heavy smokers (COMMIT Research Group 1995), and point to the need for better designed interventions. These results may also illustrate the limited role of randomized community trials in evaluating prevention strategies in a rapidly changing society (Susser 1995). Therefore, a continuing commitment to a wide variety of clinical and public health intervention and evaluation strategies is critical.

Four Other Cancers: Evidence for Risk and Intervention

Among the three-quarters of the population who are nonsmokers, the quantitatively most important cancers are breast and colon cancer in women, and colon and prostate cancer in men. These three cancers share two common features: they have no clearly documented association with cigarette smoking, although evidence is suggestive for colon cancer (Giovannucci et al. 1994a,b), they have known nondietary risk factors that are quantitatively important, although few are potentially modifiable (with the exception of physical activity and colon cancer), and diet has been suggested as an important etiologic factor for all three, largely on the basis of strong international correlations. We also consider malignant melanoma, the cancer with the greatest rate of increase in incidence in

the total population from 1973 to 1990. Although the nonsmoking population includes former smokers, the contribution of past smoking to cancer risk is relatively short-lived after cessation from smoking. By 10 to 15 years after cessation the risk of cancer is reduced to that of a never-smoker (U.S. Department of Health and Human Services 1990a). In this section we briefly review the role of diet and other lifestyle factors related to these cancers in an effort to identify behavior changes that may reduce risk. The scientific basis for the effectiveness of interventions in reducing these cancers is much less clear than the case of cigarette smoking cessation, indicating the urgent need for additional research.

Breast Cancer

Approximately 46,000 women died of breast cancer in 1994. The mortality rate for breast cancer has increased slightly since 1973, more among black women than white women (Ries et al. 1990). However, a more dramatic increase in incidence has been observed among women above the age of 50. The rate of increase in incidence is approximately 4 percent per year, and is observed for both in situ disease and for invasive breast cancer. Most, although not all, of this increase can be attributed to increased screening (Feuer and Wun 1992).

Reproductive factors, including age at menarche, age at first birth, parity, and age at menopause, are related to risk of breast cancer but are limited in how they may be potentially modified via either clinical or public health interventions. These risk factors suggest a role for endogenous estrogens, and evidence from epidemiological studies supports this possibility, although the results of studies do not consistently single out the specific hormone responsible for increasing risk (Key and Pike 1988). Exogenous estrogens, taken for menopausal symptoms and to reduce risk of osteoporotic fractures later in life, may also increase risk of postmenopausal breast cancer when taken for longer durations (Grady and Ernster 1991; Brinton and Schairer 1993). Counterbalancing this risk of breast cancer is the beneficial impact of replacement estrogen therapy on risk of fractures and coronary heart disease (Stampfer et al. 1991). Resolving the trade-off between these risks and benefits remains complex. Because the shift to reproductive patterns that increase risk of breast cancer is the result of social factors, the public health approach to preventing breast cancer should receive renewed emphasis.

The relation of diet and breast cancer has been reviewed elsewhere (Willett 1989; Hunter and Willett 1993). Briefly, for the last decade the dominant etiologic hypothesis has been that high fat intake—animal fat in particular—is the primary cause of the large difference in breast cancer mortality between countries. This notion is largely derived from the striking international correlation between per capita fat intake and breast cancer rates. The major limitation of this information is that it can be potentially confounded by other predictors of breast cancer risk because the countries with high fat intake are all affluent Western nations. In more detailed studies using case-control and cohort designs, little or no association between fat intake and breast cancer risk has been observed. Although imprecision in the assessment of diet is postulated as one reason for the lack of association in these studies, this does not explain the lack of association in the prospective cohort studies. To date, prospective data from nine cohorts with a total of 3,580 cases of breast cancer show that not one study observed a significant relation between fat intake and breast cancer, and the average relative risk comparing highest to lowest intake of fat was 1.03 (95 percent confidence interval [CI] = 0.91–1.18) (Hunter and Willett 1993).

Overall, the evidence that reductions in fat intake by middle-aged women will have a major effect on breast cancer incidence is weak, although the possibility that some effect might be achieved is almost impossible to exclude. Whether reductions in fat intake earlier in life, before age 10 to 20 years, might influence breast cancer risk is unknown. While secular trend data in Japan and other countries whose diets have changed dramatically might in principle be informative, it will be extremely difficult to disentangle the effects of positive energy balance and rates of growth during childhood and adolescence from those of dietary fat composition (Henderson, Ross, and Pike 1991) and changing reproductive patterns. Continued fundamental research into the specific behaviors tied to components of diet and their relation to risk of breast cancer should be a high research priority. Although total fat intake was hypothesized to be linked to increased risk of breast cancer, the contribution of specific fatty acids now deserves far closer attention.

Although it was not even an hypothesis more than a decade ago, a rapidly accumulating body of evidence supports an association between alcohol intake and risk of breast cancer (Longnecker et al. 1988; Hiatt 1990). Typically, a one-and-a-half- to two-fold elevation in risk has been seen at modest levels of intake. Further evidence in support of a causal

association comes from a randomized trial. Women had a significant (28 percent) elevation in estradiol levels and a 21 percent increase in estrone during the periovulatory phase while on the diet that included alcohol. These changes were followed by increases in urinary estrogens during the luteal phase (Reichman et al. 1991). Although causality remains to be determined, this may be a potentially modifiable risk factor of some importance to regular drinkers.

Multiple approaches have been taken to alter alcohol intake in populations, including programs focused on restricting drinking and driving. Despite the apparent protection that alcohol provides against cardiovascular disease and death, cancer remains a major adverse effect. As in the case of cigarette smoking, a substantial body of literature indicates that increases in taxes reduce consumption of alcohol (Lewitt, Coate, and Grossman 1981; Ornstein and Levy 1983), although although there is no evidence that such interventions have prevented breast cancer.

Energy balance may play a role in breast cancer incidence. In animal models, restricting energy intake reduces the occurrence of mammary and colon tumors, and accumulating evidence suggests that reduced energy intake, particularly early in life, may reduce breast cancer in humans. Among postmenopausal women, the association between adiposity and breast cancer is positive, but generally weak (Willett 1989; Tretli 1989). Physical activity during adolescence and early adult life has also been found to offer protection against breast cancer (Frisch et al. 1985; Bernstein et al. 1994).

The hormonal aspects of breast cancer etiology remain a major potential area for preventive interventions. Antiestrogens have been advocated as one possible means of prevention among older women (Prentice 1990), as have manipulations of hormones through synthetic replacement therapy for adolescent females to induce amenorrhea (Pike et al. 1989) in order to reduce the subsequent risk of breast and ovarian cancer. Such hormonal manipulations may, however, contain as yet unknown risks, which, together with social and cultural considerations, preclude widespread use. Tamoxifen, an antiestrogen in the breast, is also being evaluated as a chemopreventive approach to breast cancer among women at high risk (Bush and Helzlsouer 1993). Such clinical interventions among women at high risk must be balanced by the parallel development of public health interventions because the majority of breast cancer cases are diagnosed in women who are not in the categories generally accepted as high risk.

In sum, deficiencies in the knowledge base concerning fundamental biological processes and the epidemiology of modifiable risks for breast cancer highlight the need for focused research in these areas.

Colon Cancer

In contrast to breast cancer, epidemiological studies provide substantial, but not conclusive, evidence that animal fat or meat intake is associated with risk of colon cancer (Steinmetz and Potter 1991a,b). A strong correlation between colon cancer and these variables has been demonstrated internationally. Fiber intake may protect against colon cancer, although the evidence is weak. Inverse associations with intake of fruits and vegetables have been observed in most studies (Trock, Lanza, and Greenwald 1990; Steinmetz and Potter 1991a); whether this relation is due to the fiber content of these foods or to other factors is not clear (Steinmetz and Potter 1991b). Intake of grain fiber has not been associated with risk of colon cancer in most studies. However, prospective data relating diet to risk of adenomatous colon polyps, precursor lesions for colon cancer, show an inverse association for all types of fiber, and a positive association for saturated fat intake (Giovannucci et al. 1992). These data, taken together, suggest that fiber and fat may act at different stages in the carcinogenic pathway.

Alcohol intake is positively associated with colon cancer (Longnecker et al. 1990), and also with incidence of colon polyps. A possible mechanism for this association is provided by studies of the interaction between folate and alcohol intake, which suggest that the adverse effect of alcohol intake is more marked among those with low dietary folate (Giovannucci et al. 1992).

Obesity appears to be unrelated to colon cancer among women, but shows a consistent, though weak, positive relation among men in several prospective studies (Lew and Garfinkel 1979). Physical activity is inversely related to risk of colon cancer in the majority of studies, whether activity is defined by usual occupation (Garabrant et al. 1984; Gerhardsson 1986; Vena et al. 1985, 1987; Paffenbarger, Hyde, and Wing 1987), or by leisure-time activity (Wu et al. 1987; Severson et al. 1989; Ballard-Barbash et al. 1990).

Research into the biological processes of colon cancer has kept pace with the research into the epidemiology of its risk factors: the genetic al-

terations leading to colon cancer have been documented (Powell et al. 1992), and genetic markers for familial colon cancer have been reported (Aaltonen et al. 1993). Such markers may not prove to offer hope for prevention beyond clinical interventions among family members at risk. The convergence of biological knowledge and understanding of epidemiological risk factors suggest that both clinical and public health interventions to decrease red meat consumption, increase intake of fruits and vegetables, and encourage physical activity may substantially reduce the burden of colon cancer.

As already discussed, there is some evidence that alcohol use can be influenced by taxation, and there is limited evidence for the effectiveness of clinical interventions to treat obesity; neither intervention has been demonstrated to reduce colon cancer. We likewise have little information about the effectiveness of programs to increase consumption of fruits and vegetables and decrease consumption of red meat. The national 5-A Day program funded by National Cancer Institute has shown some success in raising knowledge of the health benefits of fruits of vegetables and improving behavioral intentions to consume more fruits and vegetables (Produce for Better Health Foundation 1993), although, again, we have no evidence of cancer prevention. Reductions in intake of dietary fat, saturated fat, and cholesterol have been a major focus of programs aimed at reducing coronary heart disease, and there is some clinical evidence that men at risk of heart disease can lower that risk by reducing blood cholesterol level (Lipid Research Clinics Program 1984). We have no direct evidence that clinical or public health interventions to reduce dietary fat prevents colon cancer. There are many intervention approaches to increasing levels of physical activity among populations; while we have no direct evidence that cancer incidence diminishes as a result of increasing activity, improving physical activity levels will also reduce risks of coronary heat disease and is consistent with lowered colon cancer risk.

In sum, the scientific base is sufficient to justify lifestyle changes that are likely to significantly reduce risk of colon cancer. Social intervention strategies to implement these changes and evidence of the effectiveness of intervention, however, are lacking. Further, the political will (that is, society's desire and commitment to support or modify old programs or develop new ones) to bring about major changes in diet and physical activity has not been sufficient to advance colon cancer prevention to date.

Prostate Cancer

Cancer of the prostate has become the leading incident cancer among men. The age-adjusted incidence rate for cancer of the prostate is 50 percent higher among black males than among white males. Although some of the increase in incidence may be due to the growing use of transurethral resections of the prostate to treat benign prostatic hypertrophy, the rise in mortality of 0.6 percent per year from 1973 to 1987 indicates that some of the increase in cancer of the prostate is not simply the result of improved detection, but reflects as well the fact that rates are truly on the rise.

Like breast and colon cancer, rates of prostate cancer correlate with national per capita intake of fat (Armstrong and Doll 1975). The majority of case-control studies support an association between some aspect of animal fat and risk of prostate cancer (Giovannucci 1995). In addition to red meat and animal fat, prospective studies suggest that specific types of fat or fatty acids may increase incidence and enhance growth of prostate cancer. The fatty acid with the strongest association in the prospective Health Professionals Follow-up Study was alpha-linolenic acid (Giovannucci et al. 1993b). This finding was replicated in a nested case-control study of plasma samples obtained from participants in the Physicians Health Study. Plasma alpha-linolenic acid was significantly related to risk of prostate cancer (Gann et al. 1994). Carotenoids have also been studied for their potential to reduce risk of prostate cancer. Preliminary data from four prospective studies also suggest a consistent decrease in risk of prostate cancer among men with higher lycopene levels measured either by their intake of tomatoes (rich in lycopene) or by their blood levels. Lycopene is a carotenoid that may inhibit proliferation of prostate cancer.

Although far from conclusive, the existing data on diet and prostate cancer do provide reason to study this relation in more detail, with more comprehensive dietary assessments. Some of this motivation stems from our almost complete lack of identifiable risk factors for this malignancy. Emerging evidence points to a relatively consistent increase in risk of prostate cancer 20 or more years after vasectomy (Giovannucci 1993a,c). For each of these recent epidemiological associations, there is no biological model to explain convincingly the mechanism for such a relation.

Deficiencies in the knowledge base for both the fundamental biological processes and the epidemiology of modifiable risks must be urgently remedied. Until a more substantial scientific basis for prevention of pros-

tate cancer is available, development of intervention strategies (either designed for individuals or using public health methods) is premature.

Malignant Melanoma

We focus attention on this cancer because the incidence rate for malignant melanoma has risen more rapidly than that for any other cancer during the interval from 1973 to 1990. The overall annual percent change over the 15-year period was 4.4 percent among whites. Malignant melanoma is one of the few specific forms of cancer in which a known, major preventable etiology exists that is not related to cigarette smoking. Although there appears to be an important predisposition among family members to developing this disease, there is no question that repeated, unprotected sun exposure by those with a propensity to burn is a significant risk factor (Weinstock et al. 1989).

Intervention strategies to prevent melanoma take two forms. A primary issue is avoiding repeated episodes of sunburn at any age, but particularly during youth and adolescence when melanin pigment is being mobilized. For those with significant numbers of moles, clinical prevention entails repeated examination to identify changing lesions. This is a form of secondary prevention in that early removal of precancerous lesions reduces risk. In both cases, public education, perhaps with warning labels on sun-tanning and sun-blocking agents, may be warranted. A sun tan is a highly valued social symbol among young persons; fashion and advertising may have played a part in establishing a sun tan as desirable. Data from Australia, a nation with an extremely high incidence of melanoma, indicate that teenagers, more than any other age group, want to obtain a dark sun tan in the summer and consider it worth a great deal of effort to do so (Marks and Hill 1988). For adolescents, currently perceived rewards of a behavior far outweigh any long-term consequences, no matter how severe these may be. Thus, prevention strategies among teenagers must take account of these important determinants of adolescent behavior. Prevention should be incorporated into comprehensive, school-based health programs. In addition, social marketing may play a role in promoting the use of sun screens, hats, and long-sleeved shirts to reduce sun exposure and to avoid exposure during peak hours of ultraviolet flux (10 AM to 3 PM). To date, we have no evidence that such preventive interventions are effective.

Other Cancers

The remaining causes of cancer mortality account for 50 percent of cancer deaths, but are spread over numerous sites, each with its own causes and paths to prevention. Focusing on any one site, however, cannot have a major impact on total cancer mortality unless common underlying biological processes that have not been defined to date are influenced by a common set of modifiable behavioral, environmental, or genetic risks. Endometrial cancer can be avoided by reducing energy intake and obesity. Ovarian cancer is reduced by suppressing ovulation either through use of oral contraception or through pregnancy. A reduction in incidence by 40 percent may be seen among women who have used oral contraceptives for five or more years (Hankinson et al. 1992).

Discussion

National expenditures on cancer are predominantly allocated to early detection and treatment of disease. Using a liberal definition of primary prevention, it was estimated that 17 percent of the NCI budget went to primary prevention in 1992. Patient treatment and basic research remain the major areas funded. This current allocation of NIH funding reflects the evolution of university-based research centers that tend to investigate hospitalized patients; thus, treating the sick, rather than maintaining the health of the well, is rewarded. This emphasis in academic medicine, described decades ago (Richmond 1969), persists in the ongoing public debate. The current mechanisms for research and demonstration project support by NIH still shore up this predominant emphasis.

Using U.S. cancer mortality data as a measure of the progress against cancer, we recommend, as did Cairns (1985) and Bailar and Smith (1986), new strategies for prevention. These strategies should include priorities in each of the two areas defining the scientific basis for prevention:

1. our knowledge base of fundamental biological processes and epidemiology, which identify modifiable risks that are biological, behavioral, or environmental in nature
2. our knowledge of the effectiveness of interventions to reduce modifiable risks and cancer prevalence and mortality

Our review of cancer etiology and intervention evidence highlights various research areas that hold strong promise for reducing cancer rates in the United States. One clear finding of our analysis is that the main modifiable causes of cancer have a common behavioral pathway: substances that people put in their mouths, including cigarettes, smoking pipes, chewing tobacco, and food. Other clearly modifiable risks stem from lack of physical activity (and associated obesity) and exposure to ultraviolet light. The strong social, behavioral, and economic components to these risks must be acknowledged when funding is provided for intervention research.

Our knowledge of modifiable risks and intervention effectiveness is particularly solid with respect to cancers caused by smoking. Our brief review of evidence for effective interventions either to prevent cancer directly or to indirectly affect reductions in risks for cancer (e.g., smoking cessation interventions) has documented evidence for effectiveness across a broad array of options, from clinical interventions like smoking counseling, to population interventions like taxation on cigarettes. However, the government currently is undertaking and funding only some of these intervention strategies. One important area of intervention, taxation of tobacco and alcohol, has a strong potential to reduce cancer risk. For most of the cancers, however, there is little evidence of effective intervention strategies (see table 1).

It is also clear that the biological processes of carcinogenesis leading to colon cancer have been well described, and some modifiable risks have been identified; this is also the case for malignant melanoma. Regarding breast cancer and prostatic cancer, however, little evidence for either substantial modifiable risks or effective intervention has been produced; the greatest need thus remains intensive research focused on discovering new modifiable risks.

One limitation of our analysis is its focus on only a sample of cancers. A similar analysis, however, could be carried out for other cancers, reviewing the evidence for modifiable risks and preventive interventions. Our assessment is that none of the risks so identified will result in numbers of potential preventable cancers of a magnitude similar to those we have targeted in this analysis. From another perspective, our analysis is also limited in the potentially modifiable risks we have examined. For example, there is broad exposure of the population to environmental risks posed by air (car and industrial) pollution, electromagnetic fields (Poole and Trichopoulos 1991), and pesticides. Estimates indicate, how-

TABLE 1
Summary of Scientific Basis for Cancer Prevention and Evidence for Intervention Strategies to Reduce Cancer Incidence in the United States

Cancer type	Scientific basis/knowledge of risks		Evidence for effective intervention strategies	
			To reduce cancer	To reduce risk factors
Lung cancer	Smoking	Strong evidence	Many examined; some effective Many receive little emphasis (e.g., taxation)	Much evidence for effective intervention Many received little emphasis
	Diet	Inconsistent evidence	No clear evidence	Not examined
Breast cancer	Adult diet			
	Fat	Little evidence	No clear evidence	Clear evidence for effective intervention; public health approaches (e.g., labeling) not clearly indicated
	Alcohol	Consistent relation	Not examined	Clear evidence, but lack of public policy evaluation (e.g., taxation)

	Reproductive factors			
	Menarche	Strong evidence	Not examined	Not examined
	Parity	Strong evidence	Not examined	Not examined
	Hormones	Strong evidence	No clear evidence	Not examined
Colon cancer	Adult diet		No clear evidence	As per adult diet and breast cancer
	Fat	Strong evidence		
	Fiber	Strong evidence		
	Physical activity	Strong evidence	Not examined	Clear evidence in clinical research; limited population intervention evidence
	Obesity	Strong evidence	Not examined	Clear evidence in clinical research; limited population intervention evidence
Prostate cancer	Diet	Evidence increasing	Not examined	As per adult diet and breast and colon cancer
Melanoma	Adolescent sun exposure	Strong evidence	Not examined	Limited population Limited interventions

ever, that these exposures account for only a small proportion of cancers (Doll and Peto 1981).

Summary

The knowledge base may be advanced by concentrating on primary prevention of cancer, which in turn will inform the development of effective and efficient intervention strategies for prevention that may substantially reduce cancer incidence. Several priority areas have been identified, and with new multidisciplinary approaches spanning the biological, epidemiological, social, behavioral, and economic sciences, new initiatives in primary cancer prevention may lead the way toward reducing cancer mortality through primary prevention.

References

Aaltonen, L.A., P. Peltomaki, F.S. Leach, et al. 1993. Clues to the Pathogenesis of Familial Colorectal Cancer. *Science* 260:812–16.

American Public Health Association. 1991. *Healthy Communities 2000: Model Standards. Guidelines for Community Attainment of the Year 2000 National Health Objectives*, 3d. ed. Washington.

Andrews, L.B., J.E. Fullarton, N.A. Holtzman, and A.G. Motulsky (Eds.). 1994. *Assessing Genetic Risks. Implications for Health and Social Policy*. Washington: National Academy Press.

Armstrong, B., and R. Doll. 1975. Environmental Factors and Cancer Incidence and Mortality in Different Countries, with Special Reference to Dietary Practices. *International Journal of Cancer* 15:617–31.

Bailar, J.C. III, and E.M. Smith. 1986. Progress against Cancer? *New England Journal of Medicine* 314:1226–32.

Ballard-Barbash, R., A. Schatzkin, D. Albanes, et al. 1990. Physical Activity and Risk of Large Bowel Cancer in the Framingham Study. *Cancer Research* 50:3610–13.

Bernstein, L., B.E. Henderson, R. Hanisch, et al. 1994. Physical Exercise and Reduced Risk of Breast Cancer in Young Women. *Journal of the National Cancer Institute* 86:1403–8.

Boyle, P., P. Maisonneuve, R. Saracci, and C.S. Muir. 1990. Is the Increased Incidence of Primary Malignant Brain Tumors in the Elderly Real? *Journal of the National Cancer Institute* 82:1594–6.

Brinton, L.A., and C. Schairer. 1993. Estrogen Replacement Therapy and Breast Cancer Risk. *Epidemiologic Reviews* 15(1):66–79.

Bush, T.L., and K.J. Helzlsouer. 1993. Tamoxifen for the Primary Prevention of Breast Cancer: A Review and Critique of the Concept and Trial. *Epidemiologic Reviews* 15:233–43.

Bush, P.J., A.A. Zuckerman, P.K. Theiss, V.S. Taggart, C. Horowitz, M.J. Sheridan, and H.J. Walter. 1989. Cardiovascular Risk Factor Prevention in Black Schoolchildren: Two-Year Results of the "Know Your Body" Program. *American Journal of Epidemiology* 129: 466–82.

Cairns, J. 1985. The Treatment of Diseases and the War against Cancer. *Scientific American* 253:51–9.

Centers for Disease Control and Prevention. 1993. Cigarette Smoking among Adults—United States, 1991. *Morbidity and Mortality Weekly Report* 42:230–3.

Cleary, P.D., J.L. Hitchcock, N. Semmer, L.J. Flinchbaugh, and J.M. Pinney. 1988. Adolescent Smoking: Research and Health Policy. *Milbank Quarterly* 66:137–71.

Cochrane, A.L. 1972. Effectiveness and Efficiency: Random Reflections on Health Services. London: Nuffield Provincial Hospitals Trust.

COMMIT Research Group. 1991. Community Intervention Trial for Smoking Cessation (COMMIT): Summary of Design and Intervention. *Journal of the National Cancer Institute* 83:1620–28.

———. 1995. Community Intervention Trial for Smoking Cessation (COMMIT): II. Changes in Adult Smoking Prevalence. *American Journal of Public Health* 85:193–200.

Connell, D.B., R.R. Turner, and E.F. Mason. 1985. Summary of Findings of the School Health Education Evaluation: Health Promotion Effectiveness, Implementation, and Costs. *Journal of School Health* 55(8):316–23.

Davis, D.L., D. Hoel, J. Fox, and A. Lopez. 1990. International Trends in Cancer Mortality in France, West Germany, Italy, Japan, England and Wales, and the USA. *Lancet* 336:474–81.

Devesa, S.S., W.J. Blot, and J.F. Fraumeni. 1989. Declining Lung Cancer Rates among Men and Women in the United States: A Cohort Analysis. *Journal of the National Cancer Institute* 81:1568–71.

Doll, R., and R. Peto. 1981. The Causes of Cancer. Quantitative Estimates of Avoidable Risks of Cancer in the United States Today. *Journal of the National Cancer Institute* 66:1191–1308.

Errecart, M.T., H.J. Walberg, J.G. Ross, R.S. Gold, J.L. Fiedler, and L.J. Kolbe. 1991. Effectiveness of Teenage Health Teaching Modules. *Journal of School Health* 61(1):26–30.

Extramural Committee to Assess Measures of Progress against Cancer.

1990. Measurement of Progress against Cancer. *Journal of the National Cancer Institute* 82:825–35.

Feuer, E.J., and L.-P. Wun. 1992. How Much of the Recent Rise in Breast Cancer Incidence Can Be Explained by Increases in Mammography Utilization? A Dynamic Population Approach. *American Journal of Epidemiology* 136:1423–36.

Frisch, R.E., G. Wyshak, N.L. Albright, et al. 1985. Lower Prevalence of Breast Cancer and Cancers of the Reproductive System among Former College Athletes Compared to No-Athletes. *British Journal of Cancer* 52:885–91.

Gann, P., C.H. Hennekens, F.M. Sacks, F. Grodstein, E. Giovannucci, and M.J. Stampfer. 1994. A Prospective Study of Plasma Fatty Acids and Risk of Prostate Cancer. *Journal of the National Cancer Institute* 86:281–6.

Garabrant, D.H., J.M. Peters, T.M. Mack, and L. Bernstein. 1984. Job Activity and Colon Cancer Risk. *American Journal of Epidemiology* 119:1005–14.

Gerhardsson, M., S.E. Norell, H. Kiviranta, N.L. Pedersen, and A. Ahlbolm. 1986. Sedentary Jobs and Colon Cancer. *American Journal of Epidemiology* 123:775–80.

Giovannucci, E. 1995. Epidemiologic Study of Prostate Cancer. *Cancer* 75;1766–77.

Giovannucci, E., M.J. Stampfer, G.A. Colditz, E.B. Rimm, and W.C. Willett. 1992. Relation of Diet to the Risk of Colorectal Adenoma in Men. *Journal of the National Cancer Institute* 84:91–8.

Giovannucci, E., A. Ascherio, E.B. Rimm, G.A. Colditz, M.J. Stampfer, and W.C. Willett. 1993a. A Prospective Cohort Study of Vasectomy and Prostate Cancer. *Journal of the American Medical Association* 269:873–7.

Giovannucci, E., E.B. Rimm, G.A. Colditz, et al. 1993b. A Prospective Study of Dietary Fat and Risk of Prostate Cancer. *Journal of the National Cancer Institute* 85:1571–9.

Giovannucci, E., T.D. Tosteson, F.E. Speizer, A. Ascherio, M.P. Vessey, and G.A. Colditz. 1993c. A Retrospective Cohort Study of Vasectomy and Prostate Cancer. *Journal of the American Medical Association* 269:878–82.

Giovannucci, E., G.A. Colditz, M.J. Stampfer, et al. 1994a. A Prospective Study of Cigarette Smoking and Risk of Colorectal Adenoma and Colorectal Cancer in US Women. *Journal of the National Cancer Institute* 86:192–9.

Giovannucci, E., E.B. Rimm, M.J. Stampfer, et al. 1994b. A Prospective Study of Cigarette Smoking and Risk of Colorectal Adenoma and Colorectal Cancer in US Men. *Journal of the National Cancer Institute* 86:183–91.

Giovino, G.A., M.W. Schooley, B. Zhu, J.H. Chrismon, S.L. Tomar, J.P. Peddicord, et al. 1994. Surveillance for Selected Tobacco-Use Behaviors—United States, 1990–1994. *Morbidity and Mortality Weekly Report* 43:1–43.

Glass, A.G., and R.N. Hoover. 1990. Rising Incidence of Breast Cancer: Relationship to Stage and Receptor Status. *Journal of the National Cancer Institute* 82:693–6.

Grady, D., and V. Ernster. 1991. Invited Commentary: Does Postmenopausal Hormone Therapy Cause Breast Cancer? *American Journal of Epidemiology* 134:1396–1400.

Greenwald, P., and E.J. Sondik. (Ed). 1986. *NCI Monographs. Cancer Control Objectives for the Nation: 1985–2000*. Bethesda, Md.: National Cancer Institute.

Grieg, N.H., L.G. Reis, R. Yancik, and S.I. Rapoport. 1990. Increasing Annual Incidence of Primary Malignant Brain Tumors in the Elderly. *Journal of the National Cancer Institute* 82:1621–4.

Hankinson, S.E., G.A. Colditz, D.J. Hunter, T.L. Spencer, B. Rosner, and M.J. Stampfer. 1992. A Quantitative Assessment of Oral Contraceptive Use and Risk of Ovarian Cancer. *Obstetrics and Gynecology* 80:708–14.

Harris, J.E. 1987. The 1983 Increase in the Federal Cigarette Excise Tax. In *Tax Policy and the Economy* (vol. 1, 87–111), ed. L.H. Summers. Cambridge, Mass.: M.I.T. Press.

Henderson, B.E., R.K. Ross, and M.C. Pike. 1991. Towards the Primary Prevention of Cancer. *Science* 254:1131–8.

Hiatt, R.A. 1990. Alcohol Consumption and Breast Cancer. *Medical Oncology and Tumor Pharmacotherapy* 7:143–51.

Hunter, D.J., and W.C. Willett. 1993. Diet, Body Size, and Breast Cancer. *Epidemiologic Reviews* 15(1):110–32.

Key, T.J., and M.C. Pike. 1988. The Role of Oestrogens and Progestagens in the Epidemiology and Prevention of Breast Cancer. *European Journal of Cancer and Clinical Oncology* 24:29–43.

Keyfitz, N. 1982. What if Cancer Were Eradicated? In *Population Change and Social Policy*, chap. 17. Cambridge, Mass.: Abt Books.

Killen, J.D., M.J. Telch, T.N. Robinson, N. Maccoby, J.W. Farquhar, and C.B. Taylor. 1988. Cardiovascular Disease Risk Reduction for Tenth Graders. A Multiple-Factor School-Based Approach. *Journal of the American Medical Association* 260:1728–33.

Lew, E.A., and L. Garfinkel. 1979. Variations in Mortality by Weight among 750,000 Men and Women. *Journal of Chronic Diseases* 32:563–76.

Lewitt, E.M., D. Coate, and M. Grossman. 1981. The Effects of Government Regulation on Teenage Smoking. *Journal of Law and Economics* 24:545–70.

Lichtenstein, E., L. Wallack, and T.F. Pechacek. 1990–91. Introduction to the Community Intervention Trial for Smoking Cessation (COMMIT). *International Quarterly of Community Health Education* 11(3):173–85.

Liff, J.M., J.F.C. Sung, W.-H. Chow, R.S. Greenberg, and W.D. Flanders. 1991. Does Increasing Detection Account for the Rising Incidence of Breast Cancer? *American Journal of Public Health* 81:462–5.

Lipid Research Clinics Program. 1984. The Lipid Research Clinics Coronary Primary Prevention Trial Results: I. Reduction in the Incidence of Coronary Heart Disease. *Journal of the American Medical Association* 251:351–64.

Longnecker, M.P., J.A. Berlin, J. Orza, and T.C. Chalmers. 1988. A Meta-Analysis of Alcohol Consumption in Relation to Risk of Breast Cancer. *Journal of the American Medical Association* 248:1465–7.

Longnecker, M.P., M.J. Orza, M.E. Adams, J. Vioque, and T.C. Chalmers. 1990. A Meta-Analysis of Alcoholic Beverage Consumption in Relation to Risk of Colorectal Cancer. *Cancer Causes and Control* 1:59–68.

Manning, W.G., E.B. Keeler, J.P. Newhouse, E.M. Sloss, and J. Wasserman. 1991. *The Costs of Poor Health Habits.* Cambridge: Harvard University Press.

Marks, R., and D. Hill. 1988. Behavioral Change in Adolescence: A Major Challenge for Skin-Cancer Control in Australia. *Medical Journal of Australia* 149:514–15.

Miller, B.A., L.A.G. Ries, B.F. Hankey, et al. (Eds.). 1993. *SEER Cancer Statistics Review: 1973–1990* (NIH pub no. 93-2789). Bethesda, Md.: National Cancer Institute.

Muir, C.S. 1990. Epidemiology, Basic Science, and the Prevention of Cancer: Implications for the Future. *Cancer Research* 50:6441–8.

National Center for Health Statistics. 1990. *Health. United States, 1989.* Hyattsville, Md.: U.S. Public Health Service.

Ornstein, S.I., and D. Levy. 1983. Price and Income Elasticities of Demand for Alcoholic Beverages. In *Recent Developments in Alcoholism* (vol. 1, 303–45), ed. M. Galanter. New York: Plenum Press.

Paffenbarger, R.S., R.T. Hyde, and A.L. Wing. 1987. Physical Activity and Incidence of Cancer in Diverse Populations: A Preliminary Report. *American Journal of Clinical Nutrition* 45:312–17.

Peto, R., A.D. Lopez, M. Thun, and C. Heath. 1992. Mortality from Tobacco in Developed Countries: Indirect Estimation from Vital Statistics. *Lancet* 339:1268–78.

Pierce, J.P., M.C. Fiore, T.E. Novotny, E.J. Hatziandreu, and R.M. Davis. 1989. Trends in Cigarette Smoking in the United States: Educa-

tional Differences Are Increasing. *Journal of the American Medical Association* 261:56–60.

Pierce, J.P., A. Farkas, N. Evan, et al. 1993. Tobacco Use in California, 1992. A Focus on Preventing Uptake in Adolescents. Sacramento: California Department of Health Services.

Pike, M.C., R.K. Ross, R.A. Lobo, T.J.A. Key, M. Potts, and B.E. Henderson. 1989. LHRH Agonists and the Prevention of Breast and Ovarian Cancer. *British Journal of Cancer* 60:142–8.

Poole, C., and D. Trichopoulos. 1991. Extremely Low-Frequency Electric and Magnetic Fields and Cancer. *Cancer Causes and Control* 2: 267–76.

Potosky, A.L., L. Kessler, G. Gridley, C.C. Brown, and J.W. Horm. 1990. Rise in Prostatic Cancer Incidence Associated with Increased Use of Transurethral Resection. *Journal of the National Cancer Institute* 82:1624–8.

Powell, S.M., Y. Beazer-Barclay, T.M. Bryan, S.R. Hamilton, S.N. Thibodeau, B. Vogelstein, and K.W. Kinzler. 1992. APC Mutations Occur Early during Colorectal Tumorigenesis. *Nature* 359:235–7.

Prentice, R.L. 1990. Tamoxifen as a Potential Preventive Agent in Healthy Postmenopausal Women. *Journal of the National Cancer Institute* 82:1130–1.

Produce for Better Health Foundation. 1993. More Americans Think 5. *5 A Day News* 3:1,5.

Reichman, M.E., J.T. Judd, C. Longcope, et al. 1991. Alcohol Consumption and Hormone Levels in a Controlled Diet Study of Premenopausal Women. *American Journal of Epidemiology* 134:715. (abstract)

Richmond, J.B. 1969. *Currents in American Medicine. A Developmental View of Medical Care and Education*. Cambridge: Harvard University Press.

Richmond, J.B., and M. Kotelchuck. 1984. Co-ordination and Development of Strategies and Policy—The United States Example. In *Textbook of Public Health*. Oxford: Oxford University Press.

Ries, L.A.G, B.F. Hankey, and B.K. Edwards. (Eds.). 1990. *Cancer Statistics Review 1973–1987* (NIH pub. no. 90-2789). Bethesda, Md.: National Cancer Institute.

Rose, G. 1982. Strategy of Prevention: Lessons from Cardiovascular Disease. *Lancet* 282:1847–51.

———. 1985. Sick Individuals and Sick Populations. *International Journal of Epidemiology* 14:32–8.

Severson, R.K. 1990. Have Transurethral Resections Contributed to the Increasing Incidence of Prostatic Cancer? *Journal of the National Cancer Institute* 82:1597–8.

Severson, R.K., A.M.Y. Nomura, J.S. Grove, and G.N. Stemmermann. 1989. A Prospective Analysis of Physical Activity and Cancer. *American Journal of Epidemiology* 130:522–9.

Stampfer, M.J., G.A. Colditz, W.C. Willett, J.E. Manson, B. Rosner, F.E. Speizer, and C.H. Hennekens. 1991. A Prospective Study of Postmenopausal Estrogen Therapy and Cardiovascular Diseases: Ten-Year Follow-Up from the Nurses' Health Study. *New England Journal of Medicine* 325:756–62.

Steinmetz, K.A., and J.D. Potter. 1991a. Vegetables, Fruit, and Cancer. I. Epidemiology. *Cancer Causes Control* 2:325–57.

———. 1991b. Vegetables, Fruit, and Cancer. II. Mechanisms. *Cancer Causes Control* 2:427–42.

Susser, M. 1995. Editorial: The Tribulation of Trial Interventions in Communities. *American Journal of Public Health* 85:152–8.

Tomatis, L. (Ed.). 1990. *Cancer: Causes, Occurrence and Control.* (IARC scientific pub. no. 100). Geneva: World Health Organization.

Tretli, S. 1989. Height and Weight in Relation to Breast Cancer Morbidity and Mortality. A Prospective Study of 570,000 Women in Norway. *International Journal of Cancer* 44:23–30.

Trock, B., E. Lanza, and P. Greenwald. 1990. Dietary Fiber, Vegetables, and Colon Cancer: Critical Review and Meta-Analyses of the Epidemiologic Evidence. *Journal of the National Cancer Institute* 82: 650–61.

U.S. Department of Health and Human Services. 1986a. *The Health Consequences of Involuntary Smoking. A Report of the Surgeon General.* Rockville, Md.: U.S. Public Health Service.

———. 1986b. *The Health Consequences of Using Smokeless Tobacco.* Washington.

——— 1989. *Reducing the Health Consequences of Smoking: 25 Years of Progress. A Report of the Surgeon General* (DHHS pub. no. [CDC]89-8411). Washington.

——— 1990a. *The Benefits of Smoking Cessation. Report of the Surgeon General.* Washington.

———. 1990b. *Healthy People 2000: National Health Promotion and Disease Prevention Objectives.* Washington.

——— 1991. *HHS News.* October 4.

U.S. Preventive Services Task Force. 1989. *Guide to Clinical Preventive Services.* Washington: U.S. Department of Health and Human Services.

Vena, J.E., S. Graham, M. Zielezny, M.K. Swanson, R.E. Barnes, and J. Nolan. 1985. Lifetime Occupational Exercise and Colon Cancer. *American Journal of Epidemiology* 122:357–65.

Vena, J.E., S. Graham, M. Zielezny, J. Brasure, and M.K. Swanson. 1987. Occupational Exercise and Risk of Cancer. *American Journal of Clinical Nutrition* 45:318–27

Wald, N.J., K. Nanchahal, S.G. Thompson, and H.S. Cuckle. 1986. Does Breathing Other People's Smoke Cause Lung Cancer? *British Medical Journal* 293:1217–21.

Walter, H.J., A. Hofman, R.D. Vaughan, and E.L. Wynder. 1988. Modification of Risk Factors for Coronary Heart Disease. Five-Year Results of a School-Based Intervention Trial. *New England Journal of Medicine* 318:1093–100.

Warner, K.E., L.M. Goldenhar, and C.G. McLaughlin. 1992. Cigarette Advertising and Magazine Coverage of the Hazards of Smoking. A Statistical Analysis. *New England Journal of Medicine* 326:305–9.

Weinstock, M.A., G.A. Colditz, W.C. Willett, M.J. Stampfer, B.R. Bronstein, M.C. Mihm, and F.E. Speizer. 1989. Nonfamilial Cutaneous Melanoma Incidence in Women Is Associated with Sun Exposure before Age Twenty. *Pediatrics* 84:199–204.

White, E., C.Y. Lee, and A.R. Kristal. 1990. Evaluation of the Increase in Breast Cancer Incidence in Relation to Mammography Use. *Journal of the National Cancer Institute* 82:1546–52.

Willett, W. 1989. The Search for the Causes of Breast and Colon Cancer. *Nature* 338:389–94.

Windsor, R.A., J.B. Lowe, L.L. Perkins, D. Smith-Yoder, L. Artz, M. Crawford, et al. 1993. Health Education for Pregnant Smokers: Its Behavioral Impact and Cost Benefit. *American Journal of Public Health* 83:201–6.

Winkelstein, W. 1985. Some Ecological Studies of Lung Cancer and Ischemic Heart Disease Mortality in the United States. *International Journal of Epidemiology* 14:39–47.

Wu, A.H., A. Paganini-Hill, R.K. Ross, and B.E. Henderson. 1987. Alcohol, Physical Activity and Other Risk Factors for Colorectal Cancer: A Prospective Study. *British Journal of Cancer* 55:687–94.

Acknowledgment: Members of the Cancer Prevention Working Group are Julius B. Richmond (Chair), Frederick Mosteller (Co-Chair), Dean Hashimoto, Mary Knudson, Gerald S. Lesser, Frederick P. Li, Stephen E. Sallan, Gerald Shklar, Frank E. Speizer, and Walter C. Willett.

Address correspondence to: Graham A. Colditz, MD, DrPH, Department of Medicine, Channing Laboratory, Harvard Medical School, 180 Longwood Avenue, Boston, MA 02115-5899.