Environmental Health Perspectives
Vol. 81, pp. 95-101, 1989

Cancer Risk Assessment and Prevention: Where Do We Stand?

by Alice S. Whittemore*

This paper reviews selected aspects of progress and setbacks in cancer risk assessment and prevention during the four decades since the founding in 1947 of the Institute of Environmental Medicine at the New York University Medical Center. The period has been marked by substantial gains in quantifying the risks posed by exposures to known human carcinogens such as tobacco and ionizing radiation. By contrast, the search for sensitive and specific laboratory screens for human carcinogens has met setbacks, and epidemiological data still are needed to monitor the adverse effects of environmental exposures. The determination of acceptable levels of exposure to potential human carcinogens remains a formidable task, one for which no scientific framework yet exists. Future challenges in cancer risk assessment include the validation and use of biological markers of exposure and effective monitoring of risk among exposed populations. Future challenges in cancer prevention include the elimination of tobacco consumption and the acquisition of knowledge needed to prevent nutritionally and hormonally related cancers such as cancers of the bowel, prostate, and breast.

Introduction

This year marks the fortieth anniversary of the Institute of Environmental Medicine at the New York University Medical Center. When the Institute began in 1947, the Western world had just turned its attention from a major war to domestic public health problems such as urban and industrial air pollution and occupational health hazards. A few clinicians were beginning to suspect that human cancers could be caused by exposures to tobacco, ionizing radiation, and chemicals encountered in the workplace. The past four decades have seen considerable research focused on our interaction with the environment and how it affects our health. The Institute of Environmental Medicine has distinguished itself as a leader in much of this research. At this fortieth anniversary celebration it is appropriate to inquire where we stand in the battle against environmentally induced cancer and to identify the major unfinished tasks before us. To address these questions, I shall review selected aspects of our progress and setbacks in evaluating human cancer risks from substances in the environment and describe some of the future challenges in cancer risk assessment and prevention. I shall use the word environment in a broad sense, allowing it to include ways of living such as tobacco use and diet.

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Detecting and Estimating Carcinogenic Risks

I shall begin with a discussion of progress and problems in risk estimation for two known human carcinogens: tobacco and radiation. I shall also give a brief overview of progress and problems in monitoring risk from potential carcinogens—that is, substances whose carcinogenic effect in humans is less certain.

Known Carcinogens: Tobacco

The beneficial/deleterious effects of tobacco have been debated since its introduction to Europe in the late sixteenth century. However, it was not until the late 1940s that the issue was studied epidemiologically. The year 1950 saw publication of results from five studies comparing the smoking habits of patients with cancers of the lung to those of control subjects (*1-5*). These studies present strong evidence of a causal relationship. Results from subsequent cohort studies and animal experiments have established beyond reasonable doubt that cigarette smoking causes cancers of the mouth, esophagus, respiratory system, bladder, and pancreas. Experimental work in the Institute of Environmental Medicine at NYU by Van Duuren and his colleagues showed that many of the chemical constituents of cigarette smoke act as carcinogens, cocarcinogens, and promoters in mouse skin (*6*).

The dose response and temporal features of tobacco-induced lung carcinogenesis are now relatively well understood. The epidemiological data indicate that lung cancer death rates increase with the first or second power of smoking rate and with the fourth or fifth power of smoking duration (Figs. 1 and 2). The difference in rates between exsmokers and nonsmokers appears to remain roughly constant in time after smoking has ceased. This pattern, however, is less well established.

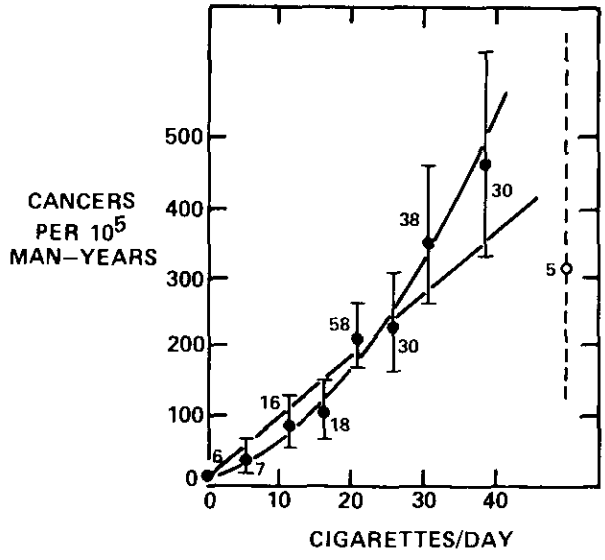

FIGURE 1. Lung cancer incidence rates versus smoking rate in male British physicians who were regular smokers (*42*).

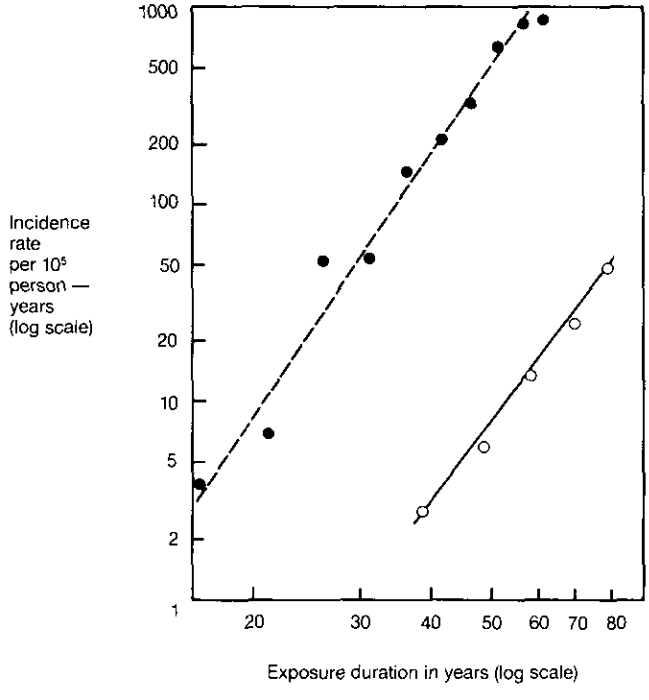

FIGURE 2. Lung cancer incidence rates versus duration of cigarette smoking in male British physicians who were regular smokers and versus age in lifelong nonsmokers. From Doll (*43*).

These and other features of the epidemiologic data have several implications for monitoring lung cancer mortality. They imply that doubling one's daily smoking rate roughly triples one's lung cancer risk, but that doubling one's smoking duration may increase it more than 20-fold. They also imply that smoking habits early in life have a strong effect on lung cancer rates in old age. Therefore, changes in national lung cancer rates must be interpreted in terms of tobacco consumption several decades earlier, and cohort effects must be considered when evaluating trends. Figure 3 shows temporal trends in cigarette consumption and in lung cancer death rates among men and women in the United States from 1920 to 1980. The two curves are nearly parallel. A simple linear regression of death rates against consumption 20 years earlier indicates that cigarette consumption explains about 93% of the temporal variance in lung cancer mortality.

Several investigators have interpreted the temporal features of the smoking-lung cancer relationship in terms of a theory of carcinogenesis in which bronchial stem cells undergo two or more heritable changes prior to generating a malignant clone (*7–9*). Cells in intermediate stages of the process may have increased clonal proliferation rates relative to normal stem cells. Cigarette smoking increases the rate at which cells undergo the first change and the rate at which they undergo the penultimate change (the one before the final malignant change). Although the epidemiological data appear to be consistent with this theory, they do not prove its validity. Despite this, the theory provides a framework within which to predict future mortality associated with present and past smoking rates, to analyze data on smokers' exposures to other carcinogens, and to evaluate the potential effects of intervention strategies. For example, Gaffney and Altshuler (*7*) have noted that carcinogens that strongly affect transition rates to an early stage in the multistage process induce cancers that occur long after exposure has started. They are more dangerous than those that affect only a late change, because years may elapse before they are detected.

Known Carcinogens: Radiation

In 1947, at the founding of the Institute of Environmental Medicine, only 2 years had elapsed since the atomic explosions in Hiroshima and Nagasaki—a time insufficient to appreciate the resulting long-term carcinogenic effects. The epidemics of lung cancer among uranium miners in the U.S. and Czechoslovakia, although known to some, were not widely appreciated. Since then the risks of radiation-induced human cancers have been the subject of extensive research, much of it contributed by investigators at NYU. Several examples are particularly relevant to the issues we are facing today in dealing with risks from radon in homes.

Harley and Pasternack (*10*) postulated that the lung cancer rate induced by a single radon exposure is independent of time since exposure (after a short period during which no cancers occur). These researchers were among the first to note that radon-induced lung cancer rates increase with age at first exposure, an observation now sup-

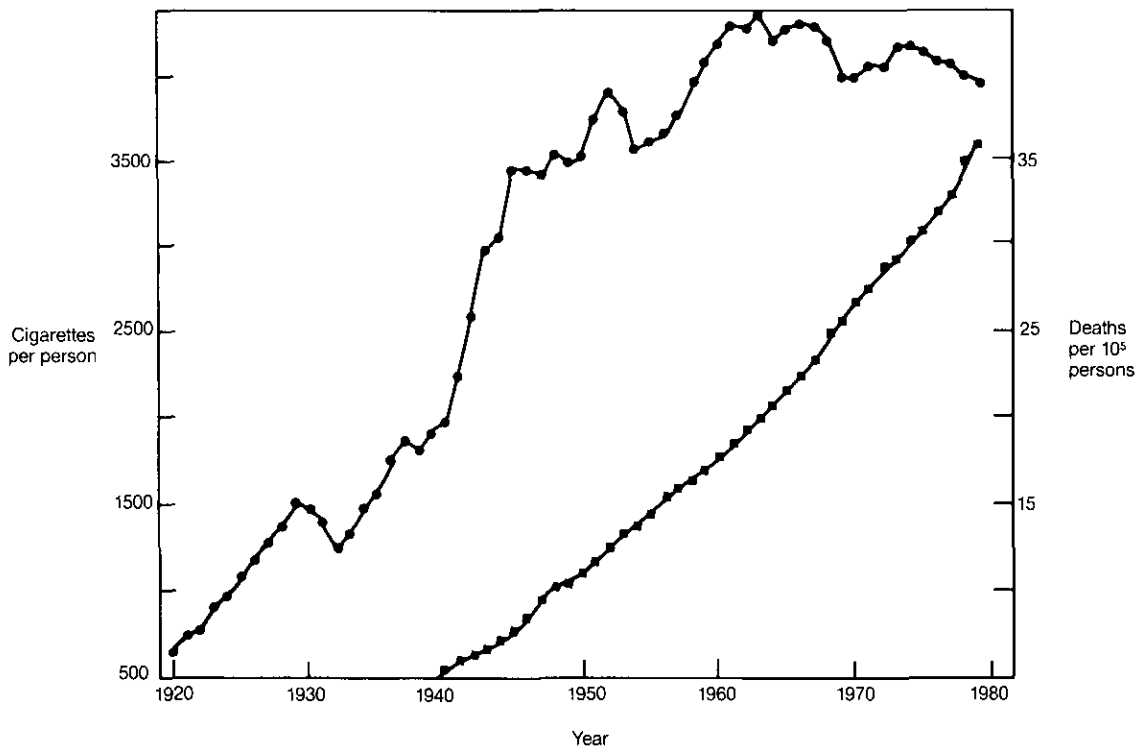

FIGURE 3. Annual U.S. cigarette consumption in cigarettes per capita from 1920–1979 (●). U.S. respiratory cancer mortality rates for both sexes combined, from 6th or 7th International Classification of Diseases (ICD) codes 162–164 for 1940–1959 and 8th ICD code 162 for 1960–1979 (■). From Kristein (*44*).

ported by the recent BEIR IV analysis of four cohorts of miners (*11*). To account for this observation, Harley and Pasternack revised their original formulation and postulated instead that radon-induced rates decrease with time since last exposure. However, recent follow-up of the miner cohorts suggests that radon-induced rates do not vary appreciably with time since cessation of mining, in agreement with Harley and Pasternack's original formulation. Thus, the increase in risk with age at exposure cannot be explained by a waning or repair effect after exposure ceases, as Harley and Pasternack conjectured.

Peto (*12*) has proposed an alternative explanation that allows the rates to remain constant with time since exposure: Radon affects the penultimate stage in a multistage process. This hypothesis, when combined with the theory described previously for tobacco-induced lung cancer, predicts that smokers have higher radiation-induced rates than do nonsmokers. This prediction appears to agree with the data (*11*). Peto's hypothesis implies that radon is most damaging to the elderly and that reducing residential radon levels will have short-term beneficial effects on lung cancer risk.

The data on temporal effects of other forms of ionizing radiation are less clear. On the one hand, evidence from the cohort of atomic bomb survivors and the cohort given X-ray treatments for ankylosing spondylitis (*13,14*) indicate excess rates that increase with age at irradiation and that remain constant with time since irradiation. These patterns suggest that a late-stage action also applies to the induction of nonhormonal epithelial cancers by all forms of ionizing radiation. However, the skin cancer data among children given X-ray treatment for ringworm of the scalp (*15*) indicate that radiation-induced rates increase sharply with time since irradiation, a temporal pattern more consistent with an early-stage effect of radiation. Further long-term follow-up of these irradiated cohorts is needed to test Peto's conjecture.

The temporal behavior of radiation-induced breast cancer rates differs from that of other epithelial cancers, according to data from cohorts of atomic bomb survivors, and of women X-irradiated for postpartum mastitis and tuberculosis (*16,17*). These suggest that risk is highest among women who were irradiated during adolescence, when breast epithelial cells are rapidly dividing. In contrast to the picture for radon and lung cancer, the breast cancer data also indicate that radiation-induced rates increase with time since exposure, suggesting that radiation induces an early neoplastic change in breast epithelial cells.

An important goal for future work is to develop a unifying theory for radiation-induced human carcinogenesis that allows reliable predictions of risk among various population subgroups. These predictions are needed to determine exposure limits and set priorities for abatement procedures.

All of the human data suggest that radiation-induced cancer rates are proportional to radiation dose, at least in the lower dose ranges. For radon, a linear dose-response relationship implies relatively large lung cancer risks associated with indoor levels in U.S. homes. In

reviewing all of the relevant epidemiological data, Thomas and McNeill (*18*) estimated the lifetime probability of radon-induced lung cancer to be 0.65 cancers per 1000 persons per working-level month (WLM). Radon levels in many U.S. homes are about 1 picocurie per liter of air (1 pCi/L), which produces an exposure roughly equivalent to 0.25 WLM per year (*19*). Thus, 70 years in a home with 1 pCi/L of radon gives an exposure of $70 \times 0.25 = 17.5$ WLM, and a lifetime risk of $17.5 \times 0.65 \times 10^{-3} = 1.14\%$. This risk estimate is an oversimplification: It is based largely on data among smokers and must be reduced by at least a factor of two for nonsmokers, it assumes that risk is proportional to radiation dose, and it ignores the age-at-exposure effects discussed earlier. Nevertheless, it is useful in setting priorities. For example, it differs by three orders of magnitude from the estimated lifetime lung cancer probability of 1/100,000 associated with living in a home containing nonfriable asbestos insulation (*20*), a fact of relevance when considering the merits of expending large sums to remove asbestos insulation from public buildings.

Monitoring Risks from Potential Carcinogens

An interdisciplinary group such as the Institute of Environmental Medicine provides an ideal setting for the early detection of human carcinogens, as illustrated by the history of the compound bischloromethyl ether (BCME) (*21*). At NYU, Van Duuren and his colleagues studied classes of chemicals in order to relate chemical structure to probable carcinogenicity (*22,23*). The chlorinated ethers were singled out, and rodent experiments determined that BCME was the most carcinogenic. Because humans inhale this compound in occupational settings, further inhalation studies in rats were conducted (*24*). These studies indicated that BCME was a lung carcinogen in rats. The results prompted an epidemiologic study of men occupationally exposed to BCME, which found an excess of lung cancer (*25*). The totality of this work prevented cancers by allowing early introduction of protective measures.

The BCME experience and others like it raised hopes that human cancer risks could be controlled by eliminating chemicals that test positive in animal experiments. In an invited address to NYU Medical Center in 1974 entitled "Carcinogens are Mutagens," Bruce Ames raised the further possibility that short-term tests for mutagenicity and other genotoxic effects could screen for carcinogens (*26*). Animal experiments could be supplemented or even replaced by rapid and inexpensive test batteries that would detect human carcinogens with high sensitivity and specificity.

These hopes have not been realized. Laboratory experiments are still imperfect tools for detecting human cancer, for several reasons. One is the great variability across species in response to chemicals and our lack of understanding about the causes of this variability. The International Agency for Research on Cancer has determined that there is sufficient evidence from human observations, but limited, inadequate, or nonexistent evidence from animal experiments to classify as carcinogens the compounds listed in Table 1. The fact that most of these compounds have tested positive in one or more of the short-term tests reflects not the sensitivity of the test battery, but rather the intense scrutiny the compounds have received relative to those for which no human data are available.

Another shortcoming of laboratory tests as screens for human carcinogens is their lack of specificity; one or more of them have tested positive for a number of chemicals occurring naturally in the foods we eat and the products we use. This lack of specificity is related to the inability of laboratory work to mimic the complex mix of carcinogens and cocarcinogens to which human cells are exposed. We now know that response to one carcinogen depends on other exposures, endogenous hormone levels, and myriad other factors. Work conducted at NYU and elsewhere has revealed a variety of pathways through which carcinogens work on somatic cells. These include nuclear effects such as the formation of DNA adducts and oncogene expression, and extranuclear effects such as mitotic acceleration. For example, experimental mouse skin carcinogenesis indicates that the dose-response curve for initiating carcinogens can be altered by the presence of other promoting agents (*27*).

For all of these reasons, laboratory tests do not yet provide a reliable screen for human carcinogens, and human data continue to be needed, despite the obvious desirability of discovering hazards before human exposure to them. In particular, occupationally exposed populations should be monitored routinely for cancer risks, as described in the next section. The most promising developments in the monitoring of exposed populations involve the use of biological exposure markers in blood, tissue, urine, feces, hair, or nail samples, as discussed elsewhere in this symposium (*28*). Such markers have the potential to document exposure levels, identify and quantify unusual susceptibility to environmental toxicants, detect neoplastic precursors, and provide etiologically supportive links between exposure and disease.

Although early hopes for a simple and consistent laboratory test battery were overoptimistic, laboratory tests nevertheless make important contributions to risk assessment. Specifically, they provide chemical profiles useful in evaluating potential human risks. This is not to imply that such profiles can produce precise estimates of human cancer numbers associated with low exposures. We still have no scientific basis for such estimation, but in our ignorance we have no choice but to use the profiles for crude and comparative estimates of risk.

For example, recent risk estimates have been based on

Table 1. Chemicals or industrial processes with sufficient[a] evidence for carcinogenicity in humans but not in experimental animals.[b]

Manufacture of auramine
Underground mining of hematite
Manufacture of isopropyl alcohol (strong acid process)
Nickel refining

[a]As defined by the International Agency for Research on Cancer (*41*).
[b]Taken from IARC (*41*).

comparative potency, whereby chemicals are ranked relative to one another. Relative ranks in humans at low doses are assumed equal to those in other test systems at experimental doses (*30,31*). This method has been used by Albert and colleagues at the Environmental Protection Agency to estimate human lung cancer risk from diesel particulate emissions (*30*). Several investigators have proposed that we regard as *de minimus* those levels of a carcinogen calculated to produce no more risk than that associated with an exposure we now tolerate, e.g., the amount of chloroform accepted in drinking water by the Environmental Protection Agency (*29,31*). The calculations are based on estimated potencies relative to that of chloroform. While not a panacea for the uncertainties created by lack of scientific evidence, this procedure seems a rational *pro tem* alternative to policies that effectively ban the use of all animal carcinogens.

Laboratory experiments also are needed to validate biological markers of human exposure by correlating them with exposure and disease in controlled settings. Perhaps most importantly, they provide insight and guidance about carcinogenic mechanisms that is needed to motivate observational studies in humans.

Future Challenges in Cancer Prevention

The absence of reliable laboratory screens for human carcinogens mandates aggressive monitoring of exposed populations, such as certain occupational groups, patients undergoing chemotherapy, and those living near nuclear facilities and toxic waste dumps. In particular, industrial epidemiologists should work with industry physicians in keeping computerized, annually updated and linkable medical, job, and smoking histories for all current and former employees. Continued morbidity and mortality monitoring after retirement is particularly important in view of increasing trends in certain cancer rates among older age groups that cannot be explained by increased diagnostic accuracy (*32*). Doll (*33*) has observed that this monitoring makes sense from the industrial point of view, because most such studies would reveal no excess risk, and the accumulated negative human evidence, coupled with estimates of exposure levels for various agents, would be useful in resisting overzealous regulation. The monitoring also makes sense from the workers' point of view, because real hazards would be detected earlier than they otherwise might be. Finally, it makes sense for the public who would learn that prolonged exposure to many agents feared harmful have not produced observable human hazards.

While such monitoring is important in preventing future cancer epidemics, it is unlikely to have much impact on the existing cancer burden, which is dominated by smoking-induced lung cancer and by cancer sites whose causes are yet unknown. Figure 4 shows estimates of the percentage of all cancers diagnosed in the U.S. in 1985 occurring among the major sites for men and women separately. Among men, cancers of the lung, bowel, and

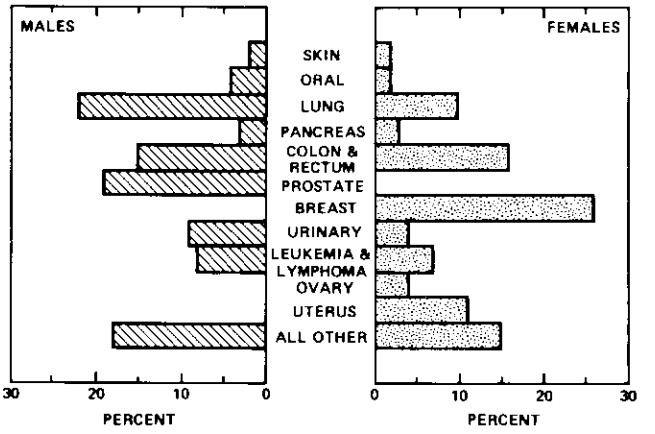

FIGURE 4. Estimated percentage of all incident cancers occurring by site of origin in U.S. males or females in 1985, excluding nonmelanoma skin cancer and carcinoma *in situ* (*45*).

prostate account for about 56% of all new cancers (an 57% of all cancer deaths). Among women, cancers of the lung, bowel, and breast comprise 52% of all new cancers (and 51% of all cancer deaths). Thus, preventive strategies in the U.S. and other industrialized countries must focus on these cancer sites.

However, the past 40 years have seen disappointingly slow progress in amassing the knowledge needed to prevent cancers of the breast, prostate, and bowel. We have fared better in understanding tobacco-induced lung carcinogenesis, and the U.S. and Great Britain have made some progress in avoiding this preventable disease. Figure 5 shows a modest but clear downward trend with year of birth in age-specific lung cancer rates among young

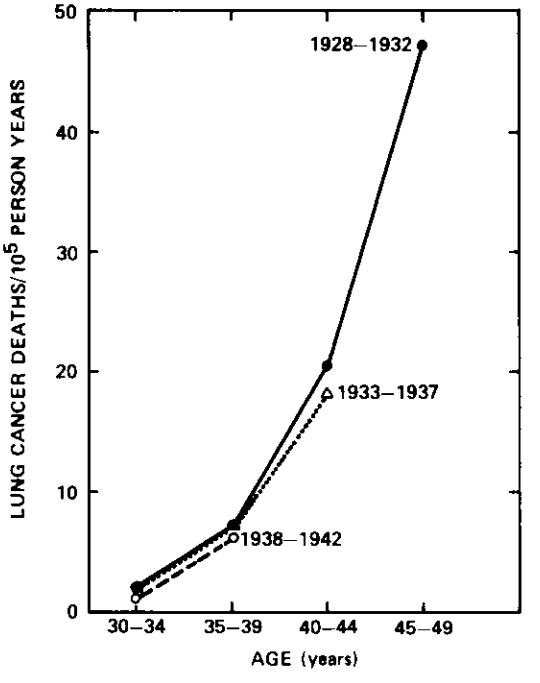

FIGURE 5. Age-specific lung cancer mortality rates in U.S. white male cohorts (*46*).

U.S. white males. Each successive birth cohort contains fewer men who started smoking, and among those who did, a higher proportion who smoked low tar cigarettes.

A different picture emerges for young women, whose smoking prevalence has increased within the past four decades. The increasing rates among young women shown in Figure 6 mark the start of an alarming rise in female lung cancers that will continue to manifest itself into the twenty-first century.

Equally alarming is the widespread use of smokeless tobacco by young men in the U.S. If not checked, this practice bodes an epidemic of oral cancer in the coming decades. Eliminating tobacco consumption is a major challenge in cancer prevention. In particular, all elementary and secondary schools should include programs on ways to cope with the peer pressures of tobacco use and on the health consequences of tobacco use.

Results from both experimental and epidemiological studies indicate that risk for cancers of the bowel and prostate may be amenable to manipulation by nutritional factors. However, the full picture needed for prevention has not yet emerged. The search for chemopreventive foods is a worthwhile approach, because the prescription of certain exposures is inherently more appealing than the proscription of others. Work at NYU and elsewhere on the anticarcinogenic effects of vitamin A and its precursors, of the protease inhibitors in seeds and certain beans (*34–37*), and of the allyl sulfides in onion and garlic oils (*38*) provide promising first steps in reducing risk for these and other cancers.

Our current ignorance of the ways to prevent cancers of the breast, bowel, and prostate mandates increased efforts to screen high risk populations (*39,40*). Information is needed to identify those for whom screening is most warranted, to determine cost-efficient screening schedules, and to devise incentives to ensure timely screening. Armed with this information, industrial firms could provide older employees with free or low-cost screening for cancers of the breast, cervix, colon, and skin. Those with computer-based records could remind employees when screening is due, and even offer monetary incentives for timely screening.

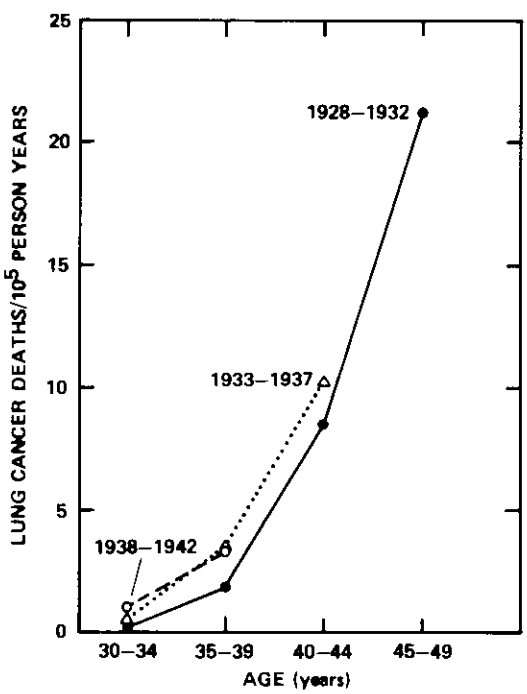

FIGURE 6. Age-specific lung cancer mortality rates in U.S. white female cohorts (*46*).

In conclusion, the past 40 years have seen substantial gains in knowledge of the cancer risks associated with tobacco, radiation, asbestos, and certain chemicals. However, we have been slow to put this knowledge to use in preventing cancers, particularly those associated with tobacco consumption. Increased efforts are needed to eliminate tobacco consumption and to encourage timely screening among high risk groups. Research is needed to find nutritional factors to prevent those malignancies that account for the bulk of cancers in the western world. Until laboratory tests can predict human risk more reliably, epidemiological monitoring of exposed populations is needed to protect against the unwitting introduction of new carcinogens into the environment.

This work is dedicated to Norton Nelson, whose encouragement, inspiration, and leadership have motivated my research. Work was supported by NIH grant CA 23214, and by a grant to SIMS from the Environmental Protection Agency.

REFERENCES

1. Doll, R., and Hill, A. B. Smoking and carcinoma of the lung. Br. Med. J. ii: 739 (1950).
2. Levin, M. L., Goldstein, H., and Gerhardt, P. R. Cancer and tobacco smoking. JAMA 143: 336–338 (1950).
3. Mills, C. A., and Porter, M. M. Tobacco-smoking habits and cancer of the mouth and respiratory system. Cancer Res. 10: 539–542 (1950).
4. Schrek, R., Baker, L. A., Ballard, G. P, and Dolgoff, S. Tobacco smoking as an etiologic factor in disease: Cancer. Cancer Res. 10: 49–58 (1950).
5. Wynder, E. L., and Graham, E. A. Tobacco smoking as a possible etiologic factor in bronchogenic carcinoma. JAMA 143: 329–336 (1950).
6. Van Duuren, B. L., and Goldschmidt, B. M. Cocarcinogenic and tumor-promoting agents in tobacco carcinogenesis. J. Natl. Can. Inst. 56: 1237–1242 (1976).
7. Gaffney, M., and Altshuler, B. Public health implications of carcinogenic exposure under the multistage model. Am. J. Epidemiol. 124: 1021–1030 (1986).
8. Peto, R. Epidemiology, multistage models, and short-term mutagenicity tests. In: Origins of Human Cancer, Book C, Human Risk Assessment, Vol. 4 (H. H. Hiatt and J. D. Watson, Eds.), Cold Spring Harbor Conferences on Cell Proliferation, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, 1977, pp. 1403–1428.
9. Whittemore, A. S. Effect of cigarette smoking in epidemiologic studies of lung cancer. Stat. Med., 7: 223–238 (1988).
10. Harley, N. H., and Pasternack, B. S. A model for predicting lung cancer risks induced by environmental levels of radon daughters. Health Phys. 40: 307–316 (1981).
11. Health Risks of Radon and Other Internally Deposited Alpha-Emitters. BEIR IV. National Academy Press, Washington, DC, 1988.
12. Peto, J. Comments on "Modelling the relative and absolute risks of radiation-induced cancers" by C. R. Muirhead and S. C. Darby

(J. R. Stat. Soc. A 150: 83-100, 1987). J. R. Stat. Soc. A 150: 104 (1987).
13. Darby, S. C., Nakashima, E., and Kato, H. A parallel analysis of cancer mortality among atomic bomb survivors and patients with ankylosing spondylitis given X-ray therapy. JNCI 75: 1-21 (1985).
14. Darby, S. C., Doll, R., Gill, S. K., and Smith, P. F. Long-term mortality after a single treatment course with X-rays in patients treated for ankylosing spondylitis. Br. J. Cancer 55: 179-190 (1987).
15. Shore, R. E., Albert, R., Reed, M., Harley, N., and Pasternack, B. Skin cancer incidence among children irradiated for ringworm of the scalp. Radiat. Res. 100: 192-204 (1984).
16. Land, C. D., Boice, J. D., Shore, R. E., Norman, J. E., and Tokunaga, M. Breast cancer risk from low-dose exposure to ionizing radiation: Results of parallel analysis of three exposed populations of women. J. Natl. Can. Inst. 65: 353-376 (1980).
17. Shore, R. E., Hildreth, N., Woodward, E., Dvoretsky, P., Hempelmann, L., and Pasternack, B. Breast cancer among women given X-ray therapy for acute post-partum mastitis. JNCI 77: 689-696 (1986).
18. Thomas, D. C., McNeill, K. G., and Dougherty, C. Estimates of lung cancer risks resulting from Rn progeny exposure. Health Phys. 49: 825-846 (1985).
19. Nero, A. V., Schwehr, M. B., Nazaroff, W. W., and Revzan, K. L. Distribution of airborne radon-222 concentrations. Science 234: 992-997 (1986).
20. Doll, R., and Peto, J. Effects on Health of Exposure of Asbestos. Health and Safety Commission. Her Majesty's Stationery Office, London, 1985.
21. Nelson, N. Cancer prevention: Environmental, industrial, and occupational factors. Cancer 47: 1065-1070 (1981).
22. Van Duuren, B. L., Goldschmidt, B. M., Katz, C., Langseth, L., Mercado, C., Sivak, A., and Zaldivar, R. α-Halo-ethers: A new type of alkylating carcinogen (abstr. 80). Am. Ind. Hyg. Assoc. J. 29 (suppl.): 110 (1968).
23. Van Duuren, B. L., Goldschmidt, B. M., and Seidman, I. Carcinogenic activity of dii- and trifunctional alpha-chloro ethers and of 1,4-dichlorobutene-2 in ICR/Ha Swiss mice. Cancer Res. 35: 2553-2557 (1975).
24. Kuschner, M., Laskin, S., Drew, R. T., Cappiello, V., and Nelson, N. Inhalation carcinogenicity of alpha halo ethers: 3. Lifetime and limited period inhalation studies with bis(chloromethyl)ether at 0.1 ppm. Arch. Environ. Health 30: 73-77 (1975).
25. Albert, R. E., Pasternack, B. S., Shore, R. E., Lippmann, M., Nelson, N., and Ferris, B. Mortality patterns among workers exposed to chloromethyl ethers. A preliminary report. Environ. Health Perspect. 11: 209-214 (1975).
26. Ames, B. N. Identifying environmental chemicals causing mutations and cancer. Science 204: 587-593 (1979).
27. Burns, F., Albert, R., Altshuler, B., and Morris, E. Approach to risk assessment for genotoxic carcinogens based on data from the mouse skin initiation-promotion model. Environ. Health Perspect. 50: 309-320 (1983).
28. Wogan, G. N. Markers of exposure to carcinogens. Environ. Health Perspect. 81: 9-17 (1989).
29. Ames, B. B., Magaw, R., and Gold, L. S. Ranking possible carcinogenic hazards. Science 236: 271-280 (1987).
30. Albert, R. E., Lewtas, J., Nesnow, S., Thorslung, T. W., and Anderson, E. Comparative potency method for cancer risk assessment: Applications to diesel particulate emissions. Risk Anal. 3: 101-107 (1983).
31. Fiskel, J. Toward a *de minimus* policy in risk regulation. J. Risk Anal. 5: 257-260 (1985).
32. Davis, D. L., Lilienfeld, A. D., Gittelsohn, A., and Scheckenbach, M. E. Increasing trends in some cancers in older Americans: Fact or artifact? Toxicol. Ind. Health 2: 127-144 (1986).
33. Doll, R. Relevance of epidemiology to policies for the prevention of cancer. J. Occup. Med. 23: 601-609 (1981).
34. Belman, S., Rossman, T., and Troll, W. Inhibition of initiation by the protease inhibitors, antipain and leupeptin (abstr.). Proc. Am. Assoc. Cancer Res. 18: 32 (1977).
35. Troll, W., Wiesner, R., Shellabarger, C., Holtzman, S., and Stone, J. O. Soybean diet lowers breast tumor incidence in irradiated rats. Carcinogenesis 1: 469-472 (1980).
36. Yavelow, J., Gidlund, M., and Troll, W. Protease inhibitors from processed legumes effectively inhibit superoxide generation in response to TPA. Carcinogenesis 3: 135-138 (1982).
37. Troll, W., Fraenkel, K., and Wiesner, R. Protease inhibitors as anticarcinogens. JNCI 73: 1245-1250 (1984).
38. Belman, S. Onion and garlic oils inhibit tumor promotion. Carcinogenesis 4: 1063-1065 (1983).
39. Dubin, N. Effect of different mammographic radiation exposures on predicted benefits of screening for breast cancer. Stat. Med. 1: 14-24 (1982).
40. 1986 Cancer Facts and Figures. American Cancer Society, New York, 1987.
41. IARC Monographs. Chemicals and Industrial Processes Associated with Cancer in Humans, Vols. 1-20. International Agency for Research on Cancer, Lyon, France, 1972-1979.
42. Doll, R., and Peto, R. Cigarette smoking and bronchial carcinoma among regular smokers and lifelong nonsmokers. J. Epidemiol. Commun. Health 32: 303-313 (1978).
43. Doll, R. The age distribution of cancer: Implications for models of carcinogenesis. J. R. Soc. A. 134: 133-166 (1971).
44. Kristein, M. M. Forty Years of U.S. cigarette smoking and heart disease and cancer mortality rates. J. Chron. Dis. 37: 317-323 (1984).
45. Silverberg, E. Cancer statistics. CA-A 35: 1935 (1985).
46. Vital Statistics of the US 1960-1979, Vol. II—Mortality, Part A. National Center for Health Statistics, Hyattsville, MD, 1984.