Primary Prevention of Cancer: Needs and Opportunities for Research

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Strategies for cancer prevention generally come from observational epidemiology and must include monitoring for the effects of the actions. The measurement-iterative loop allows us to refine our approach to cancer prevention. When available, clinical trials can also provide strategies for control. Exposure-specific strategies are described; these are such things as health promotion and behavior modification, legislative approaches, treatment for addiction, changes in the food supply, chemoprevention, occupational and environmental regulation, immunization, identification of persons with enhanced genetic susceptibility, and improved surveillance systems. For some exposures such as tobacco, zero exposure is the goal. For others, prudent avoidance or exposures as low as reasonably achievable are appropriate approaches. Research on how to impact deeply ingrained lifestyle and cultural factors has high priority. — Environ Health Perspect 103(Suppl 8):313–317 (1995)

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Introduction

In his introductory remarks to this conference, Dr. Samuel Broder indicated that we need clinical trials to guide us in our strategies for action. It is clear, however, that we cannot expect to have clinical trial data to guide us in all our approaches to the prevention of cancer. We need to combine data from observational epidemiology with monitoring of the effect of our actions—the measurement-iterative loop (Figure 1). This approach will enable us to take corrective actions when necessary to refine our approach to cancer prevention.

Tobacco

Tobacco carcinogenesis is well accepted. Except for a few cancers, we must concentrate our efforts on control by a combination of health promotion and legislative approaches; approaches must be taken in concert with approaches to the control of cardiovascular and chronic respiratory diseases and improved maternal and child health. Our recent experience in Canada, however, indicates how disease prevention may clash with political realities. The smuggling issue, which clashes with aboriginal interests, commercial and political realities, may yet turn to our long-term advantage, however. Smoking has become socially unacceptable in the dominant culture, and trends are in motion that seem inevitable, although, as Dr. Ernst Wynder emphasized (1), we still need to better understand the sociological determinants of smoking (a major research requirement, especially among children and adolescents), and how we can effectively intervene.

Additional research is still required into the determinants of quitting smoking, and how this may be accelerated in the general population by public health approaches that are realistic within the present financial climate.

Dr. Tracy Orleans emphasized the approaches to treatment of nicotine addiction (2). She urged mandating such treatment as part of health care reform. Treatment of nicotine addiction is efficacious, but data supporting this as a public health rather than a clinical therapy approach are not available nor are data on how to prevent addiction. Previous experience suggests that clinical approaches are unlikely to be fully effective at the general population level because of impediments to access, both psychological and financial, many of those we might wish to treat. Research into public health approaches is urgently required. How can the experience in the clinical setting be made generally applicable? Dr. Orleans also urged increasing the excise tax on tobacco (2). The problem in Canada arose because of the lower tobacco taxation levels in the United States than in Canada. We need to develop a North American, North American Free Trade Agreement, and, preferably, world-wide approach to tobacco control. This is a public health policy research issue.

Alcohol

There clearly is a high priority to resolve the extent that breast cancer is induced by alcohol, as well as the chemical constituents or types of alcoholic beverages that increase risk. However, for women as well as men, moderate drinking (usually defined as the amount of 1 drink!) appears to have no adverse effect on life expectancy. Nevertheless, we do not know how we can advocate no more than 2 drinks a day (or 14 per week) without risking increasing the adverse effects in a minority of all populations (the incipient and actual alcohol abusers), that has been well demonstrated to be unusually susceptible to any action that increases the availability or social acceptability of alcohol drinking.
Once again, we need research on the means to influence beneficially the determinants of heavy drinking, which takes us back, as for tobacco addiction, to the wider social environment.

**Diet and Nutrition**

Like tobacco, diet is a determinant of other chronic diseases, and our prevention strategies must be congruent with those adopted for them, especially Heart Health initiatives. Further, as Dr. Peter Greenwald reminded us, we need to recognize the nature of our changing food supply both in terms of where natural foods are produced and to what they are exposed during their production and in terms of the increasing availability of manufactured foods. The latter often involve substitutions or fortification with substances for which there may be some nutritional justification but that may, in fact, eliminate protective factors in natural foods or introduce new, unexpected hazards.

A major issue, not explicitly discussed here, is whether we should concentrate on etiologic research or whether we can, at least in part, shift to prevention research and application. Both types of research would be facilitated by establishing nutritional centers with mandates to increase knowledge on diet and cancer (and other chronic diseases) and to make acceptable interventions in the population. Many expert groups feel that there is no alternative but to attempt to apply what is now known about cancer prevention and that at least part of the prevention research agenda in this field must be at the general population level. If this is indeed true, then we must conclude, as for alcohol and tobacco, that the major public health research need is to determine how to encourage dietary modification in the direction almost uniformly agreed upon—that fruit and vegetable consumption should be increased and excess energy intake discouraged—and to promote a research strategy that Dr. Lenore Kohlmeier called the need for research into food-based intervention in communities (3). I personally still feel that the overall evidence for diet and cancer encourages substituting of saturated and polyunsaturated by monounsaturated fat. Both are clearly compatible with Heart Health initiatives.

However, cancer prevention research in the diet area is already under way in the clinical trial mode. Such research implicitly recognizes that the time relationships for cancer prevention may be different from those of cancer prevention. Dr. Kenneth Carroll many years ago produced evidence that fat reduction at a later stage of carcinogenesis reduces mammary cancer incidence in rats; we need to determine whether interventions achieve the same results in humans, by continuing with the Women’s Health Initiative, and also extending it to men. But I feel that such approaches need to be combined with community interventions, especially at young ages, that combine dietary modification with promoting physical activity and use the measurement-iterative loop approach as part of the strategy. If physical activity truly confounds the international correlations of dietary fat with breast and colon cancer, then we should take advantage of this in our interventions.

**Hormones and Medications**

The area of hormones and medications is one in which there are likely to be trade-offs between the adverse effects of cancer and overall health benefits. For those circumstances in which hormone use reduces cancer risk (e.g., combined oral contraceptives and endometrial and ovarian cancer), the benefits clearly outweigh the risks, even with increases in breast and liver cancer, except possibly for heavy cigarette smokers. But for estrogen replacement therapy, we have incomplete evidence, especially with regard to lifelong risks and benefits for noncancer conditions such as those related to bone and cardiovascular disease, particularly when estrogens are combined with progestins. As Dr. Malcolm Pike emphasized, women must be sufficiently informed to make their decisions. There is a problem related to the nature of the information currently given, however, especially by some professional groups such as gynecologists. An important prevention research issue, therefore, is to develop better mechanisms to understand the overall risks and benefits.

A prevention trial is under way—the tamoxifen trial—that asks a valid question that will give us information on etiology, but will not necessarily result in a viable public health intervention. The Women’s Health Initiative will also produce relevant data, although Dr. Barbara Hulka has reservations about the power of this study to be fully informative in this area (4). Not discussed was a similar trial of finasteride, an inhibitor of the enzyme that converts testosterone to dihydrotestosterone, the principal androgen responsible for normal and hyperplastic growth of the prostate gland. The drug has already been found to relieve symptoms of benign adenomatous hyperplasia of the prostate (BAHP) and to shrink the prostate gland. A prevention trial of 18,000 men, given either finasteride or a placebo for 7 years and followed for life, is planned by the National Cancer Institute (NCI). Given the possible benefit for BAHP, this could, in practice, have wider application than tamoxifen among women.

Medications that could induce cancer, as Dr. Paul Stolley emphasized, may be difficult to evaluate as to their carcinogenicity because of the impossibility of detecting carcinogenic effects in premarketing trials and the difficulties associated with monitoring for carcinogenic effects in postmarketing surveillance. Risk-versus-benefit considerations are important with regard to anticancer drugs, especially as related to long-term effects in children. For other agents for which long-term follow-up may not be conducted, drug plans in health maintenance organizations (and in Canada, in Saskatchewan) need to be more effectively utilized to answer some of the unresolved questions. There are also indications that some medications such as aspirin may reduce cancer risk (e.g., of the colon). Given the wide utilization of this drug and its potential utility in reducing cardiovascular disease events, it is important to use the available monitoring mechanisms to attempt to shed light on this issue.

**Occupational Exposures**

It clearly is important to reduce carcinogenic exposures in occupational environments. However, recent experience with occupational electromagnetic fields (EMF) associations suggests caution in extrapolating from the occupational to the general environment. Further, we need to bear in mind both dose and duration of exposure when comparing or combining results of different studies.

One question to be addressed is the extent to which the identification and control of occupational carcinogens has reduced risk sufficiently and if there are important risks still to be identified. For example, the risks of lung cancer among asbestos-exposed workers appears to be diminishing. The long duration of the effects of occupational exposures (sometimes into the retirement years) must be born in mind in making this assessment. However, there still are likely to be risks to be identified, particularly from complex mixtures of exposures.
Prevention of the effects of specific agents, as in agriculture, is at least in part dependent on increased understanding of the ways individuals can reduce their exposures. Once again, we must learn how to increase understanding on the extent that exposure can be reduced; this appears to be another field for behavioral research. Hazard surveillance activities, therefore, are still important but must be linked to research and information dissemination. We must increase surveillance of documented cohorts using linkage to cancer registries and the National Death Index for end points. Large-scale surveys linked to industrial hygiene measurements may help clarify the extent to which we have been successful in reducing exposures, as well as provide an important database for surveillance and monitoring in the future.

Other considerations relate to determining when information is sufficient to justify reduction in exposure. The tendency to reduce exposure even when carcinogenicity has not been established can be applauded, providing substituting other potential carcinogens is avoided and there are no other adverse economic and potentially health-limiting consequences.

**General Environmental Exposures**

It appears clear that we need to clean up our environment for reasons other than cancer risk. The methodology to determine the adverse health effects of environmental exposures is not well developed, however, so it might be wise to use less evidence to justify preventive actions. This makes it critical to use the measurement-iterative loop philosophy to evaluate the appropriateness of any actions taken. Monitoring should be adapted to environmental considerations, with linkages to databases, to determine the effects of population interventions.

Human exposure to environmental pollutants occurs through air, water, and the food chain. It is not clear how many of these pollutants are carcinogens, as many chemicals have not been fully tested for carcinogenicity. The public tends to support actions taken to produce cleaner air, purer water, and noncontaminated food. Whether recent improvements can be sustained under the present economic circumstances is uncertain, however. Better information through careful analysis of past trends may help to reinforce continued, if not expanded, control efforts. The meta-analysis presented by Dr. Robert Morris (5) suggests that chlorination of raw water has an impact on bladder cancer and rectal cancer risk. Chlorination of the water supply probably still has an overall beneficial health effect in spite of the risk of cancer. Research into equally effective and inexpensive means of securing the same ends is desirable.

The general distribution of exposures in the environment and the apparent random occurrence of cancer, possibly because of these exposures, creates severe difficulties for prevention research. Use of molecular biology advances to permit identification of persons particularly susceptible to these contaminants together with markers of exposure may help to identify subpopulations suitable for research that may clarify the need for intervention.

Dr. Hoda Anton-Culver issued a call for the conversion of existing cancer registries with a multiethnic base population to Cancer Prevention Research Registries (CPRR) (6). Many cancer registries already go some way toward performing this function. Whether they need to incorporate data on exposure and host factors as she suggested, however, is questionable. Linkage with existing databases (providing identification data are available) may serve the same purpose and cost less. A major problem encountered in building up registries with extensive baseline information is the difficulty in securing the required data in an unbiased way, the possibility that some variables could be linked to the cancer state rather than to etiologic factors, and confidentiality issues that arise at the time of diagnosis of the cancer. Methodology development for large-scale data monitoring for cancer prevention purposes is required. One approach suggested is routine sampling of the at-risk base cohort of the cancer registry for (exposure to) relevant exposures. Other information systems that may already be available, or may be developed as part of health care reform, should also be explored for cancer surveillance and prevention purposes.

**Radiation**

The range of radiation to which humans are exposed is very wide, from the ionizing radiations known to cause cancer to the nonionizing electrical and magnetic fields associated with electric power where there is suspicion of but insufficient biological data to confirm cancer risk.

Medical radiation may account for about 1% of cancer deaths, whereas occupational exposure contributes very little to the total cancer burden. Indoor radon exposure, especially for nonsmokers, is a major research issue. For smokers, interaction of radon with tobacco carcinogens is likely. Also an issue may be toxic waste sites and waste from nuclear reactors.

In the area of radiological protection, animal experiments are poor guides to human risk, so radioepidemiology is critical. Dose and age at first exposure are important for some sites. There is some evidence from miners that dose rate for radon exposure may be important, with reduced risk per unit of exposure with high exposure. Arsenic exposure in some mines may increase risk of lung cancer. Study of the Chernobyl survivors, as well as other exposed populations, is still needed to place risks into better perspective for the public.

Ultraviolet radiation exposure causes skin cancer; intense exposure in early life in genetically predisposed individuals is critical, especially for malignant melanoma. Change in behavior, rather than a decline in ozone, is the principal determinant of increases in exposure and skin cancer. Whether it is possible to reverse this trend is unclear. It is urgent to clarify the role of using sunscreens versus sun avoidance as effective and safe public health strategies. For monitoring purposes, improved efficiency in registration of cancer cases is recommended, preferably to include some means of registering nonmelanoma skin cancers, for which estimates currently are very imprecise.

The data on electrical and magnetic fields do not currently justify research on prevention. Etiologic studies are under way, however, and the situation may change within the next few years.

**Infectious Agents**

In the absence of effective immunization, reduction in the effect of oncogenic viruses requires modification of human behavior, an approach that may encounter even greater difficulties than tobacco and diet, since many viruses (e.g., human papilloma virus, human immunodeficiency virus, hepatitis B virus [HBV]) are transported by sexual reproductive factors in early-life events. HBV vaccination is expected to reduce liver cancer, while interaction with aflatoxin suggests earlier benefit might accrue from reducing such exposures in foods. Similar interactions with other environmental carcinogens associated with lifestyle (Epstein-Barr virus and nasopharyngeal carcinoma and putrefied foods) require intervention studies.

Research on immunization, if suitable products become available, must incorporate
adequate monitoring for adverse effects, a process that may require changing current attitudes of at-risk communities toward anonymity.

Of the bacterial agents, only Helicobacter pylori appears to be a potential cause of cancer of the stomach, although large bowel flora may be part of the causal chain in the development of colon cancer. On the assumption that treating H. pylori infection with antibiotics would reduce the risk of stomach cancer by 30%, the cost effectiveness of such an approach seems high. Dr. Julie Parsonnet suggests the cost to be $70,000 per year of life gained compared with $5,000 for mammography and breast cancer. Clearly, more definitive etiologic data are required before screening for infection and treatment will be justifiable in North America.

**Gender, Ethnicity, and Environment**

Sociocultural evaluation of cultural differences that have an impact on acceptance of cancer prevention interventions requires further emphasis. Poverty and lifestyle are likely to be more important than ethnicity, although genetic differences may be involved and should not be overlooked. Indeed, they may be emphasized further by the identification of differing genetically related susceptibilities to carcinogen-metabolizing enzymes that may well vary by ethnicity. The environment, both social and physical, may have an adverse impact on the effectiveness of prevention.

Although, in general, we know as much about cancer prevention in women as in men, there are obvious gaps in our knowledge such as cancer risk among white women in certain occupations and minorities in most circumstances. Small numbers of subjects and thus of cancers may pose difficulties for epidemiologic studies that require multicenter studies, or special analyses of subgroups in many studies followed by pooled analysis.

Some lifestyle factors recognized as relevant in cancer prevention (e.g., dietary habit and nonsmoking) may be more prevalent among certain minority populations than in the population in general. There is a need to reinforce such behaviors in these minority populations and extend them to the general population.

**Genetic Susceptibilities and Environmental Interactions**

Genetic–environmental interactions are important in cancer etiology and must be considered in cancer prevention. It seems likely that all cancers have a genetic basis, although few of these appear to be transmitted in ways to increase cancer risk (i.e., to induce hereditary cancer). In terms of the genetic changes that underly cancer induction by environmental factors, there may be relatively few critical oncogenes and tumor suppressor genes, so hope is increasing for cancer therapy and for identification of markers for early detection, although it is not yet clear whether they actually have a role in cancer prevention.

\( \text{p53} \) (the most important of the tumor suppressor genes so far identified) may be relevant in 50% of human cancers. Inherited abnormalities of \( \text{p53} \) have been identified in a few families with increased risk of breast cancer, although \( \text{p53} \) does not seem to have a major role in breast cancer (abnormalities of \( \text{p53} \) are detectable only in about 30% of breast cancer cases). It is now clear that discrete mutations of \( \text{p53} \) can be induced by exogenous factors (e.g., carcinogens such as aflatoxin, cigarette smoke, radon, and vinyl chloride) as well as by endogenous factors.

For inherited genetic factors, we must remember that the inherited genes are just the first hit. The second hit, the process that starts carcinogenesis, comes from environmental factors. Identifying these factors will probably be facilitated by being able to identify those women and men at increased risk in the population, particularly those in families that appear to be transmitting particular genetic changes.

Genetic research raises the likelihood that some day we will be able to identify persons who are particularly susceptible to the effects of environmental carcinogens. Whether such susceptibility will be shown to be largely inherited or in most instances acquired is quite uncertain at present even though the acquired susceptibilities are shown to have a genetic basis. The susceptibilities so far identified are largely related to differences between individuals in the metabolism of carcinogens. These appear to be particularly important in increasing risk in those experiencing low levels of exposure to the carcinogens. Combinations of genes that influence metabolism are likely to be shown to be most important.

Genetic screening raises many concerns. Although those potentially at risk who are found to be negative to the genetic marker tested will be reassured, there may be concern about false reassurance if the test is not 100% specific (and, so far, no screening test has this attribute). There also are legitimate concerns about the effects of labeling, especially if eradication of the risk of a relevant cancer cannot be guaranteed. Thus, genetic screening can only be justified as part of a defined research protocol, and only when both costs and benefits are evaluated. Such protocols initially must concentrate on those identified to be at high risk through nongenetic means. We eventually will have to face whether to extend such research into that important segment of the population that currently is not regarded to be at high risk but in whom currently the majority of cancers occur.

**Avoidable Cancers Based on Current Knowledge**

We must quantify the size of the problem, assess results of interventions, and maintain high-quality surveillance systems. Poverty (lack of education) can be regarded as a carcinogen, although it is not always advantageous to be rich. Dispersal theory recognizes that some habits are taken up first by the rich and then by the poor, as exhibited by the changing social class risks for lung cancer and the diet-associated cancers.

The list of avoidable cancers is long, headed by lung but closely followed by the other tobacco-associated cancers (oropharynx, larynx, esophagus, pancreas, bladder, kidney, and perhaps, cervix) and the diet-associated cancers (breast, colon, prostate, stomach, rectum, and pancreas, as well as lung and bladder). The overlap between these lists emphasizes both the interaction between different factors and the fact that the proportion of cancer attributable, and even more so the proportion attributable to individual factors, is controversial, although we have to bear in mind the time it takes to have full impact on the population. However, if the cancers caused by alcohol and known occupational hazards and sunlight are added, it seems clear that current knowledge theoretically permits avoidance of over 50% of our current cancer burden, if not more.

If it is preventable, why is it not prevented? The major gap in our knowledge is not about causes of cancer on which we can intervene now but the difficulty in achieving any impact on deeply ingrained lifestyle and cultural factors. Research into this area, as identified above, has very high priority for a number of factors.

**Needs for the Future**

For cancer prevention, a cautionary principle is in order: “Try not to do things that have unwelcome consequences. We do not
want to be wrong too far in the wrong direction," i.e., prudent avoidance. For ionizing radiation, the as low as reasonably achievable (ALARA) principle is well accepted. For tobacco smoking, zero exposure is the legitimate goal, but for many other known or suspect carcinogens, the ALARA principle may be the only appropriate, if not acceptable, approach.

We need new tools for exposure assessment, new approaches for studying complex mixtures, improved surveillance methods, and more qualified investigators who are able to combine biology with epidemiology in a collaborative multidisciplinary mode. However, the main need at present is to evaluate the success of what is being done, and in accordance with the measurement-iterative loop principle, increase the effectiveness and efficiency of the interventions that are applied to the general population.

Government has a role, and it is important to ensure consistency of policies, which clearly is not the case for tobacco, and possibly not for diet and other factors. This is partly a need for public health policy research, but also partly a function of effective leadership at the highest and at the cabinet levels. If government really wishes to promote human health, it should demonstrate to the public that it is serious, and carefully evaluate the health consequences of all government actions as well as the economic consequences. If economic factors predominate, the government should make this clear; if political, as in the tobacco taxation issue, this should also be made explicit. Then the public will be able to decide whether their representatives are carrying out their mandate in accordance with their wishes and act accordingly.

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