



## ***Division of Extramural Activities***

### **Report of the National Cancer Institute Cancer Prevention Program Review Group**

June 3, 1997

#### **TABLE OF CONTENTS:**

- Executive Summary  
Recommendations  
Modifiable Risk Factors  
Animal Models and Extrapolation to Human Cancer Prevention  
Genetic Predispositions to Cancers and Detection of Precursor Lesions  
Chemoprevention Trials in Human Populations  
Behavioral Research and Behavioral Interventions Trials in Prevention  
Training of Health Professionals with Expertise in Prevention Research  
Organization and Infrastructure of the NCI Prevention Division

#### **CHAPTERS:**

- Introduction  
Goals of the National Cancer Program and the Role of Prevention  
Definition of Prevention  
Human Populations in Prevention Research  
NCI Cancer Prevention Program and Budget  
Intramural Component  
Organization and Infrastructure of the NCI Prevention Division  
Extramural Component  
Focus on the Division of Cancer Prevention and Control  
Inclusion of Prevention and Control Research within a Single Division  
Charge to the Review Group  
Process of the Review Group
- Modifiable Risk Factors  
Introduction  
The Need to Better Achieve Tobacco Avoidance  
Understanding the Basic Biology of Cancer and Diet and Nutrition  
Needed Diet/Nutrition and Cancer Research  
Physical Activity and Cancer Risk  
Alcohol Consumption and Cancer Risk  
Occupational and Environmental Carcinogens  
Infections Agents and Cancer Risk  
Recommendations  
-Tobacco Exposure  
-Diet and Nutrition  
-Physical Activity

-Infectious Agents

- Animal Models and Extrapolation to Human Cancer Prevention
  - Introduction
  - Efficacy of Animal Models in Diet/Nutrition, Tobacco, Alcohol, and Physical Activity Studies
  - Animal Models as Tools for the Evaluation of Potential Chemopreventive Agents
  - Animal Models for Metabolism and Pharmacokinetic Studies
  - Animal Models for Development and Validation of Intermediate Biomarkers
  - Recommendations
- Genetic Predisposition to Cancer and Detection of Precursor Lesions
  - Introduction
  - Identification of High-Risk Populations
    - Populations with a Hereditary Predisposition to Cancer
    - Persons at Risk Due to Occupational or Environmental Exposures
    - Persons with Premalignant Lesions
    - Patients Successfully Treated with First Malignancy
  - Biomarkers as Predictors of Disease
  - Current Status of Molecular Markers
  - Feasibility
  - Technology
  - Funding Mechanisms
  - Recommendations
- Chemoprevention Trials in Human Populations
  - Introduction
  - The Clinical Trials Process
  - Preclinical Development and Selection of Candidate Agents for Human Trials
    - Populations to be Studied in Chemoprevention Trials
    - Methodological Considerations
    - Cancer Prevention Trials Group
    - Prevention Trials Committee for Biological Studies
  - Recommendations
- Behavioral Research and Behavioral Interventions Trials in Cancer Prevention
  - Introduction
  - Behavioral Interventions
  - Components of a Behavioral Research Program in Prevention
    - Epidemiology Foundations
    - Expertise in Measurement and Evaluation
    - Access to National Data on Key Behaviors
    - Knowledge of Theories of Behavior
    - Understanding of Behavior and Behavior Change

- Expertise in Cancer Risk Communication
- Strength in Intervention Design
- Expertise in Economics and Cost-effectiveness
- Mechanisms for Dissemination

Trans-NCI and NIH Collaborations and Initiatives  
Specialized Training in Behavioral Science  
Infrastructure  
Recommendations

- Training of Health Professionals with Expertise in Prevention Research
  - Introduction
  - Intramural Training Program
  - Extramural Fellowship Training Program
  - Non-Federal Sources of Support
  - Relevance of Training to Current Research
  - Recommendations
- Training of Health Professionals with Expertise in Prevention Research
  - Cancer Prevention Research Within NCI
  - Organization of DCPC
  - Create a Separate Prevention Division
  - Strengthen the External Function of the Prevention Division
  - Create a Separate Prevention Division
  - Emphasize Behavioral Research
  - Relocate the Community Clinical Oncology Program (CCOP)
  - Improve Research Efforts in Diet/Nutrition, Tobacco, Alcohol, Physical Activity, and Infectious Agents
  - Form a Chemoprevention and a Prevention Trials Group
  - Increase the Role of the Prevention Division in Training
  - Enhance Data Bases to Facilitate Cancer Prevention Research
  - Interact with Other Federal and Nonfederal Agencies
  - Recommendations

#### **APPENDICES:**

- Meetings of the Review Group and Acknowledgments

#### **Executive Summary**

More than 2 million new cancer cases will be diagnosed in 1997. One in every four deaths in the United States--approximately 550,000 individuals per year--is the result of cancer. An overall increase of 18 percent in cancer incidence and an elevation in the mortality rate of about 7 percent occurred between 1971 and 1993 (*Cancer at a Crossroads: A Report to Congress for the Nation*. National Cancer Advisory Board, 1994) despite the "War on Cancer." However, recent statistics have shown an encouraging decrease in cancer mortality, suggesting that the battle against cancer may be taking a favorable turn. This reduction is probably the result of many factors, including enhanced early detection (e.g., increased use of mammography in the diagnosis of breast cancer), and earlier, more aggressive

treatment of breast, colorectal, prostate and other cancers, although much room remains for improvement. Prevention efforts also have played an important role in the decrease in the proportion of Americans who smoke, especially adult males, and in reducing exposures to other known carcinogenic substances.

The Review Group on Cancer Prevention Research was appointed in 1996 by the National Cancer Institute (NCI) Director and the Chair of the NCI Board of Scientific Advisors. The Review Group was asked to consider how best to utilize the significant, albeit limited, resources and personnel of NCI in developing and sustaining a cancer prevention research program.

This review comes at an opportune time. There has been a growing appreciation of the role of prevention in controlling cancer. For example, the avoidance of cigarette smoking and of use of other tobacco products could reduce the incidence of lung cancer by 80 percent and significantly reduce the incidence of many other cancers (e.g., pancreas, kidney, head and neck). The adoption of diets that contain lower fat and increased fruits and vegetables could diminish the incidence of cancers of the colon and of other sites. And approximately 90 percent of skin cancers could be avoided through the adoption of various protective measures against the toxic rays of the sun.

The NCI Cancer Prevention Program Review Group strongly believes that prevention must be a principal component of the National Cancer Program if the cancer burden is to be reduced. A century-long experience with public health measures has shown that the prevention of disease is ultimately far more effective in reducing morbidity and mortality than is the treatment of already diagnosed disease. As such, it is apparent to the Review Group that over the next generation far greater reductions in cancer mortality will come from prevention than from the various treatments that are currently available or will be available in the coming years. In spite of this, a much smaller proportion of the NCI budget is committed to prevention than to various forms of treatment. Prevention must be well-represented in the programs of NCI, both intramurally and extramurally, and must have an appropriate budget. Furthermore, prevention, like all other elements of the National Cancer Program, must be founded upon excellent science, which originates from both the intramural and extramural research communities. It is through the application of excellent basic, clinical, and population-based research that effective preventive interventions can be mounted.

Because of its prime importance to the central objectives of the National Cancer Program, it is imperative that NCI's prevention efforts have outstanding leadership that will develop a creative, discovery-based, and assertive prevention research program and will utilize the strengths of both the intramural and extramural communities. Senior administrators of the prevention division also must work effectively with the NCI leadership in formulating this program.

The major responsibility for the NCI cancer prevention program lies within the

Division of Cancer Prevention and Control (DCPC). Consequently, much of the activity of the Review Group centered on an analysis of this division's role in establishing the NCI cancer prevention agenda, providing the necessary leadership, representing the research interests of cancer prevention, and serving as effective spokespersons for the intramural and extramural research communities.

After receiving oral and written testimony and conducting interviews with intramural and extramural scientists, the Review Group perceived: a) the need for a better delineated, scientifically sound, long-term strategy for directing cancer prevention research into the next century; b) a need for additional outstanding scientists in leadership roles within DCPC; and c) the need for all other NCI divisions to focus greater attention on research toward the prevention of human cancers.

The Review Group briefly considered the appropriateness of including cancer prevention and control within a single organizational unit, as currently exists within DCPC. Because of a lack of sufficient data and the existence of another NCI review group which has the responsibility for evaluating cancer control efforts, the separation of these research functions was not considered further. Nevertheless, the Review Group believes that either the inclusion of cancer prevention and control within a single unit or the separation of these research functions would be compatible with pursuing the goals of NCI. In this report, the Review Group uses the phrase "prevention division" to describe an administrative unit that has the responsibility for directing and managing the NCI cancer prevention research agenda.

*The Review Group considered the focus of cancer control to be on persons with clinically overt cancers, while that of cancer prevention to be directed at apparently healthy populations, including those at high risk and/or those with detectable precancerous lesions. Nevertheless, prevention, which develops basic scientific principles and control, which applies these principles, must be linked in some fashion to provide a continuum from bench to population.*

[top](#)

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## **Recommendations**

The Review Group offers a number of specific recommendations about management and organizational structure and about research opportunities. The Review Group organized its deliberations and recommendations around the following topics, which appear as separate sections of this report: modifiable risk factors; animal models and extrapolation to human cancer prevention; genetic predispositions to cancers and detection of precursor lesions; chemoprevention trials in human populations; behavioral research and behavioral intervention trials in the cancer prevention program; training of health professionals with expertise in prevention research; and organization and infrastructure of the prevention division.

This report is submitted to the Board of Scientific Advisors and the National Cancer

Advisory Board for its consideration. The recommendations are aimed at improving the health of Americans through a comprehensive cancer prevention research program.

[top](#)

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### **Modifiable Risk Factors**

- Increase the investment in developing effective interventions for prevention and cessation of tobacco use, particularly in populations where tobacco use has remained high, e.g., adolescents, women, and those with less education and income.
- Increase the proportion of the tobacco control investment in basic research (including behavioral research) and in the development of effective interventions, and decrease the investment in large-scale dissemination efforts, e.g., ASSIST.
- Identify respected senior scientists to assume major leadership roles within the prevention division for the development and coordination of the tobacco avoidance, diet/nutrition, and cancer prevention research agendas.
- Encourage methodologic research to clarify the most promising research designs and strategies for diet and cancer prevention research, and to streamline the conduct of dietary intervention trials.
- Encourage research to identify biomarkers of the consumption of key dietary components, particularly micro- and macronutrients and to develop objective markers of short- and long-term physical activity.
- Increase the investment in research aimed at understanding the biological mechanisms underlying putative associations between diet and cancer incidence, particularly concerning fruits and vegetables, fats, and total energy consumption, as well as determining the mechanisms whereby physical activity may reduce cancer risk.
- Develop an orderly process for the formulation and testing of dietary behavioral trials of hypothesized healthful eating patterns.
- Support intervention trials aimed at identifying behavioral strategies to enhance physical activity and to assess the impact of such enhancement on cancer risk factors.
- Emphasize basic and applied studies on the role of viruses and *Helicobacter pylori*, as factors or cofactors in the etiology of certain cancers, and initiate research on and development of appropriate vaccines.

[top](#)

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### **Animal Models and Extrapolation to Human Cancer Prevention**

- Continue to develop new in vitro and in vivo models for identifying and assessing the efficacy of chemopreventive agents that integrate present knowledge of genetic and molecular alterations involved in human carcinogenesis.

- Develop intermediate biomarkers for assessment of exposure and biological effects applicable in prevention studies and validate their use in parallel studies in animals and humans.

[top](#)

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## **Genetic Predispositions to Cancers and Detection of Precursor Lesions**

- Expand identification of high-risk healthy populations based on genetic predispositions and the development of new molecular markers.
- Investigate diverse non-genetic factors influencing the expression of genetic predisposition and the response to interventions, including the contribution of environmental exposures (radiation, exogenous and endogenous chemicals, bacteria and viruses).
- Develop new molecular markers for the early detection of cancer.
- Develop and expand existing biorepositories and provide new access with appropriate consent to such materials for the testing of new molecular detection strategies.
- Develop and improve new high throughput technologies for implementation of promising molecular diagnostic approaches in clinical and population-based trials.
- Perform comprehensive trials in targeted high-risk populations for validation and potential integration of novel prevention and detection strategies.

[top](#)

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## **Chemoprevention Trials in Human Populations**

- Ensure the conduct of randomized trials in human populations as the gold standard for scientifically demonstrating ways to reduce cancer incidence. Ensure the existence of a well-defined process of decision-making about target organ sites, appropriate populations, credible endpoints, and candidate chemoprevention agents for human trials. Large-scale studies should be preceded by extensive preclinical studies, epidemiological analyses, and toxicity assessment in humans.
- Design recruitment strategies to attract healthy people as participants in cancer prevention trials. High-risk but otherwise healthy people are identified as the following: individuals with predisposing genetic traits or a positive family history of cancer; persons engaging in high-risk behaviors; individuals with high exposures to occupational and environmental carcinogens and cancer-associated infections; and the elderly.
- Restructure the chemoprevention preclinical drug development effort.

**a)** Form an advisory committee as a subset of the NCI Board of Scientific Advisors, supplemented with other outstanding extramural basic scientists, clinical investigators, molecular epidemiologists, and

staff of NCI and the Food and Drug Administration. Mandate the committee to define the drug discovery program, stimulate creative approaches in the development and use of new animal model systems, evaluate candidate chemopreventive agents for cellular and animal screening tests, assess the evidence of efficacy and safety from animal studies, and set guidelines for selecting agents for human trials.

**b)** Continue to upgrade the in vivo animal systems for screening of efficacy and safety of chemopreventive agents through the use of the RO1 grant mechanisms in addition to the present contract mechanisms.

**c)** Continue to use the master agreement contract mechanism for routine pre-clinical toxicological testing and for routine screening for chemopreventive efficacy. However, there should be frequent, open, re-competition with clear opportunities for developers of new assay systems to also become master agreement contractors.

**d)** Develop and validate biomarkers and intermediate endpoints in concert with those being developed and assessed in humans.

- Restructure the NCI prevention division's program for Phase I, II, and III trials to reflect a stronger extramural component by establishing one multimodality cancer prevention trials group (patterned after the Oncology Therapy Trials Groups). This group will:
  - a)** develop and solicit proposals for Phase II and III cancer prevention trials with one or multiple modalities, i.e., behavioral, dietary, pharmacological, immunological, and combinations thereof.
  - b)** evaluate the scientific basis, recruitment strategies, statistical power, feasibility, and public health significance of competing proposals for trials.
  - c)** make awards for Phase II trials, and work with NCI to obtain the necessary funding needed for Phase III trials
  - d)** jointly sponsor trials, to prevent the appearance of new cancers and recurrences in patients, with established treatment trials groups to marshal the right combinations of experience and capability.
  - e)** stimulate methodologic research on efficient, cost-effective



prevention trials design.

f) provide to the scientific community administrative guidance regarding safety and efficacy monitoring boards, Food and Drug Administration Investigational New Drug applications, institutional review board policies, requirements for medical record and biological specimen retention, and how to achieve inter-institute collaboration on data collection for multiple endpoints.

- Form a special committee for biological studies which would stimulate and review proposals for ancillary biological studies on tissues and DNA of participants in prevention trials, and stimulate the use of the best available methods for validating intermediate endpoints to take better advantage of existing prevention trials. These functions could be incorporated into the recommended BSA subcommittee (see above).
- Devise and implement a mechanism for collaboration between NCI and the other NIH institutes to incorporate non-cancer endpoints into cancer prevention trials and cancer endpoints into non-cancer trials initiated by other institutes.

[top](#)

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### **Behavioral Research and Behavioral Interventions Trials in Prevention**

- Incorporate behavioral research as an integrated but independent component of the NCI prevention program.
- Conduct behavioral research at multiple levels, ranging from laboratory-based behavioral research to small scale hypothesis testing research to larger studies with the power to assess efficacy.
- Pay special attention to the development of interventions that are ethnically and culturally appropriate.
- Include as priorities for behavioral research a focus on preventing tobacco use in children and teenagers, encouragement of cessation among heavy smokers and women, increasing use of recommended early detection tests, and improvement of the behavioral outcomes of genetic testing for cancer susceptibility.
- Include the following components within an outstanding behavioral research program in prevention: epidemiologic foundations, expertise in measurement and evaluation, national data on key behaviors, knowledge of theories of behavior, understanding of behavior change, expertise in cancer risk communication, strength in intervention design, expertise in cost-effectiveness and mechanisms for dissemination.
- Conduct behavioral research initiatives through mechanisms which crosscut NCI as well as the National Institutes of Health, depending upon the focus of

effort.

- Create training programs for behavioral scientists to function in the new scientific paradigms, including genetics, chemoprevention, diet/nutrition, addiction and other pertinent areas.

[top](#)

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### **Training of Health Professionals with Expertise in Prevention Research**

- Develop and support new mechanisms for already trained health professionals to familiarize them with the field of cancer prevention and to provide them with opportunities to expand their skills to contribute to the science of prevention.
- Develop a data base of professional resources and deficiencies in the field of cancer prevention to assess current and future personnel needs, similar to that currently used to project needs for physician training.
- Form a working group to make recommendations for multidisciplinary training of prevention researchers in the new scientific paradigms and for evaluating the effectiveness of this training.
- Encourage the development of innovative training opportunities for prevention researchers to augment their training in areas such as genetics, pharmacologic intervention in prevention, epidemiology, and behavioral science.

[top](#)

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### **Organization and Infrastructure of the NCI Prevention Division**

- Ensure appropriate interactions among units that have the responsibilities for cancer prevention and control in order to facilitate translation of prevention principles into action.
- Establish a restructured cancer prevention division within NCI that has the responsibility and resources for formulating and implementing the cancer prevention agenda through the development and application of outstanding science. Enhance the senior management of the prevention division by recruitment of outstanding cancer prevention investigators who would assist in formulating and implementing a strategic plan, prioritize scientific goals, assess required resources, and facilitate interactions among the intramural and extramural research communities.
- Stimulate more effective interaction among intramural cancer prevention researchers, who are currently located in disperse laboratories and scattered across the prevention division.
- Expand the current NCI Board of Scientific Advisors (BSA) to include additional prevention research investigators and form a subcommittee of BSA, supplemented by other extramural experts, as an advisory group specific to the prevention division.

- Perform an in-depth evaluation of the Community Clinical Oncology Program to ascertain its contribution to the prevention effort and consider its relocation to the Division of Cancer Treatment, Diagnosis, and Centers.
- Continue to re-evaluate and modify, if appropriate, the programs for preclinical drug development and form a subcommittee of the Board of Scientific Advisors, supplemented by extramural cancer prevention investigators, and staff of the prevention division and the Food and Drug Administration, to assist and monitor the decision process in the preclinical and prevention trials phases.
- Form an extramural multi modality prevention trials group, patterned after the Oncology Therapy Trials Groups, which would set guidelines, make funding recommendations, and monitor the progress of prevention trials.
- Develop a mechanism to rapidly respond to new research developments, and to evaluate and fund outstanding ancillary research spinoff studies in populations represented within an ongoing prevention trial.
- Develop databases of: a) clinical cancer prevention trials, their objectives, target population, methodologies, successes, and failures; and b) the availability of blood and tissue products from clinical trials which could be accessed by all prevention researchers through a peer-reviewed mechanism.
- Strengthen collaborative relationships with other groups also involved in cancer prevention, such as the Centers for Disease Control and Prevention, the American Association of Cancer Researchers, the American Society of Clinical Oncology, and the American Cancer Society.
- Work more closely with the Food and Drug Administration on matters that affect cancer prevention, e.g., utilization of fully validated intermediate biomarkers in prevention trials.

[top](#)

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## Introduction

More than 2 million new cancer cases will be diagnosed in 1997. One in every four deaths in the United States--approximately 550,000 individuals--is the result of cancer. The leading cause of deaths from cancer by far in both sexes is lung cancer, followed by cancers of the prostate, colon and rectum, and pancreas in men, and cancers of the breast, colon and rectum, ovary, and pancreas in women. Pancreatic and pulmonary cancers are particularly aggressive with little improvement in survival despite determined efforts over the past 30 years.

An overall increase of 18 percent in cancer incidence and an elevation in the mortality rate of about 7 percent occurred between 1971 and 1993 (*Cancer at a Crossroads: A Report to Congress for the Nation*. National Cancer Advisory Board, 1994) However, recent statistics have shown an encouraging decrease in cancer mortality, suggesting that the battle against cancer may be taking a favorable turn. This reduction is probably the result of many factors, including enhanced early detection (e.g., increased use of mammography in the diagnosis of breast cancer),

and earlier, more aggressive treatment. Prevention efforts have also played an important role as evidenced by decreases in the proportion of Americans who still smoke. Progress has occurred in the treatment of breast, colorectal, and prostate cancers, although much room remains for improvement.

### **Goals of the National Cancer Program and the Role of Prevention**

In the 1997/1998 budget request for the National Cancer Institute (NCI), *The Nations' Investment in Cancer Research* (1996), it is stated that the ultimate goal of the National Cancer Program is "to eradicate this disease once and for all" or at least to "reduce the burden of cancer, . . . fewer deaths, fewer new cases." The success of the scientific discovery process during recent years has resulted in a substantial expansion of knowledge about how cancer arises and how changes in the genetic material of a cancer cell distinguish it from a normal cell. These and future insights should lead to discernible reductions in age-specific cancer incidence and mortality.

A growing appreciation has developed for the role of prevention in controlling cancer. Approximately 90 percent of the skin cancers expected to occur this year could have been avoided through the adoption of various protective measures against the toxic rays of the sun. The avoidance of cigarette smoking and of use of other tobacco products could reduce the incidence of lung cancer by 80 percent and significantly reduced the incidence of many other cancers (e.g., pancreas, kidney, head and neck). The adoption of diets that contain lower fat and increased fruits and vegetables could diminish the incidence of other cancers, for example, of the colon.

The NCI Cancer Prevention Program Review Group (hereafter referred to as the "Review Group") strongly believes that prevention must be a principal component of the National Cancer Program if the cancer burden is to be reduced. Prevention must be well-represented in the programs of NCI, both intramurally and extramurally, and must have an appropriate budget. Furthermore, prevention, like all other scientific elements of the National Cancer Program, must be founded upon excellent science, which originates from both the intramural and extramural research communities. It is through the application of excellent basic, clinical, and population-based research that effective preventive interventions can be mounted.

Because of its prime importance to the central objectives of the National Cancer Program, it is imperative that NCI's prevention efforts be championed by outstanding, widely respected leadership that will help in the development of a creative, discovery-based, and assertive prevention research program, and will use the strengths of the intramural and extramural communities in an effective manner. It is equally important that senior administrators of the prevention division have the respect of NCI leadership, and NCI's intramural and extramural research programs.

[top](#)

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### **Definition of Prevention**

As defined by the Review Group, cancer prevention research involves the

development and evaluation of strategies for reducing cancer incidence. Such strategies could be aimed at preventing the initiation of the neoplastic process or at avoiding the progression to malignancy of already initiated cells. These efforts, which may be multidisciplinary and multifactorial, can involve a broad range of studies at the molecular, cellular, organismal and population levels.

Prevention is further classified as either primary or secondary. Primary prevention refers to the direct intervention of the malignant transformation process via the identification and characterization of factors that are involved. Secondary prevention refers to early detection, using approaches that may not actually prevent the initiation of cancer (e.g., colonoscopy, mammography) but may be aimed at the identification of cancerous and precancerous lesions at an early subclinical stage when cure may be possible. Screening may cut across both primary and secondary prevention since the populations to be tested may range from the healthy to those who are at high risk for a first or second malignancy. The Review Group has included early detection within its mandate, although it recognizes that several other subcommittees are reviewing related issues and making recommendations. This level of redundancy is appropriate.

The Review Group recognized an ambiguity in the definitions of cancer prevention and control and in some overlapping research areas. The Review Group believes that cancer control research should be focused on the application at the population level of the fundamental principles that are developed through the prevention discovery process, while cancer prevention research is directed at the development of these general and specific principles in apparently healthy populations, including those at high risk and/or those with detectable precancerous lesions.

[top](#)

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## **Human Populations in Prevention Research**

Although animal models are and will be used in basic cancer prevention research (chapter 3 considers the utility of various animal models), the results from these studies must ultimately be validated in humans. This validation will occur in populations that fall into the following four general categories: 1) healthy populations involved, for example, in diet/nutrition change, smoking cessation, or other lifestyle modification, or who are screened for cancer predisposition genes; 2) high risk populations in which a hereditary disposition exists or premalignant manifestations are already present, or those who are at high risk because of their successful treatment for a first malignancy; 3) high-risk populations because of chronic exposure to occupational or environmental chemicals or physical carcinogens, or to infectious agents implicated in the malignant process (e.g., HPV, HBV); and 4) the elderly population in which the risk for cancer is increased (e.g., for prostate cancer).

The validation process usually will require a clinical trial. A fundamental difference exists between human therapeutic and prevention trials. In a cancer therapeutic trial,

the individual already has exhibited symptoms of the disease and may be in various stages of ill health. A greater tolerance for toxicity exists in the design of such a trial, so long as the potential benefit exceeds manageable toxicity. However, in a clinical prevention trial, where the individual participants are generally healthy and may not exhibit any symptoms of cancer, the guiding principle must be the absence of any significant toxicity from the intervention procedure, which may be conducted for a long duration. The conduct of human cancer prevention trials is discussed further in chapter five.

[top](#)

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## **NCI Cancer Prevention Program and Budget**

At present, the research program in cancer prevention is conducted within the intramural components of NCI and through grants and contracts awarded to the extramural community. The Review Group found it difficult to estimate the total NCI budget for prevention because various definitions are used by different institute units. The Review Group's best estimate for the total NCI cancer prevention FY 1996 budget is about \$400 million. To this figure could be added various components of physical, chemical and biological carcinogenesis, nutrition, observational epidemiology, and cancer control programs, which would increase the budget to approximately \$740 million.

[top](#)

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## **Intramural Component**

The preponderance of the cancer prevention budget is found within the Division of Cancer Prevention and Control (DCPC), approximately \$188 million for FY 1996. This figure was reduced from a previous level of \$200 million which included two research-based laboratories subsequently reassigned to other institute divisions. Of the \$188 million in DCPC, \$154 million is devoted to diet/nutrition and chemoprevention. Of the overall NCI budget, approximately 5 to 10 percent is for cancer prevention and control activities which include various clinical trials such as those conducted through the Community Clinical Oncology Program (CCOP).

[top](#)

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## **Extramural Component**

The overall FY 1996 extramural budget (grants, cooperative agreement, and contracts) for cancer prevention, including primary prevention, early detection and diagnosis, and epidemiology, primarily is distributed through traditional grants and contracts; about 68 percent for grants and 32 percent for contracts. Of the total NCI extramural prevention budget, approximately 55 percent is the fiscal responsibility of DCPC. Thus, NCI has devoted a substantial budget for cancer prevention efforts with a significant amount designated for the extramural research community.

[top](#)

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## **Focus on the Division of Cancer Prevention and Control**

As indicated above, a major responsibility for the NCI cancer prevention program lies within DCPC. Consequently, much of the activity of the Review Group centered on an analysis of this division's role in establishing the NCI cancer prevention agenda, providing the necessary leadership, representing the research interests of cancer prevention, and serving as an effective spokesperson for the intramural and extramural research communities.

After receiving oral and written testimony and conducting interviews with intramural and extramural scientists (see appendix A), the Review Group perceived: a) an apparent absence of a well-delineated, scientifically sound, long-term strategy for directing cancer prevention research into the next century; and b) a paucity of outstanding scientists in leadership roles within DCPC. These perceptions also focused the Review Group's analysis of the cancer prevention research program on DCPC.

Because this report focuses on the cancer prevention agenda as directed by DCPC, a brief review of its current administrative structure is appropriate. A more detailed organizational chart for DCPC is presented as an appendix. The division includes three programs, Early Detection and Community Oncology, Cancer Prevention Research, and Cancer Control Research, plus the Biometry Branch and several smaller efforts.

The Early Detection and Community Oncology Program includes Early Detection, Community Oncology and Rehabilitation, and Preventive Oncology branches. The Cancer Prevention Research Program includes Cancer Prevention Studies, Chemoprevention, and Diet and Cancer branches. The Cancer Control Research Program includes Special Population Studies, Applied Research Cancer Statistics, Prevention and Control Extramural, and Public Health Applications branches.

The goals of the Biometry Branch are to a) plan and conduct investigations on cancer epidemiology, prevention, screening, diagnosis, treatment, and control by using mathematical and analytical statistical methods; b) develop biostatistical and epidemiologic methodology, and mathematical modeling of cancer prevention research areas; c) provide consultation in biostatistical and study design for DCPC staff and other NCI investigators; and d) supply expertise in statistics and biometry to program managers and other decision-makers.

Of all the branches within DCPC, only the Cancer Prevention Studies Branch and the Biometry Branch are classified as "intramural." All others are considered as serving the extramural community. However, as detailed in chapter 8, the Review Group was concerned about the appropriateness of this classification.

CCOP links community cancer practitioners and primary care physicians with the clinical NCI Cooperative Groups and the NCI Cancer Centers, in order to increase

the participation of patients in clinical cancer treatment, prevention and control trials. In addition, several Minority-Based CCOPs are active in enhancing the participation of minority populations in these clinical trials. The organizational positioning of the CCOP within DCPC appears to be a remnant of the past when the Cancer Centers Program also resided in this division.

Several mechanisms have been created to fulfill the mission of DCPC in cancer prevention. The Prevention Trials Decision Network is a system for selecting preventive agents that would be incorporated into large-scale clinical prevention trials. In particular, this group, which meets quarterly, prioritizes prospective large prevention trials and makes recommendations to the NCI Executive Committee.

DCPC also operates a major Cancer Registry which has proven to be of great value to intramural and extramural investigators with interests in cancer statistics. This annually updated database-the Surveillance, Epidemiology, and End Results (SEER) Program-provides a means for monitoring the contributions of individual, organizational, and societal factors to the cancer burden within the United States. The SEER Program, which was established in 1973, provides information on cancer incidence, survival and mortality obtained from 11 state and regional registries covering approximately 14 percent of the total U.S. population. In 1992, the SEER data base was expanded to increase the representation of U.S. Hispanic, Asian/Pacific Islander, and African American populations.

As newly reorganized under the leadership of the NCI Director, DCPC does not contain any programs or branches in which "bench" research is conducted. Previously however, two DCPC laboratories, the Laboratory of Nutritional and Molecular Regulation, and the Biomarkers and Prevention Research Branch, conducted bench science. These units have been transferred to the Division of Basic Sciences and the Division of Clinical Sciences, respectively.

As the Review Group assessed the administrative structure of DCPC, the need for change became obvious. Furthermore, the necessity for an enhanced role of the prevention division in training, and in providing additional databases that could be readily accessible by the community of cancer prevention researchers, became apparent. These recommendations are detailed in chapter 8 of this report.

[top](#)

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### **Inclusion of Prevention and Control Research within a Single Division**

The Review Group briefly considered the necessity of including cancer prevention and control within a single organizational unit, as currently exists within DCPC. Because of a lack of sufficient data and the existence of another NCI review group which has the responsibility for evaluating cancer control efforts, the separation of these research functions was not considered further. The Review Group did conclude, however, that the inclusion of cancer prevention and control within a single unit or the separation of these research functions would not compromise the



goals of NCI.

In regard to a definition of the scope of prevention versus control research, the Review Group does recommend that cancer control be focused on persons with clinically-overt cancers although screening could also be included, while cancer prevention be directed at apparently healthy populations, including those at high risk and/or those with detectable precancerous lesions.

### **Charge to the Review Group**

The Review Group on Cancer Prevention was appointed in 1996 by the NCI Director and the Chair of the NCI Board of Scientific Advisors. The Review Group was asked to consider how best to utilize the significant, albeit limited, resources and personnel of NCI in developing and sustaining a cancer prevention research program. Among the questions the Review Group was asked to consider are:

- Taking into account the full set of NCI resources available in this area of research, how should judgements be made about which large-volume clinical trials to pursue and when?
- What performance criteria should be applied to long-term clinical trials to maximize their yield of knowledge in the shortest possible time?
- Of the existing resource units of NCI, which should be applied to prevention research and how should they be organized to achieve maximum efficiency?
- How should NCI organize its infrastructure to support chemoprevention trials?
- What is the most effective way to engage in investigator-initiated research in the development of an optimal NCI prevention portfolio?

The Review Group also evaluated the existing intramural cancer prevention research program as well as other program components. Based on this evaluation, the Review Group offers a number of specific recommendations, some of which concern management and organizational structure, and some of which address avenues for research opportunity. In this report, the Review Group uses the phrase "prevention division" to describe a modified administrative unit that has the full responsibility for directing and managing the NCI cancer prevention research agenda.

The Review Group organized its deliberations around the following topics, which appear as separate sections of this report: modifiable risk factors; animal models and extrapolation to human cancer prevention; genetic predisposition to cancer and detection of precursor lesions; chemoprevention trials in human populations; behavioral research and behavioral intervention trials in the cancer prevention program; training of health professionals with expertise in prevention research; and organization and infrastructure of the prevention division.

## **Process of the Review Group**

The Review Group met a number of times to accept oral testimony, review written communications, form subcommittees to address individual components of the charge, and review all recommendations of the subcommittees in order to build the consensus report. In addition, telephone conferences were conducted with subcommittee members. The formal meeting dates of the Review Group are included in appendix A, as are acknowledgments of those who assisted the committee in its deliberations by providing oral or written testimony.

This report is submitted to the Board of Scientific Advisors and the National Cancer Advisory Board for its consideration. The recommendations are aimed at improving the health of Americans through a comprehensive cancer prevention research program.

[top](#)

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## **MODIFIABLE RISK FACTORS**

### **Introduction**

The cancer prevention research effort of the National Cancer Institute (NCI) should include a central focus on the identification and avoidance of exposures that may increase cancer risk, and the identification and enhancement of behaviors that may reduce cancer risk. Research on the impact of any such exposure or behavior on other important health outcomes (e.g., vascular diseases) is also critical to related public health recommendations and policy.

In terms of potential impact on cancer incidence and mortality, the highest priority risk, factor modifications concern reductions in exposure to tobacco products and changes in diet and nutrition. Very different research efforts appear to be needed in these two crucial areas. Cigarette smoking is the major known preventable cause of human cancer mortality and the epidemiological associations with cancer of the lung and cancer of various other organs are well characterized. However, a substantial commitment to the development of effective interventions for the prevention and cessation of tobacco use is needed, with emphasis on populations where the prevalence of tobacco use continues to be high. Additional research into the determinants of cigarette consumption among groups having high smoking prevalence and basic research into addiction mechanisms are needed to formulate improved behavioral and pharmacologic interventions.

In contrast, there are few diet and cancer relationships that can be regarded as reliably determined. International comparisons, time trend, and migrant studies suggest an important role for energy and macronutrient (i.e., fat, fat subtypes, protein, carbohydrate) consumption in determining the risk of several prominent cancers, and there is support for these associations from a considerable history of animal feeding trials. However, analytic epidemiologic studies (i.e., cohort and case-

control studies) tend to suggest weak or null associations. It is not known whether the strong associations seen in aggregate studies are due to confounders, or whether the limitations of dietary self report invalidate the analytic studies, or both. There is a greater consistency of data from these same sources in support of a reduced risk of various cancers among persons having a high consumption of fruit and vegetables.

These associations are intriguing enough to properly impact dietary recommendations and to motivate the scrutiny of various substances found in fruits and vegetables in the search for cancer chemopreventive agents. However, even the reliability of the fruit and vegetable and cancer associations are reduced by measurement difficulties with self-reported diet, particularly since an adequate control of the confounding influences of macronutrient consumption is not currently possible. Evidently, to produce reliable epidemiologic information on diet/nutrition and cancer it will be necessary to strengthen study quality (e.g., by requiring the incorporating of appropriate dietary biomarkers in analytic epidemiologic studies). Methodologic research is also needed to clarify the potential of, and interplay among, aggregate studies, analytic studies, and human intervention trials, and to strengthen each type of study. Concurrent research is also needed to identify biologic mechanisms for the most plausible diet/nutrition and cancer associations, and to test such associations in clinical trials when justified on the basis of biologic and public health criteria.

*In view of the importance of the tobacco and diet/nutrition areas to NCI's cancer prevention program, a senior and respected scientist, well positioned within the NCI organization, should be charged with the coordination and development of each of the two research areas.*

There are a number of other modifiable risk factors that should not be overlooked in a renewed prevention program. These include physical activity patterns, as may be closely linked with diet in determining disease risk; the use of alcohol; exposure to environmental and physical carcinogens; and exposure to infectious agents. This chapter proceeds with some additional background and discussion of research opportunities and needs in each of these modifiable risk factor research areas, followed by a listing of corresponding summary recommendations.

[top](#)

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## **The Need to Better Achieve Tobacco Avoidance**

Smoking remains the major known cause of human cancer. The role of tobacco as a human carcinogen has been proven beyond a reasonable doubt. In addition to the more than 40 direct carcinogenic compounds in tobacco smoke, nicotine has been recognized as a precursor of its nitrosated products (e.g., NNK) which have a carcinogenic role especially in the respiratory system. Most recently, nicotine has been recognized as a highly addictive drug by the Food and Drug Administration.

Major investments in tobacco control, along with a variety of health policy

initiatives, have resulted in a reduction in the prevalence of smoking in the United States from more than 50 percent in 1965 to 28 percent in 1994 for males, and from 32 percent in 1965 to 23 percent in 1994 for females. The rate of prevalence reduction has slowed in the past several years, and more than 45 million Americans continue to smoke.

Smoking has become an activity of specific population subgroups, many of which are considered hard to reach. These include women of child-bearing age, ethnic and cultural minorities, and persons having low education, low income, and blue-collar occupations. Women appear to have greater difficulty quitting smoking than do men, and large numbers of pregnant women continue to smoke despite the known risks to the developing fetus. Heavy smokers appear to have great difficulty quitting, regardless of gender, ethnicity or socioeconomic status.

Various behavioral and pharmaceutical approaches to smoking cessation have been demonstrated to have efficacy, and some smokers have taken advantage of them. However, many smokers either are not yet ready to quit, have not had access to these approaches to quitting or have used them and failed to quit. Similarly, the mechanisms of addiction still are not completely understood, making it a challenge to provide better pharmaceutical aids.

Tobacco use prevention is a major concern in the United States. For nearly two decades the incidence of youth smoking remained high, but constant (about 27 percent of high school seniors ever smoked in the last 30 days in 1991). The recent rise in youth prevalence (34 percent ever smoked in the last 30 days and 22 percent smoked daily among high school seniors in 1996) is especially disturbing. The rates for tobacco use among adolescents not in school is two- to three-fold the rates of those in school. Most troublesome is that almost 90 percent of all smokers take up the habit during adolescence.

A major research investment in tobacco research is still required. Fundamental to understanding the problems associated with tobacco usage is knowledge of the mechanisms underlying addiction. Cessation interventions, relapse prevention, and addiction research need to be developed. More research is needed to understand the specific determinants of smoking in special population subgroups. Much more research is needed in understanding the smoking onset process, and to identify effective strategies to help children and adolescents avoid taking up smoking and other tobacco use. Because tobacco use is the major preventable source of cancer mortality, it is critical that NCI make a substantial commitment to discovery in this area.

[top](#)

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## **Understanding the Basic biology of Cancer and Diet and Nutrition**

There are good reasons to postulate a prominent role for diet and nutrition in cancer causation. These include the observation that a single crude measure of per capita fat

consumption can provide an explanation for much of the five- to ten-fold variation in the international incidence rates of several cancers, including cancers of the colon, rectum, breast, ovary, endometrium, prostate and kidney; the rather consistent observation from many (more than 200!) cohort and case-control studies that a high consumption of fruit and vegetables is associated with a relatively low incidence of several cancers, including cancers of the stomach, esophagus, oropharynx, lung, endometrium, pancreas and colon; and supportive results from a substantial history of animal feeding experiments. In fact, analyses of these and other data sources have led some reviewers to estimate that up to 40 percent of human cancer may be avoidable by means of practical changes in diet. Various organizations, including the National Academy of Sciences, the American Cancer Society, and NCI have issued dietary recommendations that call for a high consumption of fruit and vegetables and grains and the avoidance of an unnecessarily high consumption of calories and fat. The NCI-sponsored "5-a-Day Program" is also underway, with a goal of identifying effective strategies for increasing fruit and vegetable consumption.

However, as previously mentioned, there are few diet and cancer associations that can be said to have been reliably determined, despite a substantial research effort for several decades. Efforts to identify the components of fruit and vegetables that may be responsible for their putative cancer preventive effect have typically been non-conclusive. Although macronutrient consumption may well account for the largest portion of cancer risk associated with diet, different types of epidemiologic studies appear to yield inconsistent results, and no consensus has arisen concerning, for example, the role of excess energy consumption, or the role of fat consumption, in determining cancer risk.

To understand these enormous knowledge gaps, it is worth remembering that the diet is the most complex mixture of chemical substances to which humans are exposed, including many components that are present in extremely low concentrations. Many attributes of the diet may influence health, including the nature of its constituents; excesses or deficits of specific components; substances added to it; or substances produced during its preparation for consumption. Health effects of diet may be characterized by marked individual differences in susceptibility.

Various components of the diet may be relevant to health: the energy it provides in terms of calories; specific macronutrients, particularly fat, protein, and carbohydrate; specific micronutrients; and a large number of non-nutrient constituents. This complexity, along with the substantial difficulties in assessing even the recent dietary habits of individuals, may seriously undermine the reliability of available sources of epidemiologic diet and cancer data.

Consider, for example, energy consumption and breast cancer. Experimental studies in rodents indicate that calorie restriction can substantially reduce mammary tumorigenesis, but the practical implications for human breast cancer prevention are

unclear. An association between per capita calorie supply and breast cancer incidence can be detected in international correlational analyses, but available data do not permit a serious attempt to control for between-population confounding. Cohort and case-control studies have thus far relied on self reported energy consumption (e.g., using food records, recalls or frequencies) and have often been unable to detect any association between energy consumption and breast cancer.

These studies often allude to a control for measurement error in the dietary self-report data, but all available measurement error methods require at least one of the measurement instruments to be able to estimate exposures and confounding factors in an unbiased fashion. Total energy consumption is one of the few aspects of diet for which an excellent biomarker measure exists. Specifically, the doubly labeled water method can accurately estimate energy expenditure over short periods of time.

Recent studies relating self-report measures to the doubly labeled water measures of total energy indicate a systematic under reporting of energy on self-report instruments. The extent of under reporting increases with body mass and, for example, appears to be in the 25 to 50 percent range among obese women.

It is easy to see that systematic biases of this magnitude, in conjunction with the random measurement error that is evident from repeat applications of dietary self-report instruments, can dominate the results of cohort and case-control studies of energy consumption and breast (or other) cancer, to the point that even a very strong positive association would likely not be detected. On the other hand, the availability of an objective (biomarker) measure of energy intake on a subsample of study subjects, along with self-report dietary data, gives the potential for a proper measurement error correction of analyses that relate short-term calorie consumption to cancer risk, but such analyses have yet to appear in the literature. This example also illustrates the inadequacy of current epidemiologic procedures for controlling for total energy when examining the relationship between the consumption of specific nutrients or foods (e.g., fruit and vegetables) and cancer risk.

Even the availability of unbiased biomarkers does not ensure that nutrient cancer associations can be reliably studied in an observational fashion. For example, epidemiologic studies have consistently reported an inverse relationship between blood beta-carotene concentration and lung cancer risk, but recent large-scale clinical trials indicate that beta-carotene supplementation, if anything, increases lung cancer incidence. Though the reasons for such a possible adverse effect are still unclear, it may be that the high correlations of beta-carotene consumption, and blood beta-carotene, with the consumption of other micronutrients (including other carotenoids) effectively precludes a separation of their roles in observational studies. Also the consumption of foods rich in beta-carotene is negatively associated with exposure to tobacco smoke, so that observed associations between dietary, and blood, levels of beta-carotene and lung cancer may be due to residual confounding, unless an exquisite level of control for the history of cigarette and other tobacco exposures is included.

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## Needed Diet/Nutrition and Cancer Research

The diet/nutrition and cancer research area needs a revitalization with strengthened studies of various types, and an orderly development of dietary/nutritional interventions for human testing. The prevention division should play a leadership role in this revitalization.

Consider again observational studies of diet and cancer. While cohort and case-control studies that rely exclusively on self reported diet appear to have passed the point of diminishing returns, further such studies could contribute valuably if adequate substudies are included that incorporate suitable biomarkers of dietary exposure and of dietary confounding factors. Hence a noteworthy research effort is needed to identify unbiased (even if noisy) biomarkers of nutrient and food consumption, with particular emphasis on macronutrients. Improved international correlation and migrant studies that include sample surveys of dietary and confounding factors could contribute usefully even if based on self report, since aggregation provides protection against the noise aspect of measurement error. Results from such strengthened observational studies can be expected to contribute to the scientific basis for diet and cancer prevention recommendations, and to provide valuable input to the choice of interventions for testing in clinical trials.

The costs and logistics of human diet and nutrition intervention trials demand a careful development of trial rationale. This rationale will typically involve an orderly development of supporting data in observational studies and in studies of potential mechanism, with subsequent evaluation in preclinical trials, pilot and feasibility studies, and eventually full-scale clinical trials. Note, however, that it may be imprudent to await a complete understanding of the mechanisms that may be involved in a putative diet and cancer prevention hypothesis before undertaking clinical testing or implementing widespread preventive measures. In particular, testing may be merited if the public health implications are sufficiently great, or if the agents in question are being used in the general population for other reasons (e.g., aspirin for the prevention of vascular diseases; folic acid supplementation for the prevention of neural tube defects; calcium supplementation for the prevention of fractures).

Interventions in the diet/nutrition and cancer prevention area can mostly be classified as behavioral or chemopreventive. Examples of the former include the low fat (high fruit and vegetable, high grains) eating pattern being taught and tested in the NCI Polyps Prevention Trial, and the National Institutes of Health Women's Health Initiative, while there have by now been several trials of specific nutrients or nutrient combinations as chemopreventive agents. Both types of trials are needed on an ongoing basis, to address the knowledge gaps previously noted.

Dietary behavioral trials are needed to test the best current concepts concerning a

healthful diet. A systematic process is needed to identify the eating patterns that merit testing, and to develop and test nutritional and behavioral strategies for effecting the desired eating pattern changes. The type of strengthened observational studies mentioned above, as well as basic research into the mechanisms whereby eating pattern changes may protect against one or more cancers, are needed to direct this systematic process. For example, in support of an intervention to increase fruit and vegetable intake one can develop a long list of potential cancer preventive agents found in fruits and vegetables and can examine induction of detoxification enzymes, inhibition of nitrosamine formation, dilution and binding of carcinogens in the digestive tract, alteration in hormone metabolism, and antioxidant effects, as potentially important mechanisms of action.

Basic research into mechanisms as well as the other elements of the previously mentioned orderly process are likewise needed to identify the most promising nutrients, or nutrient combinations, for testing as chemopreventive agents. Other chapters of this report make recommendations concerning both the preclinical and clinical aspects of this process.

Much of the confusion and inaction in the diet and cancer prevention research area arises from methodologic issues concerning, for example, the role and reliability of observational studies in relation to intervention trials; the interplay between observational and mechanistic studies; and the ability to streamline comparative trials by focusing on very high risk study subjects or by relying on intermediate outcome measures. Research is also needed toward answering these types of questions, and toward identifying the data sources needed to address these diet and cancer methodologic issues.

### **Physical Activity and Cancer Risk**

There is a large body of evidence of the beneficial effect of physical activity and physical fitness on various aspects of health and well being, including reductions in the risk of coronary heart disease, diabetes, stroke, osteoporosis, obesity and disability. Though understudied compared to other cancer prevention strategies, evidence also exists that physical activity may be associated with a lesser risk of several common forms of cancer, most notably colon and breast cancer.

For these cancers, persons having relatively high physical activity levels have been reported to have disease rates that are 25 to 50 percent lower than those among sedentary persons, making the further development and testing of these hypotheses a high priority in the cancer prevention research agenda. Physical activity has effects on fat tissue, obesity and body fat distribution, as well as immunological, mechanical and hormonal effects, providing a range of possible mechanisms whereby physical activity may reduce cancer risk.

Observational studies of physical activity and cancer are plagued by many of the same obstacles surrounding studies in the diet and cancer area; specifically, random and systematic measurement error in physical activity self-assessment and the need



to control for the myriad of potential confounding factors, some of which also have severe measurement difficulties. In fact, the interplay between nutrition and physical activity (e.g., energy balance) may be a key determinant of the risk for colon, breast and other cancers. A greater research effort is needed to identify suitable biomarkers of short- and long-term physical activity patterns, and to identify plausible mechanisms whereby an increase in physical activity may reduce the risk of specific cancers. To date, there has been very little study of physical activity and cancer prevention using controlled intervention trials. Small scale trials to identify the effects of physical activity on disease risk factors can be justified currently with the possibility of full-scale disease prevention trials following additional hypothesis development research.

### **Alcohol Consumption and Cancer Risk**

Although apparently not a direct carcinogen, alcohol use increases the risk of liver cancer and also upper aerodigestive cancer in smokers. The mechanism of its carcinogenic effect is not well understood but it is clear that alcohol interferes with the first pass clearance of carcinogens such as those found in tobacco smoke, and may enhance mechanisms for biotransformations of procarcinogens found in tobacco smoke. In the breast and possibly the liver, its apparent carcinogenic effect may be mediated through increases in the level of estrogens in the blood. The same mechanism may be linked to a decrease in the risk of coronary heart disease.

Data on the consumption of various types of alcoholic beverages are frequently collected in cohort and case-control studies. The measurement difficulties are not so severe as for diet and physical activity, in part because a fraction of the population do not consume alcohol, and it seems reasonable to expect that sufficiently reliable information on the basic associations will be forthcoming from observational study sources.

### **Occupational and Environmental Carcinogens**

The recognition of the importance of environmental and occupational carcinogenesis derives from the original insightful observations of Sir Percival Pott in the 18th century on the occurrence of scrotal cancer in a young group of chimney sweeps. Since that time, considerable progress has evolved in the identification of carcinogenic agents that are present in the workplace and in the definition of their mechanisms of action. These carcinogens are either: a) produced or used in the workplace, such as polychlorinated biphenyls and asbestos; b) produced during a combustion process, such as the polycyclic aromatic hydrocarbons; c) formed during or following the process of chlorination of water, such as the chlorinated hydrocarbons; d) used as herbicides in agriculture or as pesticides around the home, such as chlordane; or e) incorporated in foodstuffs as additives, such as the azo dyes.

Although the occupational and environmental carcinogens have received much press, with the often noted adage-the carcinogen of the month-chronic exposure to these substances probably contributes to 5 to 10 percent of the deaths due to cancer. Nevertheless, these deaths are largely preventable, and regulatory agencies such as

the U.S. Environmental Protection Agency and the Occupational Safety and Health Administration are involved in monitoring exposure of individuals to the occupational and environmental carcinogens.

NCI as well as other institutes of NIH have been involved, largely through the use of the traditional peer-reviewed grants, in studies on mechanisms of action of the environmental and occupational carcinogens, and on the development of unique ways to prevent their carcinogenic action. Within NCI, the Division of Cancer Prevention and Control (DCPC) has only played a minor role in this area. This role will undoubtedly expand in the recruitment of individuals into chemoprevention trials who are at high risk for cancer development by virtue of elevated exposures to occupational and environmental carcinogens. This is a research area which can benefit substantially from fruitful interactions between the various divisions of NCI, including the prevention division, to exploit any unique findings that might evolve from basic science. The prevention division should in fact take the lead in these interactions.

### **Infections Agents and Cancer Risk**

The concept that viruses cause human cancer dates back to the first decade of the twentieth century when experiments on animals showed that tumors in chickens could be induced by an agent that could pass through a filter. The new tools of molecular biology have led over the last decade to profound discoveries about the role of viruses in human cancer and the mechanisms of disease causation and have provided the science base to direct efforts at preventive vaccine development.

Viruses must invade living cells in order to reproduce, generally by attaching to receptors on the surface of the target cell. Once inside the cell, they often integrate their genetic material into that of the host and alter the cell in ways which predispose to cancer through a variety of mechanisms. In some cases, the virus is thought to induce cancer directly, while in other cases, indirect effects of the virus (e.g., immunodeficiency) predispose to malignancy. Two major types of viruses that are linked to cancer have either DNA or RNA as their genetic materials.

Members of the DNA family of viruses include the papilloma viruses of humans (human papillomavirus, or HPV) and animals (bovine papillomavirus, or BPV), hepadnaviruses (hepatitis B), flavaviruses (hepatitis C), and herpes viruses (herpes simplex type 1 and 2, Epstein-Barr virus, and human herpes virus-6, -7 and -8). Members of the RNA family of viruses (retroviruses) include human T-cell lymphotropic virus types 1 and 2 (HTLV-1, HTLV-2), human immunodeficiency virus type I (HIV-1), and a variety of animal retroviruses including bovine immunodeficiency virus (BIV), simian immunodeficiency virus (SIV), feline immunodeficiency virus (FIV), caprine arthritis encephalitis virus (CAEV), and equine infectious anemia virus (EIAV).

Papillomaviruses are found in a wide variety of species and have an affinity for epithelial cells. They cause benign epithelial proliferations but have also been linked

to cancers in humans and animals. There are approximately 70 different human papillomaviruses which are associated with a variety of clinical lesions, including plantar warts, hand warts, venereal warts, and flat cervical warts (which are now recognized as potentially precancerous). Approximately 25 of the HPV types are associated with genital tract lesions, and these types can be grouped into high risk and low risk categories based on their association with genital tract cancers. The low risk HPVs, such as HPV-6 and HPV-11, are associated with venereal warts (also known as condyloma acuminata) which only rarely progress to cancer. The high risk viruses, which include HPV-16 and HPV-18, have been associated with intra-epithelial neoplasias which are benign but may progress into cancers. For instance, it is estimated that a woman with HPV-16 positive cervical lesion has approximately a one-in-thirty lifetime risk of developing cervical cancer.

Infection with hepatitis B virus (HBV) has, through case-control and prospective cohort studies, been closely associated with hepatocellular carcinoma (HCC). This is particularly evident in high-risk geographic areas for liver cancer such as Taiwan, Senegal, South Africa, Hong Kong, the People's Republic of China and the Philippines. HCC is one of the most frequently occurring human cancers worldwide, causing more than 250,000 deaths annually throughout the world. A vaccine has been developed to prevent infection with HBV, and its ability to reduce liver cancer in humans is now being field-tested. Clearly, the widespread application of the HBV vaccine in regions where there is a high prevalence of infection with this virus could have a profound impact on reducing the risk of developing primary liver cancer.

Epstein-Barr virus (EBV) has been studied exhaustively for more than 25 years as a possible etiological agent in some forms of human cancer. These studies have established that this herpes virus is the causative agent of infectious mononucleosis, and that it is linked to at least four different types of human malignant tumors. Its role in the African form of Burkitt's lymphoma and in nasopharyngeal carcinoma (NPC) is well documented. Substantial evidence also links this virus infection to many B cell lymphomas in immunosuppressed individuals, particularly after organ transplantation or HIV infection. It has also been postulated that this virus contributes to Hodgkin's disease, and occasionally DNA and EBV have been found in tumor cells that are unique to Hodgkin's disease (called Reed-Sternberg cells) as well as in other tumors. Indeed, EBV appears to be a bona fide human cancer virus, thereby raising the realistic possibility of preventing EBV-associated disease, including virus-associated malignancies, through the use of an appropriate vaccine.

Retroviruses first attracted widespread attention as oncogenic agents that replicate through DNA intermediates and involve integration of DNA copies of their genomes in the host chromosomes. Because no other class of animal viruses exhibits such profound intimacy with the host genome information gathered concerning this relationship should increase understanding of the viral-associated transformation process. Indeed, animal retroviruses isolated from many mammalian species continue to provide valuable basic information on the etiology and mechanisms(s) of cancer induction by viruses. Retroviruses may be directly or indirectly involved

in the development of malignancies. Retrovirus animal models may therefore aid in investigations of the initiation and progression of neoplasia of viral origin, provide a better understanding of the role of viruses in the etiology of human cancer, and contribute to prevention efforts against microbiological agents, especially viruses.

*Helicobacter pylori* is a bacterium whose causal association with gastric malignant neoplasms has been recently recognized. Acquisition and persistence of the infection are poorly understood and may be partially dependent on dietary practices and nutritional status. Research on the role of this bacterial infection in carcinogenesis may increase understanding of carcinogenesis in general, especially with regard to the role of DNA damage. The role of this bacterium in carcinogenesis needs further exploration by epidemiologic and laboratory techniques. The mechanisms of transmission as well as the effects of this infectious agent on human health are still poorly understood. Research on strategies to eradicate the infection needs support especially the development and testing of vaccines which have been proven to prevent reinfection and cure active infection in experimental animals. Although gastric carcinoma incidence has decreased considerably in the United States, many special populations still have high rates, such as African Americans, Native Americans, and immigrants from certain geographic regions. Gastric lymphoma linked to *Helicobacter* infection, is not a frequent disease but research on it may yield results that are highly relevant to other lymphomas.

### **Recommendations**

Tremendous opportunities exist to prevent cancer through modifying tobacco use, diet, nutrition, physical activity, and exposures to infectious agents. A well developed research base is required before interventions are implemented on a population basis, but well designed intervention trials are essential for the development of a knowledge base. In setting priorities for cancer prevention research, the Review Group recommends that the following areas be given the highest priority.

[top](#)

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### **Tobacco Exposure**

- Increase the investment in developing effective interventions for prevention and cessation of tobacco use, particularly in populations where tobacco use has remained high, e.g., adolescents, women, and those with less education and income.
- Increase the proportion of the tobacco control investment in basic research and in the development of effective interventions, and decrease the investment in large-scale dissemination efforts, e.g., ASSIST.
- Identify a respected senior scientist to assume a major leadership role within the prevention division for the development and coordination of the tobacco avoidance research agenda.

## **Diet and Nutrition**

- Encourage research to identify biomarkers of the consumption of key dietary components, particularly micro- and macronutrients.
- Increase the investment in research aimed at understanding the biological mechanisms underlying putative diet and cancer incidence associations, particularly concerning fruit and vegetable, fatty acid, and total energy consumption.
- Encourage methodologic research to clarify the most promising research designs and strategies for diet and cancer prevention research, and to streamline the conduct of dietary intervention trials.
- Identify an outstanding senior scientist to assume a major leadership role with the prevention division for the development and coordination of the diet/nutrition and cancer prevention research agenda.
- Develop an orderly process for the development and testing of dietary behavioral trials on hypothesized healthful eating patterns.

## **Physical Activity**

- Support research to identify objective markers of short- and long-term physical activity and determine the mechanisms whereby physical activity may reduce the risk of important cancers.
- Support intervention trials aimed at identifying behavioral strategies to enhance physical activity and to assess the impact of such enhancement on cancer risk factors.

## **Infectious Agents**

- Emphasize basic and applied studies of the role of viruses and *Helicobacter pylori* as factors or cofactors in the etiology of certain cancers, and initiate research and development of appropriate vaccines.

## **ANIMAL MODELS AND EXTRAPOLATION TO HUMAN CANCER PREVENTION**

### **Introduction**

Avenues through which cancer could be prevented include modifications of diet

and/or lifestyle, avoidance of exposures to carcinogens, or enhancement of host defenses through immunization or chemoprevention. Chemoprevention is defined as the administration of chemical agents to prevent neoplastic transformation, or inhibit or delay the progression of cancer from the already initiated cell. Much of the current National Cancer Institute (NCI) prevention program is based on the premise that chemoprevention represents a promising strategy for cancer prevention and control which could have more immediate impacts than dietary modification or avoidance of exposure to carcinogens. Consequently, a major objective of the cancer prevention program has been to identify and develop chemopreventive agents as drugs for use in humans.

Animal models have played a significant role in cancer prevention investigations. They serve as a tool in testing hypotheses that result from human epidemiological studies on etiology and facilitation of the cancer process, establishing and/or verifying the utility of biomarkers, in providing a system for identifying potential chemopreventive agents, and in establishing the mechanism of action of the chemopreventive substances. In addition, animal models have proven to be useful in establishing a non-toxic dose range of protective agents and in providing an initial view of the pharmacokinetics of specific chemopreventive substances.

The majority of candidate compounds entered into the program to date were identified through published reports of experimental and epidemiological studies, and from results of studies relating to chemical structures or pharmacologic properties similar to those of known chemopreventive substances. A chemopreventive drug development program has been created at NCI which accounts for chemopreventive efficacy, toxicity, pharmacokinetics, potential for clinical use, commercial availability, source, and cost. The utility of this program is considered further in chapter five.

[top](#)

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### **Efficacy of Animal Models in Diet/Nutrition, Tobacco, Alcohol, and Physical Activity Studies**

Currently employed animal models have proven to be of varying utility in cancer prevention studies. Epidemiological studies in humans have suggested a role for certain macronutrients and micronutrients in cancer development. Most of the animal models use rodents and employ carcinogens to initiate the neoplastic process. Rarely is the spontaneous incidence of tumors in animals used as the tool for assessing effects of macro- or micronutrients. The exception is the use of spontaneous tumor incidence as a marker in lifetime toxicity studies. The expense of the lifetime studies contributes to the limited use of these spontaneous tumor models. In addition, only highly inbred rodents, principally mice, are generally used in these types of studies. Unfortunately, these strains of rodents have been bred for a particular characteristic, and therefore, an entire colony of a highly inbred rodent is equivalent to only a single individual. This feature limits their utility for translation

into general human cancer prevention.

Confirmation of the hypotheses that have evolved from the epidemiological investigations in animal models has proven difficult. For example, conflicting data exist on the definitive role of fat in breast cancer development. Much of the conflict centers on distinguishing between fat per se and the amount of dietary calories. It is difficult to alter the amount of a single contributor to the diet and maintain a comparable number of calories without grossly affecting the overall dietary composition. For example, were the fat content of a diet altered, the carbohydrate composition would have to be changed simultaneously in an inverse fashion in order to maintain the new diet as isocaloric. In addition, the animal breast cancer models may not bear a suitable relationship to the human disease. This criticism unfortunately extends to many of the currently used animal models.

Animal models pose some difficulties with regard to micronutrient investigations. For example, it is almost impossible to obtain a deficiency of vitamin C in most rodents that have utility in cancer investigations. This inability reflects the difference in metabolic pathways for the production of vitamin C in most rodents, i.e., these animals inherently contain a vital enzyme in the formation of this vitamin while the human does not. Only the guinea pig is comparable to the human in lacking the final enzyme necessary for the formation of vitamin C.

The intestinal microflora in humans and rodents differ markedly. The microflora play an important role in absorption, metabolism, and reabsorption of dietary nutrients. Consequently, these phenomena which are of importance in pharmacokinetics may distinguish many rodents from humans.

Most animal models have not proven of much utility in tobacco and smoking investigations, despite studies confirming the development of cancer in beagles chronically subjected in tobacco smoke. The use of dogs as routine models in cancer prevention studies (other than in toxicity studies) has been very limited because of availability, and costs of purchase and maintenance. More recently, the exposure of certain rodents to the specific tobacco smoke ingredients such as the tobacco-specific nitrosamines, has resulted in lung cancer development; this system has been used as a basis for some chemoprevention investigations.

Alcohol studies in the common rodent have generally proven to be of little value. Rodents tend to be more tolerant of alcohol, have a higher rate of metabolism of ethanol, and exhibit slightly different metabolic pathways. An exception is the deer mouse which is deficient in alcohol dehydrogenase and is sensitive to many pharmacologic effects of alcohol. This mouse, however, has not been of any use in cancer or cancer prevention studies. The co-carcinogenic role of alcohol in tobacco-induced cancer development has not been easily demonstrated in most animal models. An exception is in the golden syrian hamster cheek pouch model which has not been widely used in prevention studies.

The effects of physical activity on cancer development, and therefore on cancer prevention, have been studied in rodents forced to run on treadmills. These systems have generally employed carcinogenic agents to initiate the neoplastic process. The subsequent effects of the increased physical activity upon the incidence of the specific cancer were determined. Although a preventive effect of this induced exercise has been demonstrated in several instances with this model the extrapolation to humans is, at best, problematic.

Finally, newer rodent models that result from the transgenic approach have been developed with increasing frequency. For example, the p53-minus mutant mouse and the min-minus mutant mouse may have significant efficacy in cancer prevention studies. This has yet to be determined. As more knowledge develops on the biology of the cancer process and this knowledge is translated into the construction of genetically modified rodents, greater applicability to the human disease is expected. The NCI Chemoprevention Branch is cognizant of the need to use some of these newer model systems and indeed, is currently testing their efficacy. Additional comments on the use of newer models are offered in chapter five.

[top](#)

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## **Animal Models as Tools for the Evaluation of Potential Chemopreventive Agents**

Candidate agents are screened in a hierarchical series of preclinical efficacy tests, including *in vitro* mechanistic assays, *in vivo* efficacy screens, and studies to determine efficacy by inhibiting development of experimentally induced cancers in animals. Results obtained in these experimental systems, as well as data from preclinical animal toxicology tests conventionally used in drug safety evaluation, and pharmacokinetic characterization in animals are used to identify agents to be considered further for application in human clinical trials. Experimental models employed to assess chemopreventive efficacy include chemically induced animal cancers, cultured animal and human cells subjected to transformation stimuli, precancerous lesions in animal tissues, mutagenicity and DNA-binding activity. Numerous agents representing many chemical classes have been found to have chemopreventive activity in one or more of these model systems.

Compounds classified as effective chemopreventive agents possess activities of three major types: carcinogen blockers (inhibit the uptake, formation, or activation of carcinogens, enhance the inactivation of carcinogens, or prevent the formation of carcinogen-DNA adducts); antioxidants that scavenge reactive electrophiles and oxygen radicals or inhibit the formation of eicosanoids; and agents that interfere with the proliferation/progression of transformed cells (modulate signal transduction or growth factor activity, inhibit or stimulate oncogene or tumor suppressor gene activity, respectively, induce apoptosis, or inhibit angiogenesis).

In the NCI prevention research program, particular emphasis has been placed on data from tests in experimental animal models in the ranking of candidate



compounds for potential applicability in human clinical prevention trials. Efficacy testing has been conducted in animal cancer models in which the target organs were selected because they were presumed to represent surrogates for human cancers. Specific animal bioassays in current use are discussed in chapter five. These experimental models may have been the best available at the time of selection, but their continued use in empirical screening of candidate compounds seems excessive, given the uncertainties involved.

Animal models in addition to those outlined above have been used by numerous investigators other than participants in the NCI prevention program for evaluation of agents in inhibiting the growth of additional tumor types, including esophagus, stomach, liver, pancreas, tongue, nasal and oral mucosa. Recent reports of several types of transgenic mice and a rat strain that spontaneously develops prostate tumors may expand the chemoprevention studies to include this tissue. No experimental animal models currently exist for the prevalent human cancers of other organs or tissues, importantly including carcinoma of the bronchus or ovary.

To date, over 2,000 agents representing at least 20 structural and pharmacological activity classes have been shown to have chemopreventive activity in or more of the above cited test systems; less than 10 percent of these have been subjected to *in vivo* testing in animal tumor models. Although these *in vitro* and *in vivo* studies have provided useful information, inherent characteristics of the models introduce major uncertainties about the validity with which the data that are derived may be extrapolated to predicting potential chemopreventive efficacy in the human. For example, the models generally use inbred rather than outbred strains of animals, which, as mentioned previously, results in far greater genetic homogeneity than is evident in human populations. Tumors are induced at high incidence by administration of potent chemical carcinogens, which in most cases are rarely, if ever, encountered by humans, and administered at doses that vastly exceed any human exposure. Of paramount importance is the major uncertainty centering on the relevance of the molecular and cellular mechanisms responsible for carcinogenesis in the animal models to those involved in human cancers.

The extent to which the multiple genetic changes underlying experimentally induced tumorigenesis are analogous to those involved in human cancer development is largely unknown. In the few instances in which comparable data are available, genetic alterations present in the animal models differ from those observed in tumors of the same tissues in humans. For example, a mutation in the ras oncogene is very prevalent in the MNU-induced rat mammary tumorigenesis model, yet this mutation is rarely seen in the comparable human cancer. Additionally, experimentally induced tumors do not always resemble human cancers of the same organ with respect to histopathology, growth and metastatic properties.

For these and other reasons, extrapolation of evidence of chemoprevention, obtained empirically in animal models, to potential use in humans is fraught with uncertainty.

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## **Animal Models for Metabolism and Pharmacokinetic Studies**

In addition to testing for efficacy, animal models are used to produce data on metabolism and pharmacokinetics that are important in assessing the possible value of chemopreventive agents for application to the human. Information generated in animal models on absorption, distribution (including placental transfer), metabolism (qualitatively and quantitatively), metabolism and excretion can often be directly compared with similar data obtained from human studies, thus facilitating cross-species extrapolation. Kinetic properties, blood and tissue concentrations, protein binding, plasma half-life, and rates of elimination all affect interpretation and extrapolation of dose-response relationships. Genetic polymorphisms affecting metabolism and disposition of substances, including carcinogens, mutagens, and chemopreventive agents, are rapidly identified in human populations. Polymorphisms exist in genes encoding enzymes responsible for activation of carcinogens, and their inactivation have been identified as determinants of cancer risk in human populations exposed to environmental carcinogens. Genetic and other determinants of metabolic competence can be assessed in animal models, which can be compared with human pharmacogenetic characteristics, providing information of great value in extrapolating effects across species. This factor will acquire greater importance as genotyping is increasingly employed for identification of subpopulations at increased or decreased risk of cancer development through carcinogen exposure.

[top](#)

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## **Animal Models for Development and Validation of Intermediate Biomarkers**

Progress in cancer prevention can be accelerated by the application of intermediate biomarkers to preclinical and clinical studies. The validation and eventual use of biomarkers that can detect early, specific changes that correlate with the reversal or progression of the carcinogenic process, is crucial for cancer prevention. Used as predictors of cancer, valid biomarkers can identify individuals at high risk who may then be recruited into intervention trials (see chapter 4). Biomarkers also have the potential for assessing the efficacy of chemopreventive agents less expensively and faster than would be possible using cancer as the endpoint. Importantly, incorporation of these developed and validated biomarkers will strengthen the rationale and enhance the human intervention trial.

One class of potentially useful biomarkers comes from studies of cancer risks in animals or humans exposed to endogenous and exogenous environmental carcinogens. Sensitive and specific analytical methods have been developed for detecting and quantifying the levels of covalent adducts of several important classes of carcinogens and blood proteins at ambient levels of exposure. Such biomarkers can be applied to the preselection of exposed individuals for study cohorts, thereby reducing the numbers of individuals that would be required for such studies.

However, successful application of these biomarkers to human prevention trials will be dependent upon prior determination of the associative or causal role of the biomarker in the carcinogenesis process, establishment of the relationship between dose and response, and appreciation of the kinetics of the adduct formation and removal. Animal models are essential for the development and validation of these biomarkers, including identifying and developing methods for the measurement of the specific biomarkers; determination of the relationships of carcinogen exposure and the level of the biomarker; establishment of the relationship between the level of the biomarker and the incidence of cancer; and assessment of modulation of the expression of the biomarker by the chemopreventive agent. Biomarkers validated in this manner in animals can be applied in parallel fashion to exposed human populations, through traditional epidemiologic studies and cohort interventions. Data generated in this manner will greatly facilitate analysis and interpretation of human chemopreventive interventions.

The success with which mechanistic information developed through the discovery process in animal systems has been adapted to the development and validation of biomarkers in this specific instance illustrates the value of close integration of experimental and human studies. Increased emphasis on this area of research within the prevention division is clearly warranted, and the approaches may serve as a useful model in the development of future research strategies.

[top](#)

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## **Recommendations**

- Decrease emphasis on screening of candidate chemopreventive agents through the existing animal model systems.
- Continue to develop new *in vitro* and *in vivo* models for identifying and assessing the efficacy of chemopreventive agents that integrate present knowledge of genetic and molecular alterations involved in human carcinogenesis.
- Develop intermediate biomarkers for assessment of exposure and biological effects applicable in prevention studies and validate their use in parallel studies in animals and humans.

[top](#)

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## **GENETIC PREDISPOSITION TO CANCER AND DETECTION OF PRECURSOR LESIONS**

### **Introduction**

The definition of a high-risk population in terms of cancer has changed dramatically in the past five years due to the explosion of knowledge in molecular genetics. These advances have designated a new category of high-risk individuals-populations with a highly penetrant predisposition to a specific cancer syndrome (e.g., inherited

*brca-1* mutations and breast and ovarian cancers). Moreover, other well-controlled studies have defined individuals in the population at increased risk for specific cancers. These advances are transforming the calculation of risk, which previously relied on the grouping of various risk factors to arrive at a statistically relevant risk threshold. This new approach to defining high-risk populations must be considered in the development of guidelines for early detection and screening. Prevention and screening strategies must take into account the distinctions among healthy populations at risk of primary cancer and those patients at risk of recurrence or second primary cancers.

These populations differ as candidates for primary prevention or secondary prevention strategies. The most immediate impact on these new high-risk populations may well come from preventive and diagnostic strategies rather than new therapeutic advances. Preventive strategies include changes in behavior, diet, and in exposure to various environmental and occupational carcinogens, as well as immunologic and pharmacologic approaches. Somewhere in the continuum between primary prevention and clinical screening lies early detection, the discovery of a clinically occult lesion still in the progression to clinically apparent cancer, and associated with a high chance for a cure.

Increasingly, standard histopathological assessment of these early lesions and their potential to progress to neoplasia are being augmented by the use of molecular and genetic markers. Even so, morphologic analysis of precursor lesions is subjective and fraught with difficulty; significant uncertainty remains regarding the malignant potential of such lesions. Molecular and genetic markers may eventually help to distinguish between lesions that are truly benign and those that are likely to progress to overt clinical malignancy, and may be useful as targets in the development of novel preventive and cancer detection strategies.

Complex social, legal, and ethical issues arise from testing affected or predisposed individuals and their families. The potential for insurance and employer discrimination, the complexities of psychosocial response to carrier and non-carrier status, and the dissemination of appropriate genetic counseling from primary care givers to patients and their families must be addressed. More direct communication and education of physicians and appropriate health care workers will be needed to integrate the new science into effective detection and screening strategies. Positive results from early detection of cancerous lesions may leave a shorter lead time before the development of overt clinical cancer than will positive results from some genetic predisposition tests. Consequently, intervention strategies may be different. It is important to distinguish between the two types of tests and educate health care providers and the population at risk.

It is likely that preventive, early detection, and screening strategies based on increasing and evolving knowledge of cancer genetics and the definition of new biomarkers will have a great impact on cancer rates in certain high-risk populations. The challenge is to find and develop new scientific and research approaches in early

detection and screening in order to develop more sensitive and accurate intervention strategies with the highest impact on survival.

[top](#)

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## Identification of High-Risk Populations

High risk populations, defined in chapter 1, include those individuals who have a hereditary disposition to the development of cancer, individuals chronically exposed to high levels of occupational or environmental carcinogens, and persons who exhibit premalignant lesions or who have been successfully treated for a first malignancy. Since cancer primarily is a family of diseases associated with increased age, older individuals might also be considered as comprising a high-risk population.

[top](#)

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## Populations with a Hereditary Predisposition to Cancer

Nowhere has the revolution in molecular genetics engendered simultaneously more hope, enthusiasm, and ethical concern than in the identification of the gene defects that underlie hereditary cancer predispositions. Cloning of several common cancer predisposition genes has occurred in recent years, including *msh2* and *mlh1* which predispose to colon cancer, and *brca1* and *brca2* which predispose to breast cancer. Although other heritable cancer genes were cloned much earlier (e.g., Rb for retinoblastoma), they are responsible for only a minute fraction of all human cancers.

Cases in families with these more common cancer predisposition genes still compose only a small fraction of all sporadic cancers, but they confer inordinate risk on carriers of these genetic alterations. Thus, their identification has helped defined new cohorts of patients with very high risk (in some cases, a near certainty) of developing specific cancers in their lifetime. However, within these cohorts there is often extensive heterogeneity in the age of the onset of disease, the tumor spectrum observed, and even survival in patients of equivalent clinical stage. Thus, new and effective early detection and screening strategies must be developed based on the biology of these cancers and the particular needs of these cohorts. The identification of these new genes has potentially opened up new opportunities for prevention and early detection. However, these new opportunities are accompanied by significant new challenges. It is apparent to this Review Group that many of the ethical and social dilemmas facing our society with regard to cancer predisposition testing can be more easily addressed if effective primary prevention, detection and screening strategies can be developed for these populations.

For the first time, we may be able to accurately determine the risk of cancer in carriers of these mutations. For example, some estimates predict that a woman with an inherited *brca1* mutation carries a lifetime risk of breast or ovarian cancer approaching 50 percent. Identifying such individuals allows consideration and

testing of new preventive and early detection strategies. In colon cancer, colonoscopy screening in high-risk families has led to a decrease in the incidence of cancer and an improvement in survival. Thus, results from such trials may provide life-saving prevention and detection strategies for affected patients. In terms of research opportunities, these high-risk populations provide extraordinary power for accurate statistical assessment of corresponding intervention strategies and appropriate validation, which could lead to the development of similar approaches in the more general population. Therefore, it is important to determine if these results can be generalized to the population at large. If so, study of these unique populations might greatly accelerate the introduction of new preventive compounds into the clinical setting and set the standard for novel diagnostic and screening approaches.

With these new opportunities, however, considerable challenges arise. The technology to accurately identify carriers through a reliable screening method is still lacking. When mutations are discovered, data are lacking for interpreting or predicting actual or lifetime risks of any specific cancers, from the more common cancers (e.g., breast) to other less common but increased neoplasms (e.g., ovary).

There are also likely to be potential functional differences between truncation mutations with complete abrogation of protein function versus missense mutations with perhaps more subtle protein alterations or none at all. Mutations also arise in individuals with diverse genetic backgrounds and different polygenic traits that can influence the risk of developing a particular cancer. These differences may be reflected in heterogeneous phenotypes in carriers with the same predisposition gene.

Despite the substantial biological and ethical challenges, precise identification of carrier status for asymptomatic individuals provides great hope for early intervention with novel preventive strategies, especially if the mechanism of action of the mutated gene is elucidated. These strategies include, but are not limited to, education for routine screening approaches, testing of novel chemopreventive agents, and implementation of new molecular detection approaches. It is probable that these preventive strategies will ultimately benefit carriers, their families, and the population at large.

[top](#)

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## **Persons at Risk Due to Occupational or Environmental Exposures**

Occupational and environmental exposures comprise a widely diverse group of risk factors that affect the general population. Although the relative risk of any of these risk factors individually may be relatively small, in aggregate, they confer a substantially yet potentially preventable risk for the population. In addition to occupational exposures, environmental exposures include, but are not limited to, radiation, various endogenous and exogenous compounds or agents that contaminate the environment as a result of increased technology, and viruses. Global prevention strategies are therefore not likely. Rather, prevention strategies should be targeted to

specific risk groups or cohorts for maximum benefit.

For patients with histories of industrial-based exposure or environmental exposures through smoking or viral infection, a relative-risk threshold has been deemed to be more appropriate. Smokers stand out in this group because they have a relative risk of approximately ten-fold over the nonsmoking general population for developing lung cancer and have a lesser increased relative risk for developing other cancers such as renal, cervical, and bladder cancers. The Review Group recommends that this population should be targeted for prevention and early detection strategies. Other exposed populations need to be considered on a case-by-case basis after appropriate epidemiological and statistical considerations for relative risk.

There are other definable populations with an increased risk of cancer. These include populations with simple allelic differences reflecting part of the general multifactorial or polygenic risk for cancer in the general population. Some of these differences may reflect catabolic pathways for certain carcinogens or have no known functions. Additionally, elderly patients can be considered at risk simply because of the increased risk of any cancer with age. In general, the Review Group felt that these risks may not cross relevant thresholds of relative risk to necessitate specific detection and screening strategies. As these risks become better defined, some cohorts may pass a critical threshold for cost-effective prevention and early detection strategies.

### **Persons with Premalignant Lesions**

Patients with a well-defined premalignant lesion are clearly at increased risk of developing cancer. Nevertheless, there is considerable evidence that these lesions may be reversible and/or potentially curable if identified. One important challenge is to identify better biologic markers suitable for predicting which of these lesions are likely to progress or to respond to chemopreventive therapy. Moreover, it is likely that more sensitive early detection techniques will increasingly identify these kinds of lesions. Therefore, the development of accurate biological markers, chemopreventive strategies, and effective screening will be necessary components in the arsenal for dealing with affected patients.

### **Patients Successfully Treated with First Malignancy**

Patients who have presented with one primary tumor are at significant risk for a second primary tumor. Increasingly effective surgical ablation, radiation, and adjuvant therapy have increased survival of patients after a first malignancy. For some of these patients, the risk of a second independent cancer may be greater than dying from a recurrence of the first tumor. Consequently, these patients must be included in more effective chemopreventive strategies. In head and neck squamous cell carcinomas, there is clear evidence that retinoids can prevent the occurrence of second primaries in these affected patients.

### **Biomarkers as Predictors of Disease**

Currently, morphologic (histopathologic) definitions of cancer progression from pre-neoplasia to neoplasia are the cornerstones of progression models. However, modern molecular genetics is rapidly improving our definition of cancer progression based on molecular-based models of progression. Much research is required in determining the risk of cancer progression for a given pre-neoplastic lesion, starting with an accepted threshold that carcinoma in situ should be a targeted lesion for early detection. A combination of one or more genetic markers may prove useful in defining the risk of progression of a subset of early lesions. Such early but high-risk lesions should then be targeted for early detection. Retrospective and prospective studies are required to define these molecular markers and to develop a definition that incorporates both morphologic diagnosis and modern molecular genetics.

### **Current Status of Molecular Markers**

DNA, RNA, and protein markers should be considered for early detection and screening. Theoretically, a simple blood test to detect the presence of early cancer lesions at specific cancer sites throughout the body would be optimal, but this is not feasible with current technology. Circulating cells presumably reflect the identification of tumors at later stages of progression. Therefore, even DNA- or RNA-based "blood" tests for early detection might be suboptimal. Circulating proteins could be secreted or shed from tumor cells and might be detectable at low levels in circulating blood if an appropriate marker was found. Theoretical sensitivity of these tests should be for a body burden of between  $10^7$  and  $10^9$  tumor cells, where  $10^9$  cells might represent a one- to two-centimeter tumor with a favorable prognosis, if identified before progression. More sensitive tests might identify lesions without a significant risk of progression and might lead to unwanted clinical intervention. Among the most important characteristics, regardless of the molecular marker developed, are sensitivity and specificity of the marker. In this regard, although DNA markers might be favored, a protein marker for a secreted protein that could achieve a high sensitivity with stringent specificity would be desirable.

With regard to DNA markers, well-defined genetic alterations including mutated oncogenes or tumor suppressor genes represent specific markers that should be further considered. Micro-satellite alterations suitable for identifying clonal populations should be further developed, but need to be better placed in terms of overall molecular progression models. Chromosomal deletions as surrogate markers of tumor suppressor genes may also be valuable, as recently demonstrated in urine screening for bladder cancer.

In terms of DNA-based testing, approximately one mutated allele among 10,000 wild-type alleles is a suitable target for diagnostic strategies. A sensitive test that might be able to identify one cell in  $10^6$  to  $10^7$  might be too sensitive and might detect a minimal clonal expansion of cells that are not destined to develop into clinical malignancy. Gene expression (e.g., RT-PCR) tests could potentially identify very specific markers present only in cancer cells. MAGE antigen in melanoma presents one of these specific extremes, while a much less specific test might



represent the detection of PSA transcripts in prostate cancer.

Emerging strategies include secreted protein targets and measurement of enzymatic activities such as telomerase. Telomerase activity is almost ubiquitous among transformed cells, providing a new potential neoplastic marker. However, the activity is not specific to transformed cells. It is also present in germline cells and some pre-neoplastic cells, lowering its sensitivity. A sensitivity of approximately 1 in  $10^4$  would be favorable for these type of techniques based on protein quantitation. Further development is needed for technology that identifies proteins relatively specific to the neoplastic transformation. In this regard, newer techniques that can trap discordant cDNA's between tumor and normal tissue or identify leader sequences that might lead to protein excretion might be favored. Sensitivity and specificity appear to be important endpoints for the development of protein markers.

[top](#)

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## Feasibility

Additional technological development must occur before new early detection strategies can be developed. Molecular biology and cancer genetics should be at the forefront of investigations to unravel the germline and somatic genetic alterations involved in cancer. Furthermore, the development of molecular progression models and the specific genetic changes involved in the progression of histopathological lesions should be emphasized. Although transgenic mouse models are important for understanding the biology of cancer, it is unclear if studies of such models will provide important insights into tumor progression in the human or the markers that may be important for early detection. Other animal studies are also important to the understanding of cancer biology but it is unclear how they will contribute to the development of human diagnostic tests.

A cooperative biorepository or other mechanism of storing and disseminating critical biological materials is crucial to the development of screening and diagnostic tests. Researchers must have access to high quality primary tumors (pre-neoplastic lesions and neoplastic lesions) with paired bodily fluids, blood, and serum. Currently, the cooperative human tissue network (CHTN) and the cooperative tumor registry provide some samples. Archival tissues are also available from the large cooperative oncology groups. However, few of these resources can provide all of the necessary materials and appropriate epidemiological data for prevention studies. There are also legal barriers to using stored human specimens or data with identifiers. The need for high quality materials cannot be overemphasized for adequately carrying out translational molecular studies.

[top](#)

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## Technology

Even the most promising new molecular markers are still limited by technical difficulties and the probable high cost of implementing them. NCI should encourage

the development and integration into new early detection strategies of new automated approaches as early as possible. The ability to lower cost and improve efficiency can greatly accelerate accurate testing of new technology for pilot studies, and eventually for larger prospective studies needed to validate their role in detection and possibly screening. Molecularly based early detection approaches might require differently automated, high-throughput and technological advances than screening approaches such as imaging.

[top](#)

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## **Funding Mechanisms**

Many of the studies that are needed to develop early diagnosis and screening strategies are more descriptive in nature and often are not hypothesis-driven. Consequently, research grant applications centering on these approaches have not fared well in the traditional peer-reviewed mechanisms. However, they are extremely important in the development of translational assays for eventual diagnostic use. It appears that a new way to evaluate these grant applications, with a specific emphasis on the use of the clinical material and translational assays, may be warranted.

NCI should facilitate interaction between groups that can develop the basic research strategies, those with promising early diagnostic techniques, and those groups that have the clinical resources to carry out the initial pilot studies and eventual clinical trials. Perhaps, interactive grant applications or facilitation of translational approaches through NCI-sponsored mechanisms might be encouraged.

Other NCI working groups have overlap with some of the important issues discussed here. In particular, the NCI Diagnostic Working Group is currently developing strategies for the isolation of good quality human material for the implementation of these studies. Moreover, the technology necessary to develop the diagnostics is appropriate for many of the strategies outlined here and these should be incorporated into an overall strategy.

The traditional mechanisms of reviewing these grants might be improved by adding molecular laboratory expertise or medical laboratory expertise (or perhaps industrial expertise) for the feasibility of some of these studies.

[top](#)

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## **Recommendations**

Better definition of the high-risk populations and of early detection techniques need to occur at the molecular level. Continued research on characteristics of individuals who carry mutated cancer predisposition genes offers great opportunity for the development of new strategies for early detection. It is important to target areas of research that may lead to the development of sensitive and specific molecular-based markers. The fledgling technology that is available to translate important findings

into clinical practice needs to be developed rapidly and interactions with other groups need to be fostered. A new type of review process and perhaps funding mechanisms should be developed to further this important translational work.

- Expand identification of high-risk healthy populations based on genetic predispositions and the development of new molecular markers.
- Investigate diverse nongenetic factors influencing the expression of genetic predisposition and the response to interventions, including the contribution of environmental exposures (radiation, exogenous and endogenous agents, and viruses) in cancer predispositions.
- Develop and discover new molecular markers for the early detection of cancer.
- Develop and expand existing biorepositories and provide new access with appropriate consent to such materials for the testing of new molecular detection strategies.
- Develop and improve new high throughput technologies for implementation of promising molecular diagnostic approaches into clinical trials.
- Perform comprehensive trials in targeted high-risk populations for validation and potential integration of novel prevention and detection strategies.

[top](#)

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## **CHEMOPREVENTION TRIALS IN HUMAN POPULATIONS**

### **Introduction**

Chemoprevention as a method of cancer control involves the administration of specific chemicals to prevent the development of cancer or to reverse or suppress carcinogenesis. The chemopreventive agents may be pharmaceuticals, supplemental vitamins or minerals, or other chemicals derived from natural products. As elaborated in chapter 3, understanding of carcinogenesis has evolved from highly controlled animal model studies. Studies of the initiation and progression of carcinogenesis have shown gene mutation and cell proliferation to be the major determinants of the rate of carcinogenic progression; there might be agents that could block the activation of potentially mutagenic carcinogens or prevent cellular hyperproliferation.

Powerful new molecular tools have made it possible to more fully understand the multi step carcinogenic process. These tools may also identify molecular markers of specific stages of the progression of cancer, which may become useful for establishing valid intermediate endpoints for chemoprevention trials. In fact, the evaluation of these intermediate endpoints might yield further insight into the progression of cancer, more refined indicators of cancer incidence, and better selection of new agents for Phase III clinical trials. The following section highlights the complexities of bringing a chemopreventive agent to a Phase III clinical trial, which has as a major endpoint reduction in cancer incidence.

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## The Clinical Trials Process

Preclinical toxicity screening in animals does not always accurately reflect toxicity in humans. Short-term Phase I chemoprevention trials are the first step in evaluating new agents for toxicity. Specifically, Phase I trials are performed to determine the dose-related safety and pharmacokinetics of a new agent or combination of agents in normal subjects or persons with premalignant lesions (e.g. actinic keratosis of the skin, adenomatous polyps of the colon, cervical intraepithelial neoplasia, bronchial metaplasia/dysplasia, atypical nevi, bladder Ta,T1 lesions, prostatic intraepithelial neoplasia, breast ductal or lobular atypical hyperplasia or carcinoma in situ, and Barrett's esophagus). The agent(s) must have Food and Drug Administration (FDA) Investigational New Drug (IND) and Good Manufacturing Practice approvals. A dose escalation scheme permits evaluation of acute and subacute toxicities, pharmacokinetics, dosage for Phase II trials and patient adherence to the regimen.

Phase II and III trials are used to test drug activity. Phase II trials are short-term assessments of potential efficacy against intermediate endpoints of cancer risk, typically precancerous lesions. Increasingly, however, sophisticated biological markers of genotypic and phenotypic changes may serve as intermediate endpoints for study. In preliminary Phase II studies, IIA, there is usually a one- to two-month period on placebo to determine adherence and obtain baseline symptom information, followed by a three- to six-month-intervention period at two or three different dose levels of the chemoprevention agent. Tissue biopsies are obtained at baseline and at the end of dosing for intermediate endpoint biomarkers which reflect genotypic and phenotypic changes. This type of trial design is especially advantageous when using potent agents with substantial dose-dependent toxicity to determine the lowest, least toxic drug dose which retains presumed chemopreventive activity.

In another type of Phase II trial, IIB, preliminary intermediate endpoint modulations are confirmed through randomized trials. The major endpoint of such studies is still modulation of biomarkers of cancer risk, such as cellular proliferation, cellular differentiation, DNA mutations, apoptosis, endocrine changes, polyamine synthesis, loss of tumor suppressor functions, oncogene expression, or other biochemical changes; safety is monitored as well.

After Phases I and II, large-scale studies can be designed to determine long-term efficacy in reduction of cancer incidence or of precancerous lesions. The majority of Phase III studies target reduction of a precancerous lesion as the primary endpoint. The advantages of the Phase III design are modest size (500 to 2,000 participants), shorter duration, and moderate cost (\$5-10 million over 5 to 8 years). For example, there are about six current U.S. studies designed to evaluate the efficacy of chemopreventive agents such as calcium, ursodeoxycholic acid, aspirin and folic acid in the reduction of colorectal adenoma recurrence. In addition, Phase III studies have been initiated in subjects with actinic keratoses, oral leukoplakia, and cervical

dysplasia.

Phase III studies involve participants at increased risk for the development of a specific cancer (e.g., breast, colon, lung, prostate) with cancer incidence as the primary endpoint. Several of these large, long duration, expensive trials have been initiated (15,000-30,000 participants; \$20-80 million over 10 to 15 years). A key aspect of their design is the development of a vanguard cohort to evaluate long-term toxicities potentially tied to cumulative dose, and allowing for early discontinuation or modification in the case of unexpected or severe adverse effects. Since relatively few Phase III studies can be conducted at any one time, it is most appropriate to consider their aggregate cost and scientific and public health benefits.

A challenge for chemoprevention trials is to validate the reliance on surrogate endpoint biomarkers and precancerous lesions in place of actual cancer incidence. These intermediate endpoints may be genetic, biochemical, or pathological. Validating biomarkers and intermediate pathological lesions as endpoints is a potential side-benefit of large trials with clinical cancer endpoints. Also, the results of the trials should stimulate much new laboratory and epidemiologic research.

A well-defined process of decision-making about target organ sites, appropriate populations, credible endpoints, and candidate chemoprevention agents is essential. Preclinical studies of efficacy and toxicity, epidemiological observations, followed by toxicity assessment and dosing studies in humans, must precede large-scale trials. The National Cancer Institute (NCI) Division of Cancer Prevention and Control (DCPC) has had a number of accomplishments during the past 10 yr in prevention trials. These accomplishments are listed in an Appendix.

[top](#)

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## **Preclinical Development and Selection of Candidate Agents for Human Trials**

Over the past 20 years, the Chemoprevention Branch of DCPC has designed an extensive, orderly process for identifying existing pharmaceuticals, dietary constituents, and other chemicals for testing as chemopreventive agents. To various degrees, the Branch works with intramural and extramural scientists and the FDA in characterizing candidate agents in a number of animal models of site-specific cancers, in mechanism-based carcinogenesis-related biological assays, and in preclinical toxicological screens. Promising agents are then placed in human Phase I safety trials and Phase II small-scale randomized efficacy trials, of which many are ongoing at the present time. The Branch has published well-documented reviews of 32 chemopreventive agents (J Cell Biochem 1994, Suppl 20; J Cell Biochem 1996, Suppl 26). In addition, it has sponsored consensus exercises on the status of intermediate endpoints for colon, prostate, bladder, upper aerodigestive tract, breast, and cervix, endometrium, and ovarian cancers.

Agents which already have full toxicological profiles, FDA approvals for other medical uses, and adequate supplies of properly formulated preparations are

assigned a preferred status for practical reasons. Of course, their availability should not override sound judgment about biological plausibility for chemoprevention.

Despite some successes, the Review Group has reservations about the relevance and currency of the NCI preclinical chemoprevention program. Ideally, animal model test systems should reflect the major tumor sites in the human; arise from a malignant transformation of the same type of cell as found in humans; be initiated with agents known to produce similar effects in humans; and respond to nutritional, hormonal, or pharmacological interventions with similar pharmacokinetics and pharmacodynamics as in humans, including analogous intermediate endpoints.

The current array of eight animal systems includes the following:

- a) methylnitrosourea (MNU)-induced hamster tracheal squamous cell cancer
- b) diethylnitrosamine (DEN)-induced hamster lung adenocarcinoma
- c) azoxymethane-induced rat colon carcinoma (and aberrant crypts)
- d) methylazoxymethane-induced mouse colon carcinoma
- e) 7,12-dimethylbenz[a]anthracene (DBMA)-induced rat mammary adenocarcinoma
- f) MNU-induced rat mammary adenocarcinoma
- g) two-stage DMBA-phorbol ester mouse skin papilloma
- h) N-butyl-N-(hydroxybutyl)-nitrosamine-induced mouse bladder cancer.

The above systems were chosen approximately seven years ago following recommendations of an external advisory committee to DCPC staff. It should be noted that MNU is not responsible for lung or breast cancer in humans, DEN, OH-BBN, and DMBA do not cause lung, bladder, or breast cancer, respectively, in humans, and the two-stage mouse model, while good for detecting anti-promoters, is limited to this particular class of phorbol esters. The models chosen do represent some redundancy for lung, colon, and breast cancers, while not studying other sites of interest. The utility of these animal models as a screen for chemopreventive agents has not been reviewed since their adoption. The Branch has recognized this problem and is currently studying the potential use of 11 transgenic mouse systems, representing seven different target organs, as models for assessing chemopreventive efficacy. As new transgenic models become available, the Branch will assess their efficacy using known positive-control chemopreventive agents, evaluate these strains for use of endpoints, and determine issues of cost and supply. It is expected that some of these models will replace the older carcinogenesis systems.

There is a perception externally that only those institutions that have previously been awarded Master Agreements and agree to conduct pre-specified protocols in these systems are eligible to bid for contracts to assess the chemopreventive efficacy of candidate agents chosen by the DCPC Chemoprevention Branch. The process has been criticized as bureaucratic and inflexible concerning introduction of newer

models and procedures, such as the min mouse and the p53-knockout mouse.

Although the Chemoprevention Branch has worked with intramural and extramural scientists in the NCI Divisions of Cancer Epidemiology and Genetics and Cancer Treatment, Diagnosis, and Centers to identify candidate chemopreventive agents, the Review Group believes that stronger links should exist between the chemoprevention program and basic cancer scientists to ensure that the best basic science supports chemopreventive efforts, to incorporate the latest findings from animal models scientists with knowledge of carcinogenic processes at the genetic, molecular, and cellular levels, and to employ initiating agents that are known human carcinogens.

Administratively, the chemoprevention drug development effort is directed almost exclusively by internal NCI staff. The Review Group recommends a change in the structure and mode of operation of this activity through establishment of a broadly based advisory committee to encourage the development of innovative screening tests, and to generate criteria for selection of candidate chemoprevention agents for animal and human trials.

*The Review Group recommends the formation of a new Preclinical Chemoprevention Drug Development Committee which would advise the director of the prevention division through the Board of Scientific Advisors of the NCI. This committee would consist of members from this Board supplemented by outstanding extramural prevention investigators, staff from the prevention division, and FDA.*

The committee would be mandated to:

- define the drug discovery program
- stimulate creative approaches in the development and use of new and most appropriate animal model systems
- evaluate candidate chemopreventive agents for cellular and animal screening tests
- assess the evidence of efficacy and safety from the animal studies
- set guidelines for selecting agents for human trials.

[top](#)

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## **Populations to be Studied in Chemoprevention Trials**

The vast majority of cancers occur in people with no presently known genetic predisposition. However, incidence rates at various organ sites differ by age, gender, and ethnic group. Thus, some people are known or can be predicted to be at higher risk than others for cancer. Such predictions should become more precise as genetic and nongenetic risk factors are better characterized, including their interactions. In addition, cancer survivors are at increased risk for the appearance of a new cancer or

recurrence of a previously diagnosed cancer. These differences in risk can be exploited in designing biologically sound investigations of the efficacy and safety of proposed chemopreventive interventions.

Scientific merit and relevance should be the guiding principles in selection of populations for investigations of mechanisms, effectiveness, and safety of chemopreventive agents. Preference should be given to cancers with the highest mortality and morbidity. However, sometimes the most compelling and feasible studies involve uncommon cancers, from which generalizable information can be extracted. Major prevention trials already have been launched in breast and prostate cancers with anti-estrogen and anti-androgen agents, respectively, and in breast, lung, and colon cancers with retinoids and carotenoids.

High-risk subpopulations can and have been defined by recognizable risk factors, e.g., family history of breast cancer, smoking history of long duration, occupational exposure to asbestos, sun exposure, infection with human papillomavirus or *Helicobacter*. Sometimes these populations can be defined by testable risk factors, such as various inherited *brca1* and *brca2* mutations, or high serum levels of prostate-specific antigen. Even in these high risk and identifiable populations, however, large sample sizes must be followed over long periods of time in order to demonstrate reduction in cancer incidence.

Chemoprevention agents may be used as adjuncts in cancer treatment protocols and as potential preventive agents after successful treatment, with the objective of reducing the incidence of recurrences and of new primary tumors in cancer survivors. The risks of such events are elevated, the tolerance for side effects may be greater than in the general population, and the motivation is likely to be high. However, the annual incidence rate is typically very low (1 to 3 percent), highlighting the necessity that studies in humans are safe and well tolerated, and that substantial numbers of participants must be recruited in order to show a statistically significant reduction in incidence rates. The whole dynamic of chemoprevention trials is different from that of aggressively treating individual patients with newly diagnosed or recalcitrant cancers.

[top](#)

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## **Methodological Considerations**

Variables to be considered in designing large chemopreventive trials include incidence rates for the disease, duration of the intervention, distribution of exposures or risk characteristics, and most importantly, the anticipated magnitude of the risk reduction from the intervention. Analyses must make provision, via stratification, matching, or regression modeling, for factors which can confound the association or intervention effect under study.

If a prevention trial aims to test reduction in the incidence of an intermediate



endpoint, rather than a clinical cancer endpoint, the incidence and the means of validating the intermediate against clinical endpoints must be assessed. Presently, there are open questions about whether responses of intermediate endpoints, such as polyps of the colon, ductal carcinoma in situ of the breast, prostate-specific antigen serum level, and polycyclic aromatic hydrocarbon-DNA adduct levels in bronchial biopsies, can reliably and proportionately reflect reduction in future incidences of cancers.

Fleming and DeMets<sup>1</sup> point out how often logical biochemical, pathological, and clinical precursor "endpoints" fail to correlate with clinical outcomes for cancer, cardiovascular disease, and overall mortality. The confidence with which laboratory and epidemiologic researchers predict benefits of various interventions and appropriateness of specific surrogate endpoints must be validated by human trials. The cost of untested presumptions can be high.

When a preventive intervention is proposed for routine application in public health, evidence of the efficacy to toxicity ratio gained from scientific investigations in carefully conducted trials in relevant populations becomes a guiding benefit/risk principle.

[top](#)

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## **Cancer Prevention Trials Group**

Having reviewed the present organization of the NCI prevention trials program, the Review Group has concluded that a major reorganization is warranted. Prevention trials in the United States are currently conducted through the Oncology Treatment Trials Groups. The major focus of these groups has been in therapy of patients who already exhibit symptoms of cancer. In addition, these Groups have used much smaller populations of patients for their studies than are required in many prevention trials. The Review Group recognizes that the Treatment Trials Groups are becoming more involved in prevention research, as is evident in the Southwestern Oncology Group, but nevertheless, the Review Group recommends the formation of a multimodality prevention trials group.

The proposed prevention trials group would be analogous to the Treatment Trials Groups found in the NCI Division of Cancer Treatment, where three large cancer treatment trials groups exist for adult patients, two for pediatric patients, as well as other small groups that are organ-oriented. The prevention trials group would have a principal investigator/director, a statistical center, administrative staff, and a board of directors representing the participating institutions. The group would receive competitive funding to be used in accordance with its priorities, with input from NCI.

To date, two prominent trials have been undertaken by the Treatment Trials Group, the Breast Cancer Prevention Trial (with tamoxifen) and the Prostate Cancer Prevention Trial (with finasteride). Nevertheless, it is universally recognized that

prevention has received low priority in the present trials groups, reflecting their treatment focus and ties to oncologist referral and recruitment sources. For primary prevention trials in high-risk, healthy volunteers and eventually in the broader population, the cancer prevention trials groups must mobilize trial designs, recruitment strategies, and infrastructure distinct from those of the standard treatment trials. The Review Group encourages the Treatment Trials Group to continue increasing their efforts in prevention research. Through the combined efforts of both the Prevention Trials Group and Treatment Trials Groups, prevention opportunities would be available through larger numbers of individuals which would result in a significant impact upon cancer incidence.

The physicians responsible for the Community Clinical Oncology Program (CCOP) sites and Minority CCOP sites, generally medical oncologists, can be important allies in the development and conduct of Phase II and Phase III chemoprevention trials. Criteria for participation and funding for recruitment and maintenance of participants need to be developed. As indicated, the CCOP sites and Minority CCOP sites generally participate in studies on treatment so their administrative location within the prevention division might not represent the best solution. This deserves further study.

[top](#)

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## **Prevention Trials Committee for Biological Studies**

The Review Group recommends an organizational structure to more closely link elements of the National Cancer Program with a prevention trials program. Administratively, this committee could represent a subset of the Board of Scientific Advisors, to be supplemented on an ad hoc basis by appropriate extramural and intramural expertise to ensure adequate representation in the relevant scientific areas.

*Specifically, the Review Group recommends that a prevention trials committee for biological studies be formed within the Board of Scientific Advisors of the NCI, comprising outstanding basic cancer scientists, clinical investigators, and molecular epidemiologists. It is conceivable that a single subcommittee of the BSA could fulfill the responsibilities assigned to the preclinical chemoprevention drug development committee and the prevention trials committee for biological studies.*

This committee should:

- stimulate and review proposals for ancillary biological studies on tissues and DNA from participants in prevention trials
- stimulate the use of the best available methods to validate intermediate molecular, biochemical, pathological, and clinical precursor endpoints against clinical cancer endpoints
- identify approaches to elucidate carcinogenic mechanisms, including studies of previously unsuspected properties of candidate

chemopreventive agents.

[top](#)

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## **Disease Prevention Trials with Endpoints Other than Cancers**

Although a focus on a single primary cancer outcome is feasible in early phase trials and possibly in efficacy trials among very high risk subgroups, it is usually important to consider a range of other outcomes. For the general population, specific cancer endpoints, or even total cancer endpoints, may constitute only a modest portion of the expected morbidity and mortality.

A need exists for the formal development of methods for risk versus benefit assessment in disease prevention trials. External Safety and Data Monitoring Committees that review and evaluate evolving data during the trial need guidelines for joint examination of multiple important endpoints and weighted judgment.

The Review Group recommends that the NCI prevention division collaborate with other institutes of NIH to incorporate non-cancer endpoints into cancer prevention trials and to request that cancer endpoints (and sufficient statistical power) be incorporated in trials initiated by other institutes.

[top](#)

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## **Recommendations**

- Ensure the conduct of randomized trials in human populations as the gold standard for scientifically demonstrating ways to reduce cancer incidence. Ensure the existence of a well-defined process of decision-making about target organ sites, appropriate populations, credible endpoints, and candidate chemoprevention agents for human trials. Large-scale studies should be preceded by extensive preclinical studies, epidemiological analyses, and toxicity assessment in humans.
- Design recruitment strategies to attract healthy people as participants in cancer prevention trials. High-risk but otherwise healthy people are identified as the following: individuals with predisposing genetic traits or a positive family history of cancer; persons engaging in high-risk behaviors; individuals with high exposures to occupational and environmental carcinogens and cancer-associated infections; and the elderly.
- Restructure the chemoprevention preclinical drug development effort.

**a)** Form an advisory committee as a subset of the NCI Board of Scientific Advisors, supplemented with other outstanding extramural basic scientists, clinical investigators, molecular epidemiologists, and staff of NCI and the Food and Drug Administration. Mandate the committee to define the drug discovery program, stimulate creative approaches in the development and use of new animal model

systems, evaluate candidate chemopreventive agents for cellular and animal screening tests, assess the evidence of efficacy and safety from animal studies, and set guidelines for selecting agents for human trials.

**b)** Continue to upgrade the in vivo animal systems for screening of efficacy and safety of chemopreventive agents through the use of the RO1 grant mechanisms in addition to the present contract mechanisms.

**c)** Continue to use the master agreement contract mechanism for routine pre-clinical toxicological testing and for routine screening for chemopreventive efficacy. However, there should be frequent, open, re-competition with clear opportunities for developers of new assay systems to also become master agreement contractors.

**d)** Develop and validate biomarkers and intermediate endpoints in concert with those being developed and assessed in humans.

- Restructure the NCI prevention division's program for Phase I, II, and III trials to reflect a stronger extramural component by establishing one multimodality cancer prevention trials group (patterned after the Oncology Therapy Trials Groups). This group will:
  - a)** develop and solicit proposals for Phase II and III cancer prevention trials with one or multiple modalities, i.e., behavioral, dietary, pharmacological, immunological, and combinations thereof.
  - b)** evaluate the scientific basis, recruitment strategies, statistical power, feasibility, and public health significance of competing proposals for trials.
  - c)** make awards for Phase II trials, and work with NCI to obtain the necessary funding needed for Phase III trials
  - d)** jointly sponsor trials, to prevent the appearance of new cancers and recurrences in patients, with established treatment trials groups to marshal the right combinations of experience and capability.
  - e)** stimulate methodologic research on efficient, cost-effective prevention trials design.
  - f)** provide to the scientific community administrative guidance regarding safety and efficacy monitoring boards, Food and Drug

Administration Investigational New Drug applications, institutional review board policies, requirements for medical record and biological specimen retention, and how to achieve inter-institute collaboration on data collection for multiple endpoints.

- Form a special committee for biological studies which would stimulate and review proposals for ancillary biological studies on tissues and DNA of participants in prevention trials, and stimulate the use of the best available methods for validating intermediate endpoints to take better advantage of existing prevention trials. These functions could be incorporated into the recommended BSA subcommittee.
- Devise and implement a mechanism for collaboration between NCI and the other NIH institutes to incorporate non-cancer endpoints into cancer prevention trials and cancer endpoints into non-cancer trials initiated by other institutes.

[top](#)

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## **BEHAVIORAL RESEARCH AND BEHAVIORAL INTERVENTIONS TRIALS IN CANCER PREVENTION**

### **Introduction**

There is strong evidence for a role of behavioral factors (alone or in combination with other risk factors) in determining cancer incidence and mortality. Studies using death certificate data to analyze causes of death in the United States for 1990 concluded that at least 50 percent of mortality could be attributed to external, non-genetic factors, most important, behavior. Use of tobacco, overuse of alcohol, improper diet (e.g., too little fiber or too much fat), exposure to sunlight, and failure to take precautions to reduce exposure to occupational/environmental hazards are all behaviors that have been linked to cancer causation. In addition, some behaviors, such as smoking, may be especially risky for people who have certain genetic predispositions.

Behavior change strategies should be a fundamental component of a National Cancer Institute (NCI) program in primary cancer prevention and early detection. Although the sources of data supporting this assertion vary, as does the strength of the evidence, there is more than sufficient evidence that the behavioral causes of disease can be modified. Behavioral science methods are critical in achieving both primary and secondary cancer prevention. Behavior strategies should focus on behaviors for which there is scientific evidence linking the behavior to changes in cancer incidence and mortality. In addition, the expected changes should be feasible and realistic.

Efforts to modify cancer-related behaviors have contributed to a reduction in the total cancer burden. For example, since 1965 the proportion of Americans who smoke have decreased from 52 percent to 26 percent, and lung cancer rates in men have declined. In addition, an increased understanding of barriers to cancer screening has made it possible to develop effective strategies to promote adherence to breast and cervical cancer screening. From 1987 to 1992, the period in which the application of behavioral interventions increased substantially, the proportion of National Health Interview Survey (NHIS) respondents who reported having a recent mammogram increased at least twofold for women in every age and ethnic group.

Behavioral research has also made major contributions to the knowledge of individual and treatment-related variables that affect quality of life in persons with cancer. This knowledge has been translated into effective psychosocial and behavioral interventions to reduce cancer pain, enhance quality of life, and in some cases, prolong survival.

Despite these successes, important needs for behavioral research in cancer prevention remain. While overall smoking rates and mortality have declined in men, the rates have declined more slowly in women and minorities and have increased in children and teenagers. These are populations that should be addressed through all levels of intervention research. In addition, few interventions have succeeded with heavy smokers.

Although about 30 percent of mortality from breast cancer in women over age 50 and nearly all mortality from cervical cancer can be avoided by increasing screening, adherence to both breast and cervical cancer screening is still sub-optimal among some population subgroups, for example, women of low socioeconomic status. Rates of adherence to recommendations for colon cancer screening remain extremely low among all age-eligible Americans.

At a 1996 NCI-sponsored meeting on Behavioral Research in Cancer Control, participants reviewed the needs for behavioral research and made recommendations for priorities. Several of these are in the area of prevention and should be a major focus of NCI's prevention program. They include the following.

- Prevent tobacco use in children and teenagers.
- Enhance the accurate understanding of cancer risk by the public and health professionals and facilitate informed decision-making about genetic susceptibility testing for cancer and cancer screening.
- Improve the behavioral outcomes of genetic testing for cancer susceptibility- this includes helping people make informed decisions about testing and its aftermath and cope with the results of testing.
- Enhance long-term survivorship of cancer patients by encouraging adoption of healthy behaviors and adherence to appropriate follow-up regimens (also a cancer control topic).
- Promote a healthful diet and physical activity.

- Integrate prevention and early detection services into changing health delivery systems, most notably, in managed care organizations. These changes in health care delivery may require conceptually different approaches to intervention.

Beyond direct links between behavior and cancer, there are other needs for behavioral interventions, for example, to determine appropriate strategies for facilitating recruitment to prevention trials, and to encourage adherence to preventive interventions. Thus, behavioral interventions not only are important by themselves but also may be supportive for other cancer prevention interventions. The strategy proposed here should be seen as part of a larger plan to strengthen behavioral research in cancer control.

[top](#)

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## **Behavioral Interventions**

If the primary function of NCI is discovery, then one of the goals should be the understanding of the biological and psychological bases of behavior and development of effective behavioral interventions to change behavior in order to reduce cancer incidence and mortality. Such interventions should reduce cancer incidence and mortality by reducing exposure to harmful agents or increasing use of positive agents. Program emphasis should reflect the strength of the scientific evidence and the potential for reducing the cancer burden. Discovery should proceed, as in other fields, from basic, often laboratory-based research, to small-scale hypothesis testing research, and then to studies with the power to conduct efficacy tests (Phase I through IV clinical research).

There is an urgent need for laboratory-based behavioral research to identify mechanisms of response and to conduct some of the precursor research for intervention development. Too often, expensive efficacy tests have been conducted before optimal interventions have been refined through smaller scale research studies. A careful development process is essential to high quality behavioral research. Review committees need to be educated to understand the importance of this multi-level approach. In addition, research should occur in many settings, such as clinics, work sites, and the community. Proactive interventions that reach people who may not be motivated to seek treatment also are needed and may prove to be cost effective.

There still are few proven behavioral interventions in prevention, but progress has occurred, and successful interventions have been demonstrated in a number of areas. For example, research over the last decade has shown that brief, provider-initiated interventions achieve modest but significant reductions in smoking, combinations of the nicotine patch and behavioral interventions result in 12-month quit rates of 30 percent or more, brief telephone counseling can triple the odds that women will

obtain mammograms, and tailored interventions can increase the use of fiber, decrease fat intake, and increase smoking cessation. More recently, some interventions have been found effective in reducing distress associated with cancer risk and in improving comprehension of risk. Similarly, integrated nutritional and behavioral interventions have been developed that appear to be capable of inducing and maintaining major dietary changes.

Yet to date few interventions have been effective in preventing tobacco use by children and adolescents and substantially more research must be conducted to develop more effective interventions to help smokers, including heavy smokers, quit smoking. Such approaches should include the development of more effective pharmacologic strategies. Moreover, although there have been some effective strategies for reducing dietary fat or increasing fiber, these have been disappointingly few, and more research in this area is needed.

Increasingly, prevention investigations should focus not only on the population as a whole but on high risk subgroups, such as cancer survivors, those with pre-malignant lesions, and people with genetic susceptibility or exposure to certain carcinogens. (These groups are discussed in chapter 4.) Attention should be paid to the many ethical issues, cultural, social, and legal issues that arise in conducting research on high-risk individuals, especially in areas related to genetic susceptibility.

[top](#)

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## **Components of a Behavioral Research Program in Prevention**

The NCI prevention program should be a leader in behavioral research intervention, and should provide intellectual leadership in this critical area. A vital, innovative, outstanding behavioral research program should include nine components.

[top](#)

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## **Epidemiology Foundations**

There must be a strong connection between epidemiology and behavioral research. Whenever practical, the scientific foundation should be demonstrated before behavior change is encouraged on a population basis, although behavioral interventions might be a component of a risk factor reduction trial that focuses on reduction in cancer incidence. Epidemiology can also contribute information about subgroups of people who may be appropriate targets for intervention because of genetic susceptibility or those who may suffer more harm from exposure to a carcinogen. There must be a systematic process for assessing when a particular area is ready for behavioral intervention. Only when epidemiologists and behavioral scientists work collaboratively will the knowledge of one science lead to changes in behavior than can, in turn, reduce cancer incidence.

[top](#)

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## **Expertise in Measurement and Evaluation**

NCI can serve as a leader to improve the validity and precision of measurement in areas such as dietary assessment, risk perception, and reporting of cancer screening behavior. There should be a recognition of both systematic and random measurement errors. NCI should encourage more standardization and appropriate research on measurement tools and models. Understanding of special design issues for behavioral trials also is needed in order to assess the impact of interventions. For example, large community trials are expensive when the unit of randomization is the community. More attention should be paid to methodological solutions that would permit researchers to answer questions in community settings without the large expense and long time frames involved in multi community randomized trials.

[top](#)

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## **Access to National Data on Key Behaviors**

There are substantial national databases that can provide excellent data for planning and evaluating behavioral interventions. Unfortunately, these data bases are too infrequently used by the scientific community. In order to assess what behaviors require intervention, to identify subgroups that require intervention and to assess progress, national data on key behaviors should be tracked. The Surveillance End Results Registry (SEER), Behavioral Risk Factor Surveillance Survey (BRFSS), National Health Interview Survey (NHIS), and other national sources of data should be mined and used for tracking changes. In addition, the development and/or use of international databases also should be encouraged. Extramural scientists should be encouraged to use these databases, and access barriers should be reduced.

Staff at NCI must also have expertise in using claims and other data since these data sources are becoming increasingly important for the evaluation of interventions. In areas where there are knowledge deficits, NCI might commission focus groups or other qualitative or quantitative data collection. In addition, there must be staff who can make the linkage between such data and the process of identifying target populations and developing interventions.

[top](#)

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## **Knowledge of Theories of Behavior**

An understanding of behavior theory is fundamental to the development of appropriate interventions. This includes diverse theories, such as Social Learning Theory, the Stages of Change Model and the Health Belief Model. Behavioral science theory and research can provide insights into why people of diverse cultural backgrounds behave the way they do and what interventions can be used to change behaviors. NCI should encourage the continued development of research to strengthen the theoretical basis of health behavior.

[top](#)

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## **Understanding of Behavior and Behavior Change**

Behavior change can be facilitated by an understanding of the causal mechanisms that underlie health behaviors. Simplistic notions of behavior (e.g., if mammography is free, women will get mammograms) sometimes have led to the application of ineffective interventions and a focus on inappropriate populations. Research is needed at all levels in order to understand health behavior and develop effective behavior change interventions. Careful laboratory-based, and small scale research are essential to advances in understanding behavior. For example, research using MRI and other imaging techniques is helping to elucidate the biological mechanisms of addiction. Similarly, anthropological and other qualitative research can help explain how differing perceptions of cancer might be influenced by such factors as low socioeconomic status, ethnicity, and geographic area, which, in turn, might affect the behavior of populations.

[top](#)

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## **Expertise in Cancer Risk Communication**

Many of the challenges in behavior change for cancer prevention depend on effective communication about cancer risks and recommended risk reduction strategies. There is much evidence that people have biases in how they process information about cancer risk. For example, they tend to underestimate more common risks, such as those from smoking. If people are to make informed decisions about cancer prevention and early detection, they must have an improved understanding of cancer risks and the benefits and limitations of recommended interventions.

[top](#)

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## **Strength in Intervention Design**

Interventions to change cancer-related behavior are the sine qua non of behavioral research in cancer prevention. There must be expertise in developing interventions across settings, population groups, and channels, for example, home, health care practice, worksite, community populations and readiness for change. Interventions can occur at the individual level, various group levels, and the community. They may range from individual counseling interventions to community-level and policy-level interventions. Different behaviors require intervention at different levels. Some behaviors, such as smoking, may require intervention at multiple levels.

Increasingly, the development of behavioral interventions should reflect advances in other areas of science and technology, such as, the ability to develop tailored communications that are individualized to characteristics of an individual. These communications may enhance the appeal, relevance, and comprehensibility of health information.

In addition, counseling interventions should be improved, and community

applications strengthened. More attention should be paid to developing interventions that are appropriate to the needs of special populations, including the poor, low literate, older adults, ethnic minorities, and immigrants.

[top](#)

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### **Expertise in Economics and Cost-effectiveness**

Interventions should be developed with cost-effectiveness in mind. Expertise in economics, especially the development of methods for assessment of costs and cost-effectiveness, is an essential component of a behavioral research program in prevention.

[top](#)

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### **Mechanisms for Dissemination**

Although in many cases NCI will not be the appropriate organization for dissemination, it should take a proactive approach in determining how effective interventions can be disseminated. NCI should develop processes, procedures, and criteria for disseminating proven interventions through partnerships with other government agencies, such as the Centers for Disease Control and Prevention (CDC), as well as voluntary organizations, such as the American Cancer Society. Responsibility for dissemination should be part of the behavioral research mandate. While NCI cannot continue to fund successful interventions indefinitely, there should be some models to demonstrate how seamless transfer to CDC, for example, can be achieved.

[top](#)

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### **Trans-NCI and NIH Collaborations and Initiatives**

To date, most behavioral research initiatives within NCI have emanated from DCPC. It would be desirable to interact more actively and regularly with researchers throughout NCI and NIH in order to accelerate progress in preventing cancer. A few examples are provided here. Collaborations with basic scientists may provide clues regarding what animal studies might have implications for humans. Behavioral researchers should collaborate with genetic epidemiologists to identify the important behavioral issues related to genetic susceptibility testing. This is important, because many strategies transcend diseases and depend on communication, cultural, social and psychological processes that are not disease-specific. Similarly, there should be collaborations with physiologic and epidemiologic scientists studying the role of exercise and diet in cancer etiology. Behavioral researchers also should work closely with scientists who are planning chemoprevention trials. Collaborations with scientists in the treatment area might focus on testing prevention interventions in cancer survivors. Productive collaborations with the Office of Cancer Communications also are essential to develop theory-driven health communications.

A partnership with the NIH Office on Behavioral and Social Science Research is

important in developing a behavioral research plan consistent with the NIH strategy. The National Institute of Drug Abuse, the National Heart Lung Blood Institute, and CDC have been leaders in developing theory-based behavioral interventions. More active collaboration with these groups is essential and collaborations with other agencies of the Department of Health and Human Services are important. Mechanisms must exist in the infrastructure to facilitate such collaborations. In addition, collaborations should be enhanced with key professional organizations, such as the Society for Behavioral Medicine, the American Cancer Society, and the American Society for Preventive Oncology. Behavioral research must become part of the fabric of NCI and larger scientific community if substantial advances are to be made in cancer prevention.

[top](#)

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### **Specialized Training in Behavioral Science**

Trained behavioral scientists will be needed to function in the new scientific paradigms. This means, that in contrast to the current primarily generalist approaches to training, at least some trainees should develop specialized knowledge, in genetics, chemoprevention, diet, addiction or other areas. Training should encourage multidisciplinary collaborations between behavioral scientists and basic and clinical researchers. There are few models available, so the development of innovative programs should be encouraged.

While the intent of NCI's intramural Cancer Prevention Fellowship Program is laudable, it is no substitute for strong behavioral research training programs in other settings, including universities and cancer centers. Consistent with an investment in training, there must be adequate resources for small grants and other mechanisms to permit new investigators to start their research careers. Training must be offered at all levels: predoctoral, postdoctoral and people already working in the field. A variety of strategies should be used, including workshops, mini sabbaticals and short courses. Training opportunities should provide multi-disciplinary faculties who can model the kind of collaboration required to advance discovery. Finally, just as behavioral scientists should be provided with opportunities to receive specialized training in other areas, other disciplines should be encouraged to acquire significant understanding of health behavior and the behavior change process.

[top](#)

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### **Infrastructure**

At present, only about 4.5 percent of the NIH budget and 5 percent of the NCI budget is spent on behavioral research. This level of investment is inconsistent with the important role of health behavior in the major causes of mortality. Most behavioral research at NCI is located within DCPC. While NIH was mandated by Congress to establish an Office of Behavioral and Social Sciences Research and did so, there is no central focus for this research at NCI. There is no branch devoted to behavioral science, and there are only a few doctorally prepared behavioral

scientists at NCI. This is problematic and results in a serious leadership gap. Moreover, there does not appear to be a systematic process for collaborating and coordinating with other divisions of NCI, for example, and treatment, epidemiology, or even for determining needs and priorities within a more defined area DCPC. NCI has an opportunity to advance the next generation of behavioral research and intervention. A strong institutional foundation for behavioral research is essential. This is unlikely to occur without establishing behavioral research as an independent program entity with responsibilities across NCI [and NIH]. The infrastructure must support a broad definition of both behavioral research and prevention.

[top](#)

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## **Recommendations**

- Incorporate behavioral research as an integrated but independent component of the NCI prevention program.
- Conduct behavioral research at multiple levels, ranging from laboratory-based behavioral research to small scale hypothesis testing research to larger studies with the power to assess efficacy.
- Pay special attention to the development of interventions that are ethnically and culturally appropriate.
- Include as priorities for behavioral research a focus on preventing tobacco use in children and teenagers, encouragement of cessation among heavy smokers and women, increasing use of recommended early detection tests, and improvement of the behavioral outcomes of genetic testing for cancer susceptibility.
- Include the following components within an outstanding behavioral research program in prevention: epidemiologic foundations, expertise in measurement and evaluation, national data on key behaviors, knowledge of theories of behavior, understanding of behavior change, expertise in cancer risk communication, strength in intervention design, expertise in cost-effectiveness and mechanisms for dissemination.
- Conduct behavioral research initiatives through mechanisms which crosscut NCI as well as the National Institutes of Health, depending upon the focus of effort.
- Create training programs for behavioral scientists to function in the new scientific paradigms, including genetics, chemoprevention, diet/nutrition, addiction and other pertinent areas.

[top](#)

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## **TRAINING OF HEALTH PROFESSIONALS WITH EXPERTISE IN PREVENTION RESEARCH**

### **Introduction**

There is a need for a major new approach to the training of prevention scientists. A

comprehensive review of the current training mechanisms and the development of new modalities was beyond the scope of the Review Group's effort. However, the Review Group unequivocally supports such a review and the redirection of current programs toward training of prevention scientists for the future.

In this chapter the Review Group considers training at all levels, including short-term, intensive training opportunities for people already in the field as well as pre- and postdoctoral fellowships for prevention scientists. The array of training models should include opportunities for senior scientists to take mini-sabbaticals to strengthen their knowledge or skills in emerging areas of prevention. Irrespective of the level of the trainee or the intensity of the experience, training should be based on a new vision of prevention science.

Training experiences should be multidisciplinary and designed to complement a person's expertise, and interdisciplinary approaches should be implicit in all the training efforts. All prevention scientists should receive some exposure to the laboratory, be grounded in the basic principles of epidemiology, develop a firm grasp of the importance of health behavior and behavioral change, understand the principles of cancer biology, including genetics and carcinogenesis, and be well versed in biostatistics. Behavioral scientists should be encouraged to substantively enhance their knowledge and experience in one or more fields, such as chemoprevention, cancer genetics, nutrition, or addiction. A similar approach should apply to other prevention scientists. All prevention scientists at the predoctoral level should have the opportunity to participate in ongoing prevention research.

A variety of creative approaches to training should be encouraged, including those based on collaborations between multiple institutions and investigators. Short-term experiences in other laboratories or participation in intensive short courses may be useful. Moreover, attention should be paid to the development of prevention leaders who may need special training opportunities in areas such as health policy.

The following is a review of the current mechanisms for training individuals in prevention research. Wherever possible, an attempt is made to describe the nature and scope of the training program, the types of health professionals for whom the programs are targeted, and the potential strengths and weaknesses of each approach.

### **Intramural Training Program**

The National Cancer Institute (NCI) Cancer Prevention Fellowship Program has been in existence since 1985. It is a two- to three-year program which accepts six to eight new trainees per year. In addition to a comprehensive didactic component, the fellows are guided into mentored individual research projects within the Division of Cancer Prevention and Control (DCPC), other divisions of NCI, or other programs at the National Institutes of Health (NIH), depending on their background and areas of interest. The overall goal of the program is to prepare health professionals for independent careers in cancer prevention. To date, 46 fellows have completed the

program, and 19 are currently in training.

Upon finishing the program, the 46 fellows have gone on to positions in a broad range of settings, including: government (39 percent); universities (28 percent); cancer centers (11 percent); research firms (11 percent); and medical practice (4 percent). At present, there are no data available on the degree to which these positions involve cancer prevention, or the success of the fellows in obtaining prevention-related peer-reviewed funding.

The intramural fellowship training program, which provides an excellent model for advanced training in cancer prevention research, represents a significant portion of the NCI budget for long-term postdoctoral training. While there is much about the prevention oncology fellowship that is strong, there also are limitations. Among these is the lack of involvement of the fellows in ongoing cancer prevention research and the lack of mentoring by senior prevention scientists.

[top](#)

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## **Extramural Fellowship Training Program**

NCI funds several types of extramural training programs, both long-term training programs resembling the intramural fellowship program, as well as short-term courses, workshops, and research internships. Awards are made at the institutional level and to individual scientists.

The T32 Institutional Research Training Grants are broadly defined and provide support for any domestic public institutions to provide ongoing pre- or postdoctoral training in cancer research. There are currently 15 institutions receiving T32 support, averaging \$172,177 per year, in the categories of cancer epidemiology, biostatistics, cancer prevention and control, and pain management.

In addition to providing support for pre- and postdoctoral fellowship training, the R25 Institutional Cancer Education Grants provide support for short research experiences for students, cancer curriculum development, health professional education and outreach, and innovative ideas in cancer education. There are currently 42 R25 grants funded at an average annual level of funding of \$163,708, of which 55 percent specifically target training in cancer prevention. Eight of these grants are for curriculum development, and 14 are masters or doctoral level programs.

The most targeted and well-funded program for individuals are the K07 Individual Career Development Award in Preventive Oncology, which provides up to four years of support for research and teaching in cancer prevention and control for applicants with at least two years of postdoctoral experience. Applicants must secure the support of an established investigator and demonstrate a well-defined research proposal in a cancer prevention-related field of study, which will ultimately lead to a grant proposal for peer-reviewed funding review. The annual support level is

approximately \$90,000. Currently, 32 individuals are receiving K07 support for research in the fields of cancer epidemiology and biostatistics (38 percent), molecular biology and genetics (25 percent), screening (16 percent), primary prevention (13 percent), and psychosocial support and education (9 percent).

In addition to this individual award, which specifically encourages career development in cancer prevention, there are several other funding mechanisms for individuals which have a more general cancer training theme. These include the F31 Fellowships which provide up to five years support for oncology nurses, minorities and persons with disabilities to earn a doctorate in basic or applied cancer science, and a number of awards (F32, F33, K08, and K01) for postdoctoral training in basic, clinical or behavioral cancer research.

These extramural training programs provide a wide range of fairly flexible options for short- and long-term training opportunities for individuals with many related backgrounds. The relative amount of NCI funding allocated to these efforts, however, is small, and substantially less than needed by the field. There does not appear to be any associated coordinated effort to assess the training needs of the nation nor to inform the scientific community of the scope of programs currently available. None of the individual programs specifically attempts to create a broad-based interdisciplinary approach to stimulate translational research in cancer prevention which would extend molecular biology to the clinical and population-based spheres. And like the intramural program, there is no mechanism in place to evaluate the relative impact of the various training approaches, either to provide a data base for future strategic planning for training, or to set budgetary allocations to match needs and outcomes.

[top](#)

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## **Non-Federal Sources of Support**

In addition to the federally funded training programs listed above, there are a number of training initiatives supported by non-federal organizations with varying degrees of financial commitment. The American Cancer Society (ACS) has a long tradition of both public and professional education and dissemination of cancer prevention and treatment information. The American Society of Clinical Oncology (ASCO) strives to be responsive to the educational needs of its members both through Career Development Awards and spring and fall educational sessions. These efforts are not typically targeted, however, to cancer prevention. Other organizations, such as the American Society of Preventive Oncology (ASPO) support, in theory, the training of professionals in cancer prevention, but do not actively support training programs beyond the educational sessions held at their annual conventions. The American Association for Cancer Research (AACR) provides a postdoctoral fellowship in cancer prevention and is responsible for the designation of an ACS-funded award to a senior scientist in cancer prevention. The AACR also holds a number of educational sessions in cancer prevention at their annual convention and is responsible for annual workshops, some of which are



devoted to this research area. Finally, along with the growing power of the media, we are witnessing an increasing effort to disseminate prevention information to the public by the private sector and by newly created public/private ventures, including the pharmaceutical industry and nonpharmaceutical corporations.

[top](#)

## Relevance of Training to Current Research

The training of health professionals with expertise in prevention research should reflect and stimulate the scope and strength of preventive research pursued by scientists in this country and throughout the world. Training programs must reflect the needs of the research community, and can also serve to initiate new areas of research. In order to provide a snapshot of existent research in the area of prevention, all currently active RO1 grants with a major focus on cancer prevention were reviewed. A total of 191 projects, amounting to \$62,799,620 in funding, was distributed in the categories listed below. The research grants are almost evenly divided into basic and applied areas of research.

[top](#)

Research Category	Number of Grants
basic science/chemopreventive development	36
basic science/carcinogenesis	45
basic science/immunology/vaccine development	7
epidemiology	26
biostatistics	4
cancer control	
--smoking cessation	15
--diet	14
--screening, risk reduction	15
chemoprevention	
--micronutrient	11
--pharmacologic agent	3
public health policy	9
others	6

Advances in understanding of the fundamental biology of the cancer process coupled with the development of appropriate technology have led to a growing awareness of the potential impact of molecularly based cancer prevention strategies. This awareness has resulted in a tremendous enthusiasm for prevention-oriented research. Of particular promise is the growing field of translational research which

strives to further the understanding of the carcinogenic process, and to describe the biologic, environmental and behavioral components of disease. This approach is requisite to the development of novel preventive approaches.

In contrast to the rapid surge of interest and support for translational research, however, is the comparatively meager investment in training the professionals needed to carry out this research agenda and transfer it to the clinical and public health arenas. Furthermore, the paucity of fiscal support for prevention training is compounded by inadequacies in training of scientists who are sufficiently multidisciplinary in nature and who would be able to formulate interactive approaches to hypothesis generation, study design, data analysis and interpretation. A new cadre of health professionals is needed whose training and backgrounds allow them to be conversant in a wide range of disciplines, and whose orientation allows them to have a more global perspective on cancer prevention strategies. In addition to training new investigators, a concerted effort must also be made to encourage scientists already trained in one specialty--such as genetics, epidemiology, medicine, behavioral science, nutrition, health services research, and ethics--to receive specialized training in related interactive disciplines.

A variety of approaches can be applied to facilitate the training of the future prevention scientist. Although training is under the direction of other units of NCI (with the exception of the Prevention Oncology Fellowships), the prevention division must play a significant role in fostering the development of training programs for prevention science.

The approaches to training prevention scientists would include the use of the existing NIH-funded pre- and postdoctoral training mechanism (T32) through which a broadly-based, multidisciplinary team of academicians can develop a unique training vehicle that will expose the trainee to a number of the areas mentioned in this chapter. This training program should involve multiple and varied experiences in prevention research including in the laboratory and in a population-based setting. In all cases, the fundamental experiences must be translated into a cancer prevention project.

Training also may be accomplished at the level of the more senior scientist. Thus, intensive, short-term programs should be developed for broadening the information base of established scientists in such areas as cancer biology and carcinogenesis, and in other areas of prevention, such as epidemiology or behavioral research. The end result of these efforts should be the development of more collaborative research among scientists trained in different disciplines. In a similar vein, the short-term workshop approach could be targeted to scientists who are principally trained in epidemiology or behavioral research in which the education effort is devoted to cancer biology, genetics, and carcinogenesis.

Finally, the training program should undergo a periodic evaluation of its effectiveness in producing the investigator who has had a well-balanced,

multidisciplinary education and who is comfortable in bridging the gap between the laboratory experimentalist and those who are involved in population-based research.

[top](#)

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## **Recommendations**

- Develop and support new mechanisms for already trained health professionals to familiarize them with the field of cancer prevention and to provide them with opportunities to expand their skills to contribute to the science of prevention.
- Develop a data base of professional resources and deficiencies in the field of cancer prevention to assess current and future personnel needs, similar to that currently used to project needs for physician training.
- Form a working group to make recommendations for training of prevention researchers in the new scientific paradigms and who will also evaluate the effectiveness of the training program.
- Encourage the development of innovative training opportunities for prevention researchers to augment their training in areas such as genetics, pharmacologic intervention in prevention, epidemiology, and behavioral science.

[top](#)

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## **ORGANIZATION AND INFRASTRUCTURE OF THE NCI PREVENTION DIVISION**

The goal for the Cancer Prevention Research Program should be *the reduction in the incidence, morbidity, and mortality of cancer through the development, conduct, and application of outstanding science*. This goal must be reached through a concerted effort of both the intramural and extramural research communities with leadership and fiscal resources provided by the National Cancer Institute (NCI). The Review Group believes that only through an effective, cohesive and discovery-based cancer prevention research program, which can be translated to and applied in the population at large, can the cancer problem be defeated. Therefore, cancer prevention must become a principal focus of the NCI research program.

The total 1996 fiscal resources available for cancer prevention within NCI was difficult to define but a fair estimate is between \$400 million and \$740 million. The latter figure includes efforts in epidemiology, physical, chemical, and biological carcinogenesis, nutrition, and cancer control. Although the cancer prevention portfolio is distributed throughout a number of the internal components of NCI, the major concentration of research activity is in the Division of Cancer Prevention and Control (DCPC).

In order to meet the goals of cancer prevention, the Review Group emphasizes that the head of the prevention division must be an accepted leader within NCI as well as

in the external cancer prevention research community. In addition, the head of the prevention division must be a forceful spokesperson for the NCI prevention agenda.

The Review Group examined the organizational structure of DCPC and the effectiveness of its interactions with the external cancer prevention community. The Review Group recognizes that organizational structure can only facilitate fulfillment of a strategic goal; it is not a substitute for effective leadership.

In order to attain the overall objectives in cancer prevention, some changes are required in the organization and infrastructure of the NCI cancer prevention program. The recommendations contained in this report, if implemented, will facilitate the development of a strong cancer prevention division. In order to more fully illustrate the nature of problems associated with the cancer prevention program, a brief review is provided of the distribution of NCI prevention research efforts.

[top](#)

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## **Cancer Prevention Research Within NCI**

While the internal cancer prevention research program is represented mostly within DCPC, other research units with a focus on cancer prevention are located throughout NCI. Indeed, a substantial body of cancer prevention research is carried out under the auspices of another institute, the National Institute for Environmental Health Sciences (NIEHS). The efforts of NIEHS and how they interact with NCI's efforts were not considered by the Review Group.

Laboratory-based prevention research is located within the intramural Division of Basic Sciences, specifically in the Laboratories of Experimental Carcinogenesis, Molecular Carcinogenesis, Nutritional and Molecular Regulation (formerly within DCPC), Chemoprevention, Human Carcinogenesis, and Cellular Carcinogenesis and Tumor Prevention; and in the intramural Division of Clinical Sciences. Currently, DCPC does not include any laboratory-based units; it operates largely as a vehicle for facilitating cancer prevention research within the extramural research community. Other non-laboratory-based, prevention-related research occurs in the Division of Cancer Epidemiology and Genetics (DCEG) and in the Division of Cancer Biology. Interestingly, DCEG appears to have a unique mandate in both providing traditional research grants to the external community and conducting its own internal intramural research.

There is little evidence of substantial interaction among these units in the formulation of a cohesive cancer prevention research program. *The Review Group recommends that some mechanism be instituted for increasing communication and collaboration on short- and long-term planning activities among these administrative units.* Such cooperation would result in a more effective overall cancer prevention program.

[top](#)

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## **Organization of DCPC**

The organizational structure of DCPC includes three major programs-Early Detection and Community Oncology, Cancer Prevention Research, and Cancer Control Research-and one branch, Biometry. The Cancer Prevention Research Program encompasses the major components of Diet/Nutrition and Chemoprevention, while the Community Clinical Oncology Program is located in the Early Detection and Community Oncology Program.

The mission of DCPC is complicated by several factors including: the geographical scattering of prevention research across NCI; the need for outstanding laboratory research; the need to appreciate the power of discovery-based research in addressing problems in prevention; the need to understand the impact of emerging and enabling technologies on prevention research; the need for additional outstanding prevention investigators in senior leadership roles; and the need for the NCI prevention division to play a leading role in building stronger ties between the internal and external scientific communities. To fulfill these needs, the Review Group makes the following recommendations for change.

[top](#)

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## **Create a Separate Prevention Division**

The Review Group strongly endorses the concept of a separate division with a focus on cancer prevention and with lead responsibility for integrating cohesive, peer-reviewed research conducted by the internal and external cancer research communities. It is appropriate to comment on the combination of cancer prevention and control within a single unit. The Review Group has not taken a definitive position on the separation of cancer prevention and control research functions although there are no inherent advantages associated with either maintaining these responsibilities within a single division or within distinct divisions. What is important, however, is that effective collaboration and interaction exist between the elements of prevention and control since the fruits of prevention efforts will require translation into control. An advisory committee to facilitate such collaborations and interactions between units of prevention and control might be considered. Alternatively, this role could be undertaken by the NCI Executive Committee.

The importance of the prevention portfolio to the national cancer research program necessitates that the prevention division be directed by an outstanding, articulate, nationally recognized, and forceful leader. An effective management team must be assembled to develop clear goals within a viable strategic plan and to determine the resources that are necessary to fulfill the plan. The prevention program should be restructured to reflect the fundamental components of prevention science, including linkages to laboratory-based prevention research, core resources in areas such as biostatistics and epidemiology, strong programs in chemoprevention, diet/nutrition, tobacco, behavior, and methodologic research. Furthermore, it would be preferable

for the senior administrators to have a common geographical location in order to facilitate their interaction and to create a critical mass in prevention.

The function of the new prevention division would be significantly enhanced by the formation of an advisory board that would assist in establishing priorities, ensure that outstanding science was its hallmark, review progress of the internal programs and branches, and recommend resources and their distribution in order to fulfill the goals of the division. *The Review Group recommends the formation of such a body which could represent a subcommittee of the Board of Scientific Advisors of NCI, and supplemented by outstanding external cancer prevention investigators.* The supplementation by other investigators is required since the current Board of Scientific Advisors does not include a critical mass of cancer prevention scientists.

[top](#)

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### **Strengthen the External Function of the Prevention Division**

Although DCPC is currently organized to support external investigator-initiated research, it operates largely through approval of concepts and funding via RFP's, master agreements, and other contract mechanisms. The cancer prevention research effort, which is largely defined by the leadership of the programs and branches of DCPC, is judged to be of a mixed quality.

Many within the extramural research community believe that DCPC considers the external scientific community as the vehicle for fulfilling internally defined research objectives rather than as an opportunity to create and facilitate cancer prevention research. This limited outlook is evident to varying degrees in the diet/nutrition, behavioral and related areas. Although considerable progress has occurred, the preclinical chemopreventive agent development program has been limited by the dependence on largely outdated carcinogenesis models as the screening mechanism for identifying promising compounds. Recently, more meaningful animal models are under consideration as replacements. This effort should be encouraged with the goal of replacing all the previously used systems.

Few conceptual advances have evolved for defining the roles of fat, calories, fiber, or physical exercise in cancer prevention. The Review Group urges a renewed vigor in facilitating the discovery process in the diet/nutrition research area. Significant limitations exist in current tobacco interventions and there is an over reliance on very expensive programs that have outlived their research usefulness, e.g., ASSIST. This may also reflect a paucity of strength in behavioral research within the NCI, an area that is considered later in this chapter and was developed in chapter six.

The Review Group considered the effectiveness of the process for reviewing investigator-initiated grant applications. Since many of the research approaches in prevention will be multidisciplinary in nature, from laboratory- to population-based studies, a unique review team is required for appropriate evaluation. The recent successes of the discovery-based research efforts have provided many avenues of

opportunity for multidisciplinary approaches. It is the considered opinion of the Review Group that the existing study sections do not encompass the breadth of knowledge that will be required for evaluating the cancer prevention grant applications of the future.

*The Review Group strongly recommends that the use of investigator-initiated research as a mechanism for funding cancer prevention studies be maximized. In areas where gaps in the research portfolio exist, novel approaches should be encouraged through RFA and RFP mechanisms. These gaps may be better defined through reinvigorated leadership and through the advisory subcommittee of the BSA of the NCI. The Review Group also strongly recommends the formation of an appropriate study section which would have the responsibility for evaluating the multidisciplinary cancer prevention research grant applications.*

[top](#)

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### **Emphasize Behavioral Research**

In order to successfully achieve the goal of reducing the incidence, morbidity, and mortality of cancer, significant changes in behavior and lifestyle will likely be required. The ability to effect these changes in the human population will be dependent upon the development of new research approaches in health behavior, as outlined in chapter 6. Expertise in the development and application of behavioral research to the prevention agenda has been largely absent within DCPC, and indeed, within NCI. Far too little research has been conducted on the fundamental problems of tobacco addiction or on the development of appropriate methodology for effective interventions. Such interventions are needed for children, adolescents, adults in low socioeconomic situations, and some minorities. Since cancer-associated behaviors may be initiated while individuals are young, investigations on effective means for impacting positively upon adolescents and young adults might significantly affect cancer statistics.

*The Review Group recommends that a vigorous, scientifically based, effective Behavioral Research Program be developed within the prevention division (or within NCI), which would provide the required leadership in this most important area and which would be responsible for the fostering interactions between the internal and external scientific communities. This recommendation will require the recruitment of outstanding investigators in behavioral prevention research.*

[top](#)

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### **Relocate the Community Clinical Oncology Program (CCOP)**

As indicated in the organizational chart for the current DCPC, CCOP is a component of the Early Detection and Community Oncology Program. It provides a means for linking the community cancer practitioners and primary care physicians with the NCI clinical Cooperative Groups and the NCI Cancer Centers, in order to participate in cancer treatment, prevention, and control clinical trials. Its primary

activities have been in therapy trials.

The location of the CCOP program within the current DCPC may reflect a remnant of the past when the Cancer Centers Program also resided in this division. As indicated in chapter 5, there is need to reassess its effectiveness in prevention trials. Given its major emphasis on therapy trials, CCOP might be better relocated to the Division of Cancer Treatment, Diagnosis and centers (DCTDC). The proposed prevention trials group could assure appropriate linkages with CCOP and Minority CCOP in recruitment.

*The Review Group recommends that the effectiveness of CCOP in conducting prevention clinical trials as contrasted with clinical therapy trials be evaluated. If appropriate, CCOP could be relocated to DCTDC.*

[top](#)

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### **Improve Research Efforts in Diet/Nutrition, Tobacco, Alcohol, Physical Activity, and Infectious Agents**

Cutting edge research on the roles of diet/nutrition, tobacco, alcohol, physical exercise, and infectious agents in cancer prevention is a necessary component of the prevention division. Forceful, interactive leadership in many of these areas has been lacking within the current DCPC. Since tobacco usage and diet/nutrition represent major contributors to cancer incidence, morbidity, and mortality, the prevention division must include outstanding scientists who are involved in these areas in cancer prevention and who will ensure effective interaction between the internal and external scientific communities.

*The Review Group recommends that among its senior leadership, the prevention division include outstanding scientists who will assist the Director in providing the necessary drive to conduct a cutting-edge research program in the above areas (as well as in others deemed necessary by the director).*

[top](#)

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### **Form a Chemoprevention and a Prevention Trials Group**

The prevention division must assume the intellectual basis for cancer prevention founded on outstanding scientific discovery and well-designed trials to test compelling hypotheses. One major element is the use of specific chemopreventive agents in populations, defined along the lines described in chapters 4 and 5. The Review Group recommends changes in the preclinical chemoprevention drug development program to stimulate the continued development of a more appropriate and relevant screening mechanism which is based on recent scientific advances. The function of the preclinical drug development program committee has been presented in chapter 5. The committee would report to the BSA of NCI, and be composed of members of that Board supplemented by outstanding investigators from the



extramural cancer prevention community and by NCI prevention division staff.

Since the conduct of human trials may be very expensive, it is unlikely that many large-scale trials will be undertaken simultaneously. Consequently, it is imperative that the body of scientific evidence supporting chemopreventive activity be compelling and substantiated prior to embarking on large-scale human studies. Those agents which have demonstrated efficacy in animal model systems with attendant low toxicity should be evaluated. It also will be important to incorporate high-risk populations into study designs and patients who were successfully treated for a first malignancy. In so doing, studies might be successfully completed with a smaller number of cohorts and in a shorter period of time. These aspects are reviewed in detail in chapter five.

Pertinent, validated biological endpoints which reflect the progression of the neoplastic transformation to frank malignancy must be identified under the leadership of the prevention division. This effort will undoubtedly require the combined activity of both the internal and external scientific communities. If and when developed, validated biomarkers would be employed in prevention clinical trials with a significant cost saving. A mechanism should be in place that would respond rapidly in the use of fully-validated biomarkers in large-scale trials already in progress. In addition, a mechanism should be developed to facilitate the initiation of scientifically justifiable spin-off studies in already ongoing clinical prevention trials. The Review Group recommends the formation of a Prevention Biological Studies Group that would ensure that these abilities are facilitated. This aspect is considered more fully within chapter 5. The accomplishment of these tasks could also occur through the recommended preclinical drug development subcommittee of the BSA or through the BSA advisory committee to the prevention division.

*The Review Group recommends the formation of two committees to provide advice on the preclinical phase of a chemoprevention drug development program and on a multimodality prevention clinical trials, respectively. The preclinical chemoprevention group should function as a subcommittee of the BSA of NCI, and supplemented with appropriate cancer prevention investigators. The prevention clinical trials group would be patterned after the NCI Treatment Trials Groups. In addition, NCI should have the ability to respond rapidly in evaluation and funding of a new discovery for application into an already ongoing prevention trial.*

[top](#)

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## **Increase the Role of the Prevention Division in Training**

The prevention division should play a prominent role in facilitating training of cancer prevention researchers. This component is reviewed in detail in chapter 7. The current training of physicians and other professionals in cancer prevention occurs largely on the NCI campus (or within the immediate region). This approach also appears to be restricted to the internal DCPC (and NCI) community. A much greater impact on the field of cancer prevention training would be achieved through

the existing training grant mechanism but encompassing a more appropriate and broadly founded approach in laboratory-based, behavioral, and population-based research. The development of this experience should be fostered through the leadership of the prevention division and should involve interaction with the Cancer Training Branch in DCTDC and the external scientific community.

*The Review Group recommends the formulation of a unique program for cancer prevention investigators which would be multifactorial, and involve laboratory training and preparation in principles of behavior and population-based studies. The program would be directed by the leadership of the prevention division and the prevention trials groups.*

[top](#)

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## **Enhance Data Bases to Facilitate Cancer Prevention Research**

The SEER data base has proven to be of great utility to the scientific community and should be continued as a component of the prevention division. In addition to the SEER data base, additional compilations made available to the external (and internal) scientific community could facilitate the research effort in cancer prevention. These would include:

- a)** a central resource of the outcomes of NCI-supported cancer prevention interventions and clinical trials. This directory, which periodically could be made available to the scientific community through electronic transmission, would update investigators on what has already been accomplished, and on the lessons, both positive and negative, learned from the conduct of the interventions. In brief, this data base could include program objectives, target populations, methodology, outcomes and program evaluations. Such information would be invaluable for scientists planning a prospective trial.
- b)** a central resource listing the availability and location of sera, plasma, blood cells, collected during a specific clinical prevention intervention or trial. A mechanism for periodic publication of availability via hard copy communication (in journals) or electronically and a process for evaluating the proposed use of these sources and their distribution should be developed.
- c)** a biorepository of specimens maintained, operated and funded through NCI, especially after cessation of project funding. Appropriate mechanisms must be established for logging samples, including pathology, accessing the biorepository, and communication of availability to the prevention research community.

[top](#)

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## **Interact with Other Federal and Nonfederal Agencies**

Several other agencies have a major interest in cancer prevention, particularly in the

public health aspects of prevention. These agencies include the Environmental Protection Agency, the Occupational Safety and Health Administration, the Food and Drug Administration (FDA), and the Centers for Disease Control and Prevention (CDC), and the American Cancer Society (ACS). The prevention division, through its central mission of developing the scientific base for cancer prevention, should be strongly encouraged to interact further in the translation of some of this research into the public health domain through effective alliances with these other agencies, most of which are represented on the National Cancer Advisory Board. Oftentimes, the cancer prevention research mission has been considered as competitive with that of CDC. In fact, it is complementary. ACS and NCI have a history of notable interaction on cancer problems. The complementarity of the missions of the ACS and of the Prevention Division should be recognized and a greater interaction undertaken. Finally, it is important to develop a more formal level of interaction with FDA in order to facilitate the conduct of clinical trials with chemopreventive agents, particularly in regard to the use of fully validated intermediate endpoints as surrogates for cancer incidence.

[top](#)

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## **Recommendations**

- Ensure appropriate interactions among units that have the responsibilities for cancer prevention and control in order to facilitate translation of prevention principles into action.
- Establish a restructured cancer prevention division within NCI that has the responsibility and resources for formulating and implementing the cancer prevention agenda through the development and application of outstanding science. Enhance the senior management of the prevention division by recruitment of outstanding cancer prevention investigators who would assist in formulating and implementing a strategic plan, prioritize scientific goals, assess required resources, and facilitate interactions among the intramural and extramural research communities.
- Stimulate more effective interaction among intramural cancer prevention researchers, who are currently located in disperse laboratories and scattered across the prevention division.
- Expand the current NCI Board of Scientific Advisors (BSA) to include additional prevention research investigators and form a subcommittee of BSA, supplemented by other extramural experts, as an advisory group specific to the prevention division.
- Perform an in-depth evaluation of the Community Clinical Oncology Program to ascertain its contribution to the prevention effort and consider its relocation to the Division of Cancer Treatment, Diagnosis, and Centers.
- Continue to re-evaluate and modify, if appropriate, the programs for preclinical drug development and form a subcommittee of the Board of Scientific Advisors, supplemented by extramural cancer prevention investigators, and staff of the prevention division and the Food and Drug Administration, to assist and monitor the decision process in the preclinical

and prevention trials phases.

- Form an extramural multimodality prevention trials group, patterned after the Oncology Therapy Trials Groups, which would set guidelines, make funding recommendations, and monitor the progress of prevention trials.
- Develop a mechanism to rapidly respond to new research developments, and to evaluate and fund outstanding ancillary research spinoff studies in populations represented within an ongoing prevention trial.
- Develop databases of: a) clinical cancer prevention trials, their objectives, target population, methodologies, successes, and failures; and b) the availability of blood and tissue products from clinical trials which could be accessed by all prevention researchers through a peer-reviewed mechanism.
- Strengthen collaborative relationships with other groups also involved in cancer prevention, such as the Centers for Disease Control and Prevention, the American Association of Cancer Researchers, the American Society of Clinical Oncology, and the American Cancer Society.
- Work more closely with the Food and Drug Administration on matters that affect cancer prevention, e.g., utilization of fully validated intermediate biomarkers in prevention trials.

[top](#)

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## MEETINGS OF THE REVIEW GROUP AND ACKNOWLEDGEMENTS

The review Group heard oral testimony from the leadership of the divisions of the National Cancer Institute, several past Associate Directors of the Division of Cancer Prevention and Control, non-federal agencies with major commitments to prevention, and professional organizations such as the American Association for Cancer Research, the American Cancer Society, the American Society for Clinical Oncology, and the American Society for Preventive Oncology. The Review Group is particularly indebted to Dr. Peter Greenwald, Director of the Division of Cancer Prevention and Control, for the references he provided, for the planning of the presentations, and for his spirit of cooperation.

The Review Group met on the following dates:

April 15, 1996  
June 13, 1996  
August 21, 1996  
September 16-17, 1996  
October 6, 1996  
October 31, 1996  
December 17, 1996  
January 30-February 1, 1997  
February 18, 1997  
March 18, 1997

<sup>1</sup> Surrogate End Points in Clinical Trials: Are We Being Misled? *Annals of Internal Medicine* 125:605-613, 1996 (back)

[top](#)

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