Prevention of Cancer in the Next Millennium: Report of the Chemoprevention Working Group to the American Association for Cancer Research\textsuperscript{1,2}

INTRODUCTION

Twenty-five years ago, as the “War on Cancer” began, there was hope and anticipation that the mortality rates for common forms of cancer might be greatly reduced by the year 2000. Although this goal has not been attained, a primary result of the increased funding for cancer research during the past 25 years has been an immense increase in knowledge of the mechanisms whereby normal cells and tissues become malignant. Furthermore, increased funding has led to the inception of programs to use this fundamental knowledge to develop new approaches to synthesize and test new drugs to prevent cancer, as contrasted with classical chemotherapy for treatment of existing disease. This new pharmacological approach to arrest or reverse the process of carcinogenesis, and thus to prevent cancer, is called chemoprevention.

Although still in its infancy, the new science of chemoprevention has been established as an important approach to control malignancy. For the first time, it has been shown convincingly that the use of chemopreventive agents in men and women with premalignant lesions can substantially reduce the subsequent development of truly invasive cancer. Chemoprevention is now recognized as both a clinical and basic science.

Although encouraging progress toward chemoprevention of human cancer has been made, this field is still in its earliest stages of development. We are nowhere near the ultimate desired goal of possessing some safe and effective agents that could easily be given to the general population for the prevention of cancer, as fluoride can be added to drinking water for prevention of dental caries. Thus, in spite of the advances that have already occurred in chemoprevention of cancer, there is more to be done before these advances can be translated into full human benefit. If we are to meet the desired goal of widespread implementation of chemoprevention of cancer, progress will need to occur in four major areas.

First, we need to continue to enlarge the substrate of basic scientific knowledge of mechanisms of carcinogenesis. Understanding the process of carcinogenesis is the foundation for the science of chemoprevention. Second, we need to conduct more clinical studies to validate specific pharmacological agents for chemoprevention of human cancer. Proof of safety and efficacy of new drugs in controlled clinical trials is essential if this field is to progress. Third, we need to develop new and better agents for eventual use for chemoprevention in men and women. Although existing drugs have already had a significant impact, many have a significant downside in a benefit versus risk analysis. Finally, we need a more broadly based educational effort, directed at both physicians and society as a whole, to achieve better understanding and compliance with the goals of chemoprevention.

There are significant misunderstandings and apprehensions about widespread use of chemopreventive agents, centering around the misperception that it is not appropriate to treat “healthy” people with preventive agents. We need an intensive educational effort to convince people that absence of clinical symptoms may not guarantee that one is “healthy,” and that a more sophisticated understanding of risk factors can be used constructively to develop interventions that have the potential to provide better health.

In all of the above considerations, the dictum, primum non nocere, first do no harm, must be operative. There is realistic concern that poorly planned interventions can increase, rather than decrease, risk. However, from a pragmatic perspective, failure to intervene when one has the capacity to prevent disease may also be viewed as harmful. We therefore need the broadest possible societal discussion of the potential benefits and risks of chemoprevention strategies as a whole, as well as sophisticated analysis of each individual proposed preventive agent.

It is the hope that the Report of this Working Group will provide a useful framework for the evaluation and discussion of future efforts to prevent cancer. This Report does not address other highly important issues relating to lifestyle, diet, tobacco, and environmental factors in the causation and prevention of cancer. These factors are of immense significance in the total effort to prevent cancer and will be the subject of future review and recommendations by other American Association for Cancer Research Working Groups. It should also be noted that this Report is not intended to be a critique of established approaches to treatment of cancer, such as chemotherapy, surgery, or radiation. Tremendous advances have occurred in the use of all of these modalities, resulting in major benefits to patients worldwide. Nor is this document an archival survey of the entire field of chemoprevention.

Many detailed reviews on chemoprevention are referenced in the body of this Report, such as the recent comprehensive surveys by Kelloff (1) or Lippman et al. (2). Rather, this Report should be viewed as a working document to summarize both progress and problems in chemoprevention, as well as to suggest future efforts to make chemoprevention an essential component within the total effort to control cancer.

BASIC SCIENCE

Introduction. During the past 25 years, there has been a major investment in basic research on cancer. As a result, although the knowledge base is still incomplete, by now there is sufficient understanding of how cancer develops (the process of carcinogenesis) to allow the design of rational new approaches for its prevention. A major recent advance in cancer research has been the acquisition of a new body of knowledge that elucidates fundamental molecular and cellular mechanisms involved in the development of malignancy. On the basis of the understanding of these mechanisms, it is now possible to design new drugs or to use micronutrients to suppress the various stages in carcinogenesis and thus prevent invasive and metastatic cancer. This is the essential approach of chemoprevention and represents one of the ultimate goals of the large investment that has been made in basic research.

However, although advances in basic science have been impressive, a full understanding of the complex molecular, cellular, and tissue...
interactions involved in carcinogenesis does not yet exist. Beyond the
events that occur in a single cell, there is a sequence of poorly
understood, contextual interactions that occur among the different
cells that constitute the tissues and organs in which carcinomas arise,
and which ultimately lead to life-threatening invasion and metastasis.
Thus, prevention of invasion and metastasis has also become an
important goal for chemopreventive agents.

This section summarizes advances in basic science that are relevant
to chemoprevention and presents recommendations for future research
in this area.

Basic Mechanisms Relevant to Cancer Prevention: Multistage
Carcinogenesis and the Latent Period. The development of a ma-
lignant tumor involves complex interactions between several factors,
both exogenous (environmental) and endogenous (genetic, hormonal,
and immunological). In addition, carcinogenesis often proceeds
through multiple discernible but often overlapping stages (3). These
include: (a) initiation; (b) promotion (which leads to the appearance of
benign tumors); (c) progression (conversion of benign to malignant
tumors); and (d) their further evolution to tumors with increasing
degrees of malignancy. The overall process can occupy a major
portion of the life span of the individual. The transitions between
successive stages can be enhanced or inhibited by various agents.
Several types of evidence indicate that 50–80% of human cancer is
potentially preventable, because its causation, i.e., the factors that
determine the incidence, are largely exogenous. Exogenous causative
agents or factors that have been identified in humans include: cigarette
smoking, occupational and environmental chemicals, radiation, dia-
tary factors, lifestyle and socioeconomic factors, and specific viruses,
bacteria, or parasites (4–7).

It should also be emphasized that hereditary factors play critical
roles in influencing individual susceptibility and that, in certain rare
forms of human cancer, hereditary factors play a decisive role. How-
ever, in the majority of human cancers, the exogenous factors present
the most likely opportunities for interventions targeted to primary
prevention.

It is convenient to classify chemical carcinogens into two catego-
ries, genotoxic and nongenotoxic. Genotoxic carcinogens, or their
electrophilic metabolites, bind covalently to DNA and cause base
substitutions, base deletions or additions, and strand scissions; they
thus are mutagens. Highly reactive forms of oxygen and metabolites
of nitrogen oxide that are formed endogenously can also cause DNA
damage. Several nongenotoxic agents, including phorbol ester tumor
promoters, diacylglycerol, several hormones, and several halogenated
organic compounds can also enhance multistage carcinogenesis by
complex mechanisms (5–7). Therefore, as discussed below, chemo-
preventive agents may inhibit the effects of either genotoxic or non-
genotoxic agents.

A current paradigm of the cellular and molecular basis of multi-
stage carcinogenesis is based on the model of clonal evolution, first
proposed by Nowell (8). There is now direct evidence that the develop-
ment of several types of cancer involves the progressive acquisition
of mutations in multiple genes (7, 9). The occurrence of these muta-
tions involves repetitive cycles of cell proliferation, selection, and
clonal expansion. It appears that the development of genomic insta-
bility during this process plays an important role by increasing the
frequency of mutations, thereby accelerating tumor progression (10).
Epigenetic (i.e., nonmutational) changes probably also contribute to
this process by altering gene expression and differentiation in ways
that lead to one or more heritable changes that enhance cellular
proliferation (7). The underlying mechanisms are not known; as
stressed below, this aspect requires more intensive study.

The complexity of the multistage process of carcinogenesis prob-
ably explains a characteristic feature that is observed both in experi-
mental animal models and in humans, i.e., the long period of latency
between the first exposure to carcinogenic factors and the develop-
ment of a malignant tumor. An optimistic aspect of this latency period
is that it offers numerous opportunities for intervention before mali-
nant tumors develop. Chemopreventive strategies are possible at dif-
f erent levels (1, 2, 11–13). Thus, chemopreventive agents can include:
substances that reduce the synthesis of carcinogens in the body (e.g.,
vitamin C, which inhibits the formation of nitrosamines in the stom-
ach); chemicals that inhibit the metabolic activation of carcinogens by
Phase I enzymes or enhance their detoxification by Phase II enzymes (e.g.,
phenobarbital, oltipraz, or benzy1 isothiocyanate in cruciferous vegetables); antioxidants that scavenge free radicals (e.g.,
selenium, β-carotene, and α-tocopherol); and chemicals that trap
ultimate carcinogens, preventing their interactions with DNA (e.g.,
ellagic acid or flavonoids, in fruits and vegetables). The latter broad
category of compounds is referred to as “carcinogen-blocking agents.”
Other compounds, referred to as “suppressing agents,” appear to
inhibit the carcinogenic process after initiation. They include reti-
noids, α-tocopherol, many antioxidants present in fruits and vegeta-
tables, the estrogen analogues tamoxifen and raloxifene, as well as
COX3 and lipoxygenase inhibitors. Dietary substances and NSAIDS
that are selective COX-2 inhibitors are of great current interest.
Experimental and epidemiological studies suggest that other sub-
stances, such as organosulfur compounds in garlic and onions, cur-
cumin in turmeric/curry, polyphenols in green tea, and various pro-
tease inhibitors might also be useful in preventing tumor formation.

The precise mechanisms of action of many suppressing agents are
not known but appear to include alterations in gene expression, cell
proliferation, and clonal expansion, as well as induction of different-
tiation, senescence, or apoptosis in preneoplastic lesions or benign
tumors. It should be emphasized that there are several agents that can
inhibit carcinogenesis in one experimental setting but enhance the
process in another. Examples include animal studies with decaffeina-
ted tea, caffeine, phenobarbital, vitamin E, all-trans-retinoic acid,
1α,25-dihydroxyvitamin D3, or tamoxifen (11, 14). Thus, although
all-trans-retinoic acid and 1α,25-dihydroxyvitamin D3 inhibit tumor
promotion caused by phorbol ester on mouse skin, the same com-
 pounds stimulate complete carcinogenesis caused by 7,12-dimethyl-
benz[a]anthracene in the same organ. These observations indicate that
an agent may be protective for a tissue in one context but harmful to
the same tissue in another context. New approaches are required to
predict whether beneficial or harmful effects will occur in humans,
before large-scale use of chemopreventive agents can be applied to
human populations. It is possible that a chemopreventive agent will
be beneficial in some individuals but harmful in others. The problem of
extrapolating results obtained in experimental systems to humans is
difficult and needs much more intensive study.

Genes Targeted during Multistage Carcinogenesis. As men-
tioned above, it is now apparent that the development of a fully
malignant tumor involves the progressive acquisition of mutations in
multiple genes, including activating mutations in dominant-acting
oncogenes and inactivating mutations in recessive tumor suppressor
genes. It is also apparent that the targeted genes play highly diverse
biochemical and biological roles (reviewed in Refs. 15 and 16). The
genes identified thus far can be divided into two broad functional
categories: (a) genes that control intracellular regulatory circuitry; and
(b) genes that influence cell surface and extracellular functions. The
3 The abbreviations used are: COX, cyclooxygenase; NSAID, nonsteroidal anti-
inflammatory drug; HPV, human papillomavirus; SERM, selective estrogen receptor
modulator; FDA, Food and Drug Administration; HCC, hepatocellular carcinoma; ATBC,
Alpha-Tocopherol, Beta-Carotene; FAP, familial adenomatous polyposis; DFMO, diflu-
oromethylornithine; IEN, intraepithelial neoplasia; NCI, National Cancer Institute; EBV,
Epstein Barr virus.
first category includes several subcategories: (a) genes that play a role in the responses of cells to external growth factors, *i.e.*, they encode growth factors, cellular receptors, coupling proteins, and protein kinases that transduce information across the cytoplasm to the nucleus, and nuclear transcription factors that increase or repress the expression of other genes; (b) genes involved in DNA replication and repair; (c) genes involved in cell cycle control; and (d) genes that determine cell fate, *i.e.*, cellular differentiation, senescence, or apoptosis. The second major category includes genes that influence cell interactions with the extracellular matrix and/or neighboring cells. This category includes various cell surface proteins, cell adhesion molecules, extracellular proteases, and angiogenesis factors. Alterations in these genes are especially relevant to tumor cell invasion and metastasis. Some of the above-mentioned genes perform multiple functions that extend across these categories (*i.e.*, p53); there is cross-talk among components in each category and among categories; and the biological effects of some of these genes are dependent upon the context of the specific cell type in which they are expressed.

Further knowledge about the genes that are targeted during multistage carcinogenesis, and the specific mechanisms by which they contribute to this process, is essential for developing more effective chemopreventive agents. The detection of mutations or altered expression of these genes in apparently normal tissues or precursor lesions could help identify individuals at increased risk of developing cancer. These genes may also provide specific targets for chemoprevention, as well as biomarkers that can be used in clinical trials as intermediate endpoints for assessing the efficacy of chemoprevention agents.

**Hereditary Factors That Influence Cancer Risk.** As mentioned above, it seems likely that in many cases exogenous factors act in combination with genetic factors to increase the risk of cancer development in specific individuals and subpopulations. Exciting progress has been made in identifying the specific genes and mutations responsible for certain familial cancer syndromes that display simple Mendelian inheritance (17). Examples include the Apc gene in familial adenomatous polyposis of the colon, DNA mismatch repair genes in hereditary nonpolyposis coli, and the BRCA1 and BRCA2 genes in hereditary breast cancer. This category, although it represents only about 10% of all cancers, provides a valuable model for piloting chemoprevention studies because of the high penetrance of the inherited gene, and the fact that molecular diagnostic tools are becoming available to identify individuals at risk with great certainty.

However, of greater numerical importance with respect to cancer risks in the general population is the inheritance of genes that influence cancer susceptibility via multifactorial interactions, *i.e.*, by influencing the response of the host to endogenous or exogenous carcinogenic factors. There is, for example, increasing evidence that specific polymorphic forms of drug-metabolizing enzymes (both phase 1 and phase 2) can influence the susceptibility of individuals to the carcinogenic effects of cigarette smoke (7, 18). It also seems likely that specific polymorphic forms of enzymes that play a role in DNA repair, or polymorphisms in proteins that influence the responses of cells to growth factors (*i.e.*, receptors, protein kinases, and transcription factors), also influence cancer susceptibility, but this remains to be established.

Individuals at high risk also include those with a history of heavy exposure to various external carcinogens, including cigarette smoke, specific occupational carcinogens, and radiation, and individuals with certain reproductive, lifestyle, or nutritional histories. Microbial agents constitute a category of cancer risk factors that is gaining increasing importance, because of the evidence for causative roles of hepatitis B and C in liver cancer, EBV in nasopharyngeal cancer and specific lymphomas, HPV in cervical cancer, and *Helicobacter pylori* in gastric cancer (6, 7). It also seems likely that specific bacteria in the intestinal flora play a role in colon cancer through the production of diacylglycerol and possibly specific mutagens (6, 7), but this remains to be established. Further efforts should be directed toward identifying the possible roles of specific microbial agents as cofactors in the causation of other prevalent forms of human cancer. Such findings would have a major impact on novel approaches to cancer prevention.

Because it is likely that many human cancers result from interactions between two or more of the above factors, the identification of individuals at high risk will often require scoring for two or more risk factors, as is now routine in cardiovascular medicine. Thus, the risk of lung cancer in cigarette smokers may be especially high in individuals exposed previously to asbestos or people with specific polymorphic forms or unique profiles of inducibility of drug-metabolizing enzymes; the risk of liver cancer may be especially high in individuals with chronic hepatitis B infection who have also had exposure to aflatoxin or other chemical carcinogens; and the risk of gastric cancer may be especially high in individuals with chronic *H. pylori* gastritis who have also had exposure to nitrosamines and suffer vitamin deficiencies. Molecular epidemiology approaches that use epidemiological methods in combination with markers for each of the suspected factors will, therefore, be required to identify accurately individuals who are at especially high risk of developing specific types of cancer (6, 7).

**Nuclear Receptor Superfamily.** Nuclear receptors have great promise as targets for chemoprevention. The nuclear receptors comprise a large superfamily of transcription factors, functions of which, in many cases, are regulated by small, lipophilic hormonal ligands that include steroids, retinoids, vitamin D, and thyroid hormone (19). In addition to the dozen or so receptors in this family that have known ligands, there also exists an increasing number (>30) of orphan receptors that by sequence homology appear to be receptors but for which ligands are initially unknown (20). As a group, these proteins regulate the transcription of genes that control a diverse set of metabolic, developmental, and differentiation pathways. Because the dysregulation of any one of these pathways may enhance carcinogenesis, it comes as no surprise that the hormones that regulate these receptors can be exploited as potent chemopreventive agents (12). Research in the last decade on the biochemical, genetics, ligand binding properties, and structures of nuclear receptors has been explosive and has further strengthened this notion. For example, virtually all nuclear receptors (both the known and orphans) share a conserved hydrophobic pocket for the binding of potential ligands. In addition, the hydrophobic nature of nuclear receptor ligands often imparts a distinct pharmacological advantage in terms of bioavailability and tissue penetration, because as drugs they can be taken orally and can easily access most cells. Thus, nuclear receptors as a class are amenable targets for the identification of both novel natural ligands and synthetic pharmacophores. Several clinical studies have already shown the practical use of nuclear receptor ligands as targets for chemoprevention. Noteworthy examples include the use of SERMs such as tamoxifen and raloxifene in the prevention of breast cancer (21, 22) and retinoid receptor agonists in preventing lung and head/neck cancers (23–25). Finally, as stated above, in addition to the classic steroid and retinoid receptors, the continued discovery of dozens of uncharacterized orphan receptors and their ligands should provide a rich source of novel targets for future chemoprevention research.

**Future Directions in Basic Research That Will Enhance the Field of Cancer Prevention.** As briefly summarized above, it is apparent that recent advances in basic research have provided major insights into the roles of both exogenous and endogenous factors in the multistage process of carcinogenesis, the large number of genes that are targeted during this process, and the roles of inherited genetic
factors in influencing cancer risks. These advances have already had a major influence in the field of cancer prevention. It is apparent, however, that there are still major gaps in our understanding of the basic mechanisms of carcinogenesis. Knowledge of these basic mechanisms will provide insights into new strategies for cancer chemoprevention. A few specific areas that seem especially relevant are listed below.

- There is limited knowledge of the numerous gene mutations and alterations in gene expression that occur in specific types of human cancer. Furthermore, it is still not possible to integrate this type of information into a coherent picture of the signal transduction pathways and the total circuitry of cancer cells (16). Recent advances in genomics, proteomics, microarray technology, and informatics may accelerate research in this area. It is likely that an understanding of this circuitry in various types of cancer cells will provide insights that may not be apparent from simply analyzing single genes or linear pathways (16).
- A better understanding is needed of the role of epigenetic factors in multistage carcinogenesis, including aspects related to abnormalities in the control of gene transcription, DNA methylation, histone acetylation, and chromatin structure.
- The roles of dietary factors in enhancing or inhibiting carcinogenesis need further study. Specific issues include the role of excess calories per se versus excess dietary fat, the specific substances in fruits and vegetables that have protective effects, and the precise role of oxidants and antioxidants. A related issue is the mechanism(s) by which exercise appears to have a protective effect.
- The roles of genetic polymorphisms and specific environmental factors in influencing individual susceptibility need clarification.
- A better understanding of the precise mechanisms of action of some of the best known chemopreventive agents is needed, as is investigation of potential new targets, including protein kinases, transcription factors, enzymes involved in lipid metabolism, factors that control angiogenesis, and components of the immune system.
- Gene therapy may be applicable to the prevention of specific types of cancer. However, this area requires much more fundamental research because of the limitations of the current vectors and constructs, as well as the potential hazards.

Further advances in basic research could provide more efficient and powerful methods for developing and validating new chemopreventive agents. These new tools include: (a) novel experimental animal models of carcinogenesis, i.e., transgenic and gene “knock-out” mice; (b) novel cell or organ culture systems; (c) cellular and subcellular “mechanism-based” high-throughput screening assays; and (d) efficient screening of various combinatorial chemistry or natural substance libraries to identify potential chemopreventive agents. Some of these approaches are similar to those being developed for identifying new cancer therapy agents. This seems logical because some agents, like tamoxifen, are known to be useful in both cancer chemoprevention and therapy. At the same time, it would be desirable to develop novel assays that are specific for chemoprevention agents, and that lack the genotoxic effects of many cancer chemotherapy agents.

Further advances in basic research will also provide novel biomarkers or surrogate molecular endpoints that can be used in chemoprevention studies for better prediction of new agents likely to be valuable for long-term effects on cancer chemoprevention. At the same time, it is essential to develop assays and biomarkers that will detect possible carcinogenic or other toxic effects of agents being considered for long-term use in cancer chemoprevention.

Summary. Several major themes have emerged from basic research on cancer that are directly relevant to the development of more effective strategies of cancer prevention, especially chemoprevention. These include: the multistage nature of the carcinogenic process, the long latent period in the development of malignant tumors, the diversity of factors and mechanisms that can either enhance or inhibit specific stages of the process, the multiplicity and diversity of genes that are targeted during tumor development, and the complex interactions among both exogenous agents and inherited susceptibility factors. In view of these complexities and the known heterogeneity of tumors and precursor lesions, specific types of cancer chemoprevention may have to be tailored to specific types of cancer and to specific individuals, based on knowledge of the exogenous causative factors, individual genetic differences, and the molecular profile of the specific type of cancer or precursor lesion. Because of these complexities, it is also likely that the effective chemoprevention of several types of cancer will require the use of combinations of agents and preventive strategies. Fortunately, current and future advances in our understanding of the cellular and molecular basis of carcinogenesis, coupled with powerful new technologies, should accelerate this multidisciplinary approach to cancer prevention. At the same time, major new resources and interdisciplinary teams of investigators will be required to accomplish the complex and challenging goal of preventing cancer.

CLINICAL STUDIES

Introduction. Thoughtfully designed and carefully executed clinical trials have proven essential to the successful development of cancer chemoprevention thus far and will remain one of the most critical components of cancer chemoprevention development in the future. The United States FDA requires clinical trial data for the approval and labeling of all drugs, and cancer chemopreventive agents are subjected to a high level of scrutiny. Historically, the “gold standard” for gathering clinical inferences regarding cancer prevention has been the large-scale, randomized, placebo-controlled, double-blinded clinical trial using the endpoint of cancer incidence. When they have adequate statistical power, such trials can provide definitive evidence for efficacy and safety. However, they are typically costly, both in terms of funds and investigator commitment, and can take many years to complete. This is because these types of trials are usually designed to ascertain differences in the rate of cancer development over time between treated and untreated subjects (26). For heterogeneous study cohorts drawn from the general population, cancer incidence can be quite low. Thus, to estimate an endpoint event rate difference attributable to treatment with confidence, clinical trials with small study cohorts need to be conducted over long time periods, and clinical trials conducted over short periods need large study cohorts.

New insights concerning the biochemical and molecular pathogenesis of many human cancers offer great promise for cancer prevention. For cancer chemoprevention clinical trials, these new insights have the potential to: (a) identify clinical trial study cohorts at higher risk for cancer development; (b) define new trial endpoints as surrogates for cancer development; and (c) discover new chemoprevention drug targets and new drugs. If the promise and potential are realized, future clinical trials could be conducted more swiftly and at a lower cost, resulting in an increased number of trials performed, evaluation of more chemopreventive agents, and more rapid construction of pivotal trials for FDA approval. How can these new opportunities best be applied to cancer chemoprevention development? To answer this question, the state-of-the-art for cancer chemoprevention clinical trials will be reviewed, barriers to future progress considered, and future needs identified.

The Need for Clinical Trials in Cancer Chemoprevention. Controlled clinical trials provide powerful approaches for ascertaining the
safety and efficacy of any health intervention and constitute indispensable tools for cancer chemoprevention drug development. Before introduction into clinical studies, most candidate cancer chemopreventive agents are first evaluated using preclinical models. For many candidate agents, mechanism(s) of action can be well characterized using human or other mammalian cells propagated in vitro, whereas potential toxic effects can often be anticipated by administration to animals in vivo. After data on drug mechanism and safety have been obtained, the drugs are typically administered to animals at risk for the development of specific cancers, to assess their efficacy, therapeutic index, optimum dose, and scheduling. Although these animal models have proven extremely valuable, data collected using such models do not replace the need for human clinical trials. Species differences in drug disposition and metabolism, as well as in the pathogenesis of some cancers, frequently limit the applicability of preclinical findings to humans. In addition, many human clinical trials produce results not anticipated by preclinical models. Thus, human clinical trials are required for establishing chemoprevention drug safety, efficacy, dose, and dosing schedule. For the development of cancer chemopreventive drugs, both the similarities and the differences between results of clinical and preclinical studies often prove informative. Ideally, rational chemopreventive drug development would be expedited through a translational research paradigm, where preclinical observations lead to more critical clinical trial questions and clinical observations lead to more effective preclinical development.

Epidemiological studies are also invaluable for the development of cancer chemoprevention strategies. In attempting to identify etiological factors for human cancer development, epidemiological studies have created the transcendent rationale for all cancer prevention: most human cancers can be prevented. The identification of cigarette smoking as a risk factor for lung and other cancers has led to a rational public health strategy of smoking cessation (27–31), whereas the associations of HPV infection with uterine cervix cancer (32, 33) and hepatitis B virus infection with HCC (34, 35) have led to efforts both to reduce pathogen exposure through public health measures and to develop protective vaccines against infection and resultant cancer development (36, 37). Dietary epidemiological studies of cancer development have generated new clues about micronutrients and other dietary components that may prove efficacious as cancer prevention agents. For example, epidemiological evidence of a protective effect from cruciferous vegetable consumption (38, 39) engendered a search that led to the observations that ingestion of cruciferous vegetables stimulated the metabolism of xenobiotics by phase II reactions in humans (40) and eventually to the discovery of sulforaphane, an isothiocyanate compound present at high levels in broccoli sprouts that exhibits significant cancer prevention activity in preclinical animal models (41, 42). However, cancer epidemiology cannot replace the need for controlled clinical trials, which remain the most powerful approach for testing cancer prevention approaches. Epidemiological studies define populations at risk for cancer development; chemoprevention clinical trials define populations that benefit from intervention to reduce cancer risk. Both types of studies are necessary. For instance, although the results of several nutritional epidemiological studies indicated an association between low β-carotene intake and high cancer risk (43–45), two large clinical trials of β-carotene supplementation for lung cancer chemoprevention actually demonstrated an adverse effect in heavy smokers (46, 47). Thus, although the nutritional epidemiological studies had identified a high-risk population, the clinical trial data could not establish a role for β-carotene supplementation in the chemoprevention of lung cancer. Nonetheless, the historic success of cancer epidemiological studies in identifying high risk populations has already had a profound impact on the design of cancer chemoprevention clinical trials.

As discussed earlier, recent cancer genetics studies and genetic epidemiological studies have begun to identify specific genes and genotypes conferring risk of cancer development (48–50). Certain alleles, such as those encoding specific polymorphic variants of genes that regulate carcinogen metabolism, appear to confer a vulnerability to cancer development triggered by specific environmental or hormonal exposures (49–52). These studies have the potential to define cohorts at extremely high risk for specific cancers. Such cohorts might be suitable subjects for future chemoprevention trials, and their identification may permit the design of smaller and more efficient clinical trials. In this way, cancer epidemiology and cancer chemoprevention will retain a complementary relationship in the future.

What Have We Learned from Cancer Chemoprevention Clinical Trials Thus Far? Numerous chemoprevention clinical trials have been conducted (1, 2), producing both expected and unexpected results and yielding a number of insights into the pathogenesis and prevention of human cancers. Their findings and implications have been critically dependent not only on the agent evaluated but also on the target population studied and the specific endpoints evaluated.

Breast cancer prevention trials using the estrogen analogue tamoxifen have illustrated the necessity for randomized, placebo-controlled trials to compare efficacy and toxicity, and differences in the outcomes of several trials have underscored the importance of trial subject selection. Results from a high profile series of clinical trials of tamoxifen have been reported recently (21, 53, 54), and one of these, the Breast Cancer Prevention Trial in the United States, has recently led to FDA approval of tamoxifen as a drug to reduce cancer risk. The Breast Cancer Prevention Trial enrolled 13,388 women at increased risk for breast cancer development, ages 35 and older, into a randomized trial involving treatment with 20 mg of tamoxifen daily or placebo for 5 years. An overall 49% reduction in breast cancer risk associated with tamoxifen treatment was reported, and a similar reduction in the appearance of precancerous breast lesions was also evident among the patients receiving tamoxifen. On the basis of these compelling data, new trials are planned or underway to ascertain whether treatment with other SERMs, such as raloxifene, might confer a reduction in breast cancer risk without the increase in endometrial cancer risk caused by tamoxifen. In a cohort of several thousand postmenopausal women with osteoporosis, it has recently been shown that the risk of invasive breast cancer was decreased by 76% during 3 years of treatment with raloxifene (22).

Preliminary data from two smaller tamoxifen trials, the Italian Tamoxifen Prevention Study (53) and the Royal Marsden Hospital Trial (54), failed to demonstrate a similar protective effect of tamoxifen against breast cancer development. Although the precise explanation for the different results is not known, the trials targeted somewhat different patient populations, which may have had different risks for breast cancer development and possibly different tendencies to respond to tamoxifen as a chemoprevention agent. Both of the smaller studies enrolled slightly younger women and many women on hormone replacement therapy. The Italian study also enrolled a number of women who had had ovariectomies, whereas the Marsden Hospital trial enrolled women likely to be BRCA1 or BRCA2 mutation carriers, who may be at risk of developing less estrogen-dependent breast cancers. In the future, new molecular insights into breast cancer risk and breast cancer pathogenesis may yield new strategies for identifying women at greatest risk for breast cancer development and with the greatest likelihood of responding to treatment with an estrogen analogue. Another agent that has been shown recently (55) to prevent breast cancer in premenopausal women at extremely high risk is the retinoid, 4-hydroxyphenylretinamide (fenretidine). The possibility of clinical synergy between retinoids and SERMs should now receive further investigation.
Various retinoids and carotenoids have been studied as chemoprevention agents for aerodigestive cancers and have demonstrated the utility of surrogate biomarkers, such as premalignancy, in chemoprevention drug development. The most striking results with retinoids have been obtained in clinical trials involving subjects with premalignant oral lesions and with head and neck cancers. The recognition of oral leukoplakia as a lesion at risk for progression to carcinoma (56) and as a marker of field carcinization engendered a series of particularly informative clinical trials of cancer chemoprevention using regression of leukoplakia as a clinical trial endpoint. In a landmark study (57), 44 subjects with leukoplakia were randomized to receive isotretinoin or placebo for 3 months. In the isotretinoin-treated group, 67% had regression of leukoplakia, and 54% had reversal of dysplasia. Although the beneficial effects were short-lived, a subsequent randomized study demonstrated a benefit to lower-dose isotretinoin maintenance after 3 months of high-dose induction therapy (58). Later, a randomized 12-month trial of high-dose isotretinoin versus placebo in subjects treated for a prior head and neck cancer demonstrated a significant reduction in the appearance of second primary tumors (23). More recent studies have focused on refining the surrogate biomarkers of head and neck cancer risk and establishing new biomarkers of retinoid treatment effect. Specific somatic genome alterations, appearing in oral cavity epithelial cells at risk for neoplastic transformation and assayable using the polymerase chain reaction, may prove helpful as biomarkers for future trials (59–62). Diminished expression of retinoid receptor species, such as retinoic acid receptor-β, in premalignant lesions may correlate with responsiveness to retinoid treatment (63, 64).

Several large randomized trials of retinoids and/or carotenoids were undertaken for the prevention of lung cancer prevention (46, 47, 65). The results of the ATBC Cancer Prevention Study unexpectedly revealed a deleterious effect of β-carotene supplementation on lung cancer development (47). The trial randomized 29,133 male smokers, ages 50–69, to daily treatment with β-carotene daily, vitamin E, both β-carotene and vitamin E, or placebo. After 5–8 years of follow-up, trial results indicated an increased risk of lung cancer development associated with β-carotene supplementation. A second trial, the Beta Carotene and Retinol Efficacy Trial, yielded similar alarming results (46). In this trial, 18,314 smokers, former smokers, and asbestos workers were randomized to treatment with β-carotene and vitamin A daily versus placebo. Results disclosed an increased risk of lung cancer development in the treatment group. A third randomized trial, the Physicians Health Study, included 22,071 male physicians, ages 40–84, treated with β-carotene (65). No significant increase or reduction in cancer risk was evident after 12 years of follow-up. Why did these large randomized clinical trials show a detrimental effect of β-carotene? Although the precise explanation has not been established, a few considerations merit attention:

(a) The epidemiological studies on which these trials were based found only an association of diminished β-carotene consumption or low β-carotene blood levels with increased cancer risk (43–45). This association may not have been causal; β-carotene may be a marker for other dietary components or other micronutrients affecting cancer risk (44). Of interest, a large randomized trial of nutritional supplements including β-carotene, selenium, and vitamin E in 3318 subjects with esophageal dysplasia in Linxian, China, revealed a tendency toward reversal of premalignant lesions (66, 67) as well as a decrease in overall mortality and cancer mortality (68). In contrast to the study populations of the ATBC, Beta Carotene and Retinol Efficacy Trial, and Physician’s Health Study trials, the target study population for this trial was comprised of nonsmoking subjects with low micronutrient intakes (69).

(b) A second explanation of the poor performance of β-carotene as a chemoprevention agent in some trials is that supplementation may be detrimental in smokers (70); Burton and Ingold (71) have shown that at high oxygen partial pressures, β-carotene may become an autocatalytic prooxidant instead of an antioxidant.

(c) Finally, the trials may have focused on the wrong retinoid/carotenoid, the wrong dose, or the wrong dosing schedule. In a recent trial of retinyl palmitate, treatment with 300,000 IU daily for 12 months in subjects with stage I non-small cell lung cancer produced a statistically significant reduction in new primary lung cancers (24).

Retinoid dose also may be a critical determinant of efficacy for skin cancer prevention. In a study of 2297 subjects with actinic keratoses at risk for skin cancer development (72), 25,000 IU of retinol given daily for up to 5 years was more effective than placebo in preventing the development of new squamous cell, but not basal cell, cancers. Higher retinoid doses may be needed to prevent basal cell skin carcinomas (72).

Future clinical development of retinoids and carotenoids in the prevention of aerodigestive tract cancers should first involve testing of specific agents for bioactivity against premalignant lesions, where dose and dosing schedule can be determined, and then for efficacy in preventing cancer development or cancer mortality.

Attention to secondary clinical trial endpoints often yields new hypotheses for exploration. For example, two clinical trials targeted at prevention of skin (73) and lung (47) cancers have provided some of the best leads for prostate cancer prevention strategies. The usefulness of these trials for prostate cancer prevention was determined through careful collection of adjunctive clinical data concerning secondary clinical trial endpoints. The first of these trials was a randomized, placebo-controlled, multicenter trial of selenium in 1312 subjects with a history of nonmelanoma skin cancer to prevent the development of future basal and squamous cell skin cancers (73). Selenium supplementation showed no effect on the primary endpoints of the trial, but an analysis of secondary endpoints revealed a reduction in total cancer incidence and mortality, as well as a reduction in prostate cancer incidence (74). When the analysis was restricted to the 843 patients with normal baseline serum levels of prostate-specific antigen, a striking reduction in prostate cancer incidence was evident. The second of the two trials was the previously cited ATBC Cancer Prevention Study. Although this trial failed to demonstrate any benefit in terms of lung cancer prevention from supplementation with α-tocopherol, and in fact showed a detriment for supplementation with β-carotene, analysis of secondary endpoints revealed a protective effect of α-tocopherol supplementation against prostate cancer development (75). A 32% decrease in prostate cancer incidence and a 41% decrease in prostate cancer mortality were observed. Further analysis demonstrated a deleterious effect on prostate cancer development from β-carotene supplementation, with a 23% increase in prostate cancer incidence and 15% increase in prostate cancer mortality. These results illustrate a major value of well-designed, large randomized clinical trials; when such trials are funded well enough to collect data concerning appropriate secondary trial endpoints, new insights leading to new hypotheses can be fostered.

Well-designed, large randomized clinical trials can also provide opportunities for epidemiological studies. Many prospectively accrued epidemiological cohorts constructed before the establishment of current approaches to the management of some cancers have not collected adequate clinical data for the study of these cancers. For example, many epidemiological cohorts for prostate cancer were constructed before widespread serum prostate-specific antigen screening became commonplace. Large randomized clinical trials of prostate cancer prevention may now provide new cohorts for epidemiological studies. The Prostate Cancer Prevention Trial, a randomized trial of finasteride (76, 77), is using a careful clinical monitoring algorithm.
including serum prostate-specific antigen testing and prostate biopsies. Men receiving placebo treatment in this study will undoubtedly form an attractive prospective cohort for nested case-control studies. The construction of such epidemiological cohorts for “tertiary” clinical trial endpoints associated with large randomized cancer chemoprevention clinical trials mandates additional funding to support acquisition and management of additional demographic and questionnaire data, as well as additional biological specimens such as DNA for genetic epidemiological studies.

The growing interest in aspirin and other NSAIDs for colorectal carcinoma prevention has been the result of a convergence of findings from basic science studies implicating COX-2 in colorectal carcinogenesis, epidemiological assessments of the effects of aspirin or NSAIDs on risk reduction for colorectal cancer, and clinical trials of NSAIDs in patients with FAP syndrome (78). FAP syndrome, attributable to inherited mutations in the APC gene (79), is associated with the development of large numbers of intestinal polyps and an increased risk of colorectal cancer. Three randomized clinical trials in small cohorts of FAP patients were undertaken to ascertain whether treatment with the NSAID sulindac leads to regression of premalignant intestinal polyps (80–83). These studies found a significant regression of polyps in sulindac-treated patients. One of these studies also found that the treatment effects were reversed within 4 months of treatment cessation, whereas another demonstrated a reduction in mucosal cell proliferation in polyp lesions in the sulindac-treated group. These small studies have demonstrated clear bioactivity of sulindac in modulating premalignant colonic lesions. New insights into the contribution of specific COX isozymes to the pathogenesis of intestinal adenomas in mouse and rat models have suggested that new isozyme-specific inhibitors of COX-2 might prove effective in the treatment of premalignant colonic lesions (78, 84). Such selective COX-2 inhibitors are already under study for the treatment of polyps in FAP patients.

Clinical trials aimed at the prevention of HCC, one of the world’s most common lethal cancers, have reflected a growing understanding of the mechanisms underlying the pathogenesis of this disease. HCCs tend to arise in the setting of chronic hepatitis virus infection (34, 35, 85, 86) and exposure to dietary carcinogens such as aflatoxin B1 (87, 88). In one approach to HCC prevention, clinical trials and clinical practices targeted at the prevention or treatment of chronic hepatitis have been scrutinized for effects on subsequent HCC development (36, 37, 89–91). In one such clinical trial, 90 patients with chronic active hepatitis C infection and cirrhosis were randomized to receive 125 mg of oltipraz daily, 500 mg of oltipraz weekly, or placebo for 8 weeks. In an early report describing oltipraz treatment effects on aflatoxin-albumin adducts in serum specimens (96), a significant reduction in biomarker levels was found for subjects treated with 500 mg of oltipraz weekly, compared with no consistent changes in the placebo arm or, interestingly, the group receiving oltipraz daily. Aflatoxin-albumin adduct levels were lowest by the second month of oltipraz treatment but were reversed 1 month after treatment cessation. Thus, in a clinical trial focusing on biomarker modulation in a high-risk cohort, oltipraz has already demonstrated dose- and schedule-dependent activity in reducing aflatoxin damage. Once an oltipraz dose and schedule are established, a larger clinical trial targeted at HCC prevention can be designed.

Effective secondary prevention of HCC has also been achieved using a new acyclic retinoid, polypreneic acid, in patients free of disease after treatment for a primary hepatoma. A total of 89 patients were randomized to either acyclic retinoid or placebo for 12 months. After a median follow-up of 38 months, 27% of acyclic retinoid-treated patients had developed recurrent or second primary tumors versus 49% of patients receiving placebo (97).

**Challenges for Future Chemoprevention Clinical Trials.** Exciting new insights into the molecular pathogenesis of different human cancers should lead to new opportunities for cancer chemoprevention. To best translate these new findings into clinical trial hypotheses, a number of challenges must be met. Clinical trials performed thus far have illustrated how critically results depend on the selection of both study cohorts and study endpoints. The greatest impact of new discoveries from cancer epidemiology, cancer genetics, and the molecular pathogenesis of cancer may be the potential to provide new genetic markers to refine subject selection for clinical trials, as well as new molecular biomarkers as clinical trial endpoints. To realize this potential fully, the promise of new genomic technologies must be fully exploited. However, before genetic markers can be routinely used to facilitate selection of clinical trial study subject cohorts, further studies of gene-gene interactions and gene-environment interactions predisposing to cancer development will be essential. New strategies already under development for assaying genetic markers, including high-throughput DNA sequencing and high-density nucleotide arrays, appear poised to translate the results of such studies to clinical applications. Similarly, before molecular biomarkers can be routinely used as clinical trial endpoints, increased attention to the molecular biology and molecular pathogenesis of preneoplasia, as well as neoplasia, will be required. New techniques for monitoring such biomarkers in study subjects will also be needed. Finally, to evaluate the validity of candidate biomarkers as subject selection tools or surrogate endpoints and to assess the sensitivity, specificity, and reproducibility of biomarker monitoring techniques, provisions for monitoring new biomarkers will need to be incorporated into the design of future large-scale clinical chemoprevention trials. Ultimately, the introduction of new genetic and molecular markers into cancer chemoprevention clinical trials, especially for pivotal trials possibly leading to FDA approval, will demand increasing collaboration among clinical investigators, the pharmaceutical industry, the NCI, and the FDA. Incentives for such cooperation include increased cost efficiency in the chemoprevention drug development process, decreased time required for assessment of drug activity, and a more accurate definition of indications for drug use after approval.

**Needs for the Future.** With an anticipated increase in new candidate chemoprevention agents for clinical testing, a commensurate increase in clinical trial capacity will be needed. As new biomarkers become available for new clinical trial designs, increased numbers of small clinical trials focusing on specific high-risk populations will use these new biomarkers as strategic or surrogate trial endpoints. The results of these small trials can be used for better design of larger long-term clinical trials. A major requirement for the implementation of any coherent national strategy for cancer chemoprevention clinical research will be improved coordination and collaboration with health care provider organizations. Although cancer chemoprevention will
likely introduce new health care costs, successful chemoprevention also has the potential to decrease the known high costs of cancer treatment significantly. For these reasons, health care payer organizations should have a keen interest in high quality chemoprevention clinical trial research. In fact, in the future, health care payers should consider shouldering a greater burden of clinical trial costs, particularly the costs of large randomized clinical trials assessing chemoprevention treatment efficacy.

Another need arising from greater clinical trial activity will be greater coordination and collaboration among physicians and basic scientists in different medical specialties and subspecialties. Increasingly, cancer chemoprevention clinical trials have become less medical specialty-focused and more disease- or organ-site focused. In the future, the responsibility for chemoprevention delivery and treatment monitoring will be shared across a number of medical disciplines. New chemoprevention clinical trials need to incorporate this broadening array of different health care providers.

**Summary.** Cancer chemoprevention clinical trials constitute the ultimate goal of chemoprevention drug development. Such trials critically depend on the drugs available for study in humans, the manner in which trial subject cohorts are selected, and the trial endpoints defined. New insights into the molecular pathogenesis of human cancers will likely provide new opportunities, in the form of new genetic cancer susceptibility markers and new surrogate and strategic trial endpoint biomarkers, to improve clinical trial hypotheses and clinical trial execution.

**DRUG DEVELOPMENT, BIOMARKERS, AND REGULATORY ISSUES**

**Introduction.** Beyond the basic and clinical studies discussed in the previous sections, progress in chemoprevention is ultimately dependent on the discovery of new drugs, their effective assay and screening, and their ultimate approval by the FDA for use by the public. Furthermore, better biomarkers are critically needed in both animal and clinical studies to assess the efficacy of new drugs. Progress and recommendations in these areas are presented in this section.

**The Role of Diet as a Drug Delivery System.** Numerous epidemiological studies show that individuals who consume diets rich in vegetables and fruits have a reduced cancer incidence. Many chemopreventive agents of current interest such as genistein, curcumin, indole-3-carbinol, isothiocyanates, organosulfur compounds, resveratrol, retinoids, sulforaphane, squalene, and terpenes are found in the diet (11), and it is likely that these and other phytochemicals have a positive bearing on health.

However, many foods have not yet been systematically investigated for the identification and characterization of cancer chemopreventive agents. The list of plant materials found in the human diet is enormous (98). From these materials, isolates may be used as leads for the development of new chemopreventive agents. It would then be feasible to consider the development and production of fortified foods, possibly through the use of bioengineering. Presently, additions to the diet, particularly vitamins and minerals, are common and may diminish the risk of cancer. These include calcium, folic acid, selenium, and vitamins C and E. An advantage of diet as a delivery system is that it reaches a broad section of the population, including those who because of economics, poor education, or indifference might otherwise not be optimally protected. Disadvantages include dose regulation, erratic consumption, and difficulties in monitoring efficacy.

**The Spectrum of Cancer Chemopreventive Agents.** Hundreds of agents have been identified as having some potential chemopreventive value (1, 2), mainly from data derived from one of the following categories: (a) basic mechanistic data; (b) observational studies in experimental animals; (c) observational studies in humans; and (d) selective screening systems.

The identification of chemopreventive agents on the basis of mechanistic data has obvious advantages, although this approach has identified relatively few agents thus far. A good example is provided by the ornithine analogue, DFMO, which is a suicide inhibitor of ornithine decarboxylase. Ornithine decarboxylase is critical for cell proliferation, and its activity is increased in tumors of the large bowel in humans and rodents. The chemopreventive effects of DFMO are predictable from its known mechanism of action. Other examples of agents based on mechanistic data are those that control hormone activity in responsive tissues such as breast and prostate or that induce phase I or phase II enzyme activities to inhibit initiation. Observations from animal experiments can provide an insight into selection of chemopreventive agents. Thus, the field of retinoid chemoprevention initially was stimulated by animal studies of effects of vitamin A on the respiratory tract of experimental animals. Observational studies in humans can provide useful information as to possible efficacy of drugs as chemopreventive agents, even though the compounds were originally studied for other purposes. The classic example is tamoxifen. In clinical studies aimed at evaluating its efficacy as an adjuvant for chemotherapy of breast cancer, tamoxifen was shown to have a protective effect against primary tumors in the contralateral breast. Selective screening systems can be useful for identifying compounds that may have chemopreventive efficacy. Screening systems that select for enzyme induction, inhibition of cell proliferation, induction of differentiation, apoptosis, inhibition of COXs, and inhibition of protein farnesylation all have been used to identify effective chemopreventive agents. Organ culture systems also have been used for this purpose. The tracheal ring model has been used in selecting retinoids with potential to prevent lung cancer, and mammary gland organ culture systems have been used to identify inhibitors of preneoplasia in the breast.

**Desirable/Acceptable Characteristics of Cancer Chemopreventive Agents.** The desirable/acceptable characteristics of cancer chemopreventive agents vary qualitatively and quantitatively, depending on the anticipated therapeutic utility. However, the following factors may be considered favorable general attributes:

- Efficacy in preventing cancer. This is a critical attribute.
- Knowledge about mechanism of inhibition. This characteristic is important in maximizing efficacy and minimizing toxicity. It is useful in selecting biomarkers.
- Information as to likely efficacy in the human. From epidemiological studies and from clinical observations showing preventive effects on biomarkers, intermediate endpoints or (as in the case of tamoxifen) the occurrence of cancer can be very important.
- Demonstration of efficacy in experimental animals. This attribute is valuable in terms of studies of mechanism, pharmacokinetics, dosage regimens, biomarkers, and toxicity.
- Lack of toxicity or undesirable side effects. The magnitude of the acceptable toxicity or side effects is dependent upon risk. For individuals with no increased risk for cancer, the allowable toxicity and side effects that are acceptable are extremely low. For high-risk individuals, a greater toxicity is acceptable.
- Compounds already approved by the FDA for human use or likely to be approved readily. This category includes medicinals that have been approved by the FDA for other uses. Positive features of these compounds are that they have undergone substantial toxicity studies and human dosage is known. The NSAIDs and tamoxifen are examples of such compounds.
molecules in signal transduction pathways affecting cell growth and efficacy screens) and animal model assays that evaluate activity ultimately be found useful for other cancers.

Discovery and Characterization of Cancer Chemopreventive Agents. Over the past several years, significant effort has been devoted to incorporating new in vitro (both mechanistic assays and efficacy screens) and animal model assays that evaluate activity against specific genetic and molecular targets associated with carcinogenesis. These systems should prove invaluable in characterizing new agents. Some of the molecular targets are oncogenes and other molecules in signal transduction pathways affecting cell growth and proliferation. Examples are ras oncogene inhibition as measured by protein farnesylation inhibition, epidermal growth factor receptor inhibition, and tyrosine kinase inhibition. Other useful assays measure detoxification of carcinogens or inhibition of carcinogen activation, carcinogen-DNA adduct inhibition, inhibition of free radical formation and damage, enhancement of glutathione levels, and induction of glutathione S-transferase. One can also measure more general cellular effects such as enhancement of differentiation in cultured leukemia cells, induction of apoptosis, and inhibition of angiogenesis.

Natural products have played an important role in creating the new chemopreventive agents. On the basis of the process of bioassay-guided isolation (99), recent discoveries include brassinin (100), deguelin (101, 102), resveratrol (103), and sulforaphane (42). As has been illustrated on a much broader scale with retinoids (104–106), deltanoids (107), and isothiocyanates (108–110), new agents can serve as prototypes for the generation of analogues (111) or hybrid molecules (112) that may be more efficacious. By means of combinatorial chemistry and high-throughput screening, massive strides in this direction should be anticipated in the near future. A limitation, however, will be the physiological relevance of the high-throughput screen. Thus, it is doubtful that any high-throughput screen can adequately target the entire process of carcinogenesis. If single targets of absolute critical importance exist, which is unlikely, they are presently unknown. The multifactorial nature of carcinogenesis may require the use of combination chemoprevention, which is directed at multiple molecular targets. The logic of using combination regimens that can be designed on the basis of mechanism of action is powerful. Panels of tests can be devised to achieve this goal.

Use of Traditional and Transgenic Animals That Mimic Human Carcinogenesis for Evaluating Chemopreventive Efficacy. Preclinical drug discovery requires demonstration of activity in an animal model. There are two key aspects in evaluating the use of experimental animals in chemoprevention research. The first is a match between the animal model and the human disease entity. The closer the match, the more reliable the information will be for transfer to the human situation. The importance of this attribute is the same for traditional carcinogenesis models and for transgenic models. Transgenic animals provide a broad range of experimental pathology models, but their usefulness will depend on their ability to model carcinogenic mechanisms in humans.

For the genesis of tumors at most common epithelial sites, laboratory animals have been treated with various chemical carcinogens, and these models are conventionally used for the evaluation of many chemopreventive agents. Although some of these systems are good models for human disease, this frequently is not the case. However, inhibition of tumorigenesis in one particular animal model may be suggestive of additional preventive activity. In cancer chemotherapy, agents initially approved for the treatment of one tumor type may ultimately be found useful for other cancers.

Animal models that mimic specific characteristics of human carcinogenesis are potentially useful, as is the case with transgenic and gene knock-out mice that carry specific genetic lesions. Thus, the multiple intestinal neoplasia (Min) mouse (113, 114) and other strains carrying lesions in the Apc gene have been used to screen agents for prevention of colon cancer (78, 84). Mice that are transgenic for HPV type 16 develop cervical intraepithelial neoplasia, which progresses to squamous carcinoma (115). These mice have been used to identify preventive agents such as DFMO.

Development of Bridging Strategies for Relating Activity in Animals and Humans: Biomarkers and Intermediate Endpoints. In the above discussion, the use of animal models that mimic the human neoplastic process has been emphasized. Such animal models can be used to obtain information on mechanisms of inhibition, agent selection, use of agent combinations, pharmacodynamics, toxicity, dose selection, and the periods in the carcinogenic process at which agents are effective. Because of the prolonged time and great expense of using invasive cancer as an endpoint in clinical chemoprevention studies, biomarkers and intermediate endpoints have been developed to offer a pragmatic solution to these problems.

The evaluation of the validity of biomarkers and intermediate endpoints can be facilitated by the use of appropriate animal models. In such models, the accuracy of the predictive value of biomarkers and intermediate endpoints can be determined because the ultimate endpoint, cancer, is easily measured, in contrast to clinical studies. Extensive development of new biomarker methodology needs to be carried out in animals and translated to the clinic. The clinical relevance of biomarkers has already been shown in studies of FAP and oral premalignant lesions (116).

Studies directed at more precise definition of markers of IEN, which has many properties of cancer (except invasiveness), will be particularly germane. Examples of IEN amenable to biomarker studies in chemoprevention are colorectal adenomas, breast ductal carcinoma in situ, prostatic intraepithelial neoplasia, dysplastic bronchial metaplasia, bladder dysplasia, Barrett’s esophagus, cervical intraepithelial neoplasia, actinic keratoses, and dysplastic oral leukoplasia.

However, although shorter than the period for developing cancer, the latency for IEN progression can also be long compared with the time required for a chemopreventive intervention study. Importantly, the number of precancerous lesions will far exceed the number of invasive cancers that subsequently develop in the target tissue, and those lesions that progress may have particular characteristics predisposing them to develop into cancers. Therefore, to establish chemopreventive efficacy, it is critical to ensure that virtually all precancerous lesions are arrested or that the arrested lesions are those with potential to progress. For these reasons, the sole use of conventional histology to determine drug-induced arrest or regression of IEN may not be sufficient to determine chemopreventive efficacy.

Thus, quantitative methods in pathology are necessary for studies of IEN to be practical. Descriptive histopathology that evaluates cancer risk subjectively by estimating nuclear grading should be supplemented with quantitative measurements afforded by computer-assisted image analysis. Parameters that can be measured (116) are increased nuclear size, altered nuclear shape, increased variance of nuclear size and shape (pleomorphism), altered chromatin texture, increased mitotic index, abnormal mitoses, alteration or absence of differentiation and maturation, nucleolar size and number of nucleoli/nucleus, and DNA ploidy as measured by DNA content. Several computer-assisted imaging systems are commercially available. Molecular markers also need to be considered. Stabilization or improvement of the premalignant genotype, as well as phenotype, in treated subjects needs to be evaluated. If reliable molecular markers can be developed, these will be particularly important.

Combination Cancer Chemoprevention. The usefulness of single chemopreventive agents is limited by their efficacy, potency, and
toxicity. Administration of multiple agents can increase efficacy and potency while reducing toxicity. Several drug combinations have been proposed for clinical development based on their synergistic activity in animal studies, e.g., retinoids (fenretinide and 9-cis-retinoic acid) with SERMs (tamoxifen, raloxifene, and LY-353381) in rat mammary glands and prostate (117–122), or DFMO with an NSAID in rat colon (123). Also, mechanistic data may suggest the potential synergy of two agents; an example is the enhancement of electrophile-trapping activity (hence, carcinogen detoxifying activity) that might be achieved by combination of an agent such as N-acetyl-L-cysteine, which provides substrate for glutathione synthesis, with an agent such as oltipraz, which enhances glutathione S-transferases (124, 125).

It should be pointed out that a priori one cannot assume additive or synergistic effects of the inhibitory capacity of two agents. In some instances, additive effects do occur; in others, they do not, and there may even be antagonism. Thus, when agent combinations are under consideration for human use, their effects should be studied initially in animal models to determine the usefulness of the combination as well as the toxicity produced.

**Local Delivery to Improve Therapeutic Index.** Local delivery of chemopreventive agents has the potential advantage of achieving high concentrations of the test agent at the target site with minimal systemic exposure. There are several targets that are particularly attractive for use of topical delivery, such as the skin, the cervix, and the respiratory and gastrointestinal tracts. Administration of chemopreventive agents that are selectively activated by target tissues is another means of achieving high concentrations of active drug at target sites without systemic exposure to an active agent.

**NCI/FDA Consensus Guidance (Science-based Rationale) on Developing Chemopreventive Agents for Marketing Approval.** In 1995, a collaboration between the NCI and the FDA resulted in a consensus document on an approach for developing chemopreventive agents for marketing approval (126). Briefly, the approach is applied drug development science beginning with the identification of candidate agents and the characterization of these agents with in vitro and animal chemopreventive efficacy screens. Promising agents are then further evaluated in animal models to design regimens for clinical testing and use. As for other classes of pharmaceuticals, agents judged to have potential as human chemopreventives are subjected to preclinical toxicity and pharmacokinetic studies, followed by Phase I clinical safety and pharmacokinetic trials. The most successful agents then progress to clinical chemoprevention trials.

As noted above, the impracticality of cancer incidence reduction as an endpoint is a major challenge in designing chemoprevention efficacy trials. However, increased understanding of carcinogenesis has provided a means of overcoming this obstacle, i.e., use of biomarkers that are validated as surrogate endpoints for cancer. The original NCI/FDA collaborative document acknowledged the importance of biomarkers and briefly outlined criteria for evaluating surrogate endpoints for cancer incidence. Current discussions between NCI and FDA focus on both the conceptual and practical issues of demonstrating chemoprevention based on surrogate endpoints. As noted above, quantification of the extent and severity of the lesions of IEN provides useful primary surrogate endpoints. The demonstration of clinical benefit in asymptomatic subjects is a major challenge in documenting efficacy by modulation of surrogate endpoints. In this regard, IENs are prototypes, in that arrest or regression of lesions could result in net clinical benefit, for example, as evidenced by longer periods between invasive surveillance procedures (e.g., subjects with sporadic colorectal adenomas) and allowing organ preservation (e.g., Barrett’s esophagus and superficial bladder lesions). Phase II and small Phase III clinical chemoprevention trials may be conducted in patients with IEN. These cohorts provide tissue samples that can be used for rigorous dose-response studies to establish efficacy. Quantitative measurements of cell and tissue changes induced by chemopreventive agents may be evaluated in these lesions as potential surrogate endpoints.

**Consensus with FDA on Strategies for Attaining Marketing Approval with Surrogate Endpoints.** Several practical issues arise in applying surrogate endpoints to the evaluation of chemopreventive efficacy. At least three issues need to be addressed before marketing approval can be obtained for chemopreventive agents on the basis of surrogate endpoints: (a) clinical benefit from arrest or reversion of surrogate lesions; (b) effects on quality of life; and (c) the need for continuing monitoring for adverse effects that might not be observed in short-term surrogate endpoint studies.

The degree of clinical benefit that might be derived from efficacy as measured by a surrogate endpoint is an important issue (127). FDA approval requires that the drug provide net clinical benefit, i.e., benefits of drug administration should outweigh risks. Theoretically, a drug without demonstrated clinical benefit might not be approved. Initially, the criteria described for selecting surrogate endpoints support drugs with clinical benefit directly related to lowering cancer incidence. However, as more data are developed on modification of genotypic and other specific molecular changes in carcinogenesis, the demonstration of effects on surrogate endpoints that predict clinical outcome may also support chemopreventive drug approvals.

Chemopreventive drugs may ultimately be given to asymptomatic populations for years or decades. Therefore, minimal toxicity is essential. Determining standards in terms of allowable type and frequency of side effects and impact on quality of life will be critical issues as chemopreventive drugs are introduced. It is also possible that life-threatening toxicities compromising the long-term use of a drug would not be detected within the time frame of surrogate endpoint-based efficacy trials.

On the basis of these considerations, there will likely be multiple, and sometimes sequential, approaches to establishing chemopreventive health claims based on surrogate endpoint modulation. One approach will be to develop data supporting health claims for the arrest and regression of lesions that are putative surrogate endpoints for cancer, where these lesions are a significant health risk themselves and/or are widely recognized as precancers. One example is the prevention or regression of adenomatous colorectal polyps, particularly in FAP patients and in other patients with previous polyps.

A second approach would follow the accelerated pathway for gaining marketing approval as defined in 21 CFR Section 314.500. This mechanism uses surrogate endpoints for disease incidence in the setting of life-threatening disease. Since its introduction in 1987, this mechanism has been applied to drugs for the treatment and prevention of AIDS and to cancer chemotherapeutics but not as yet to cancer chemopreventives. To obtain approval, it is expected that the chemopreventive agent modulates a surrogate endpoint, and that the surrogate endpoint is “reasonably likely” to predict clinical benefit (e.g., cancer incidence reduction) compared with existing treatments. Because accelerated approval permits marketing before clinical benefit is fully demonstrated, two additional conditions are imposed: (a) the Sponsor agrees to carry out controlled studies with “due diligence” to verify net clinical benefit to patients, in this case, cancer incidence reduction; and (b) the provision for accelerated withdrawal of the drug, if the post-approval controlled studies fail to show the anticipated net clinical benefit. Initially, accelerated approval is likely to be most successful in settings where the onset of cancer is relatively close in time to the appearance of the surrogate endpoint, as in patients with previous bladder or head and neck cancers who have high incidences of new cancers within 1–2 years.

Marketing approval of a chemopreventive agent based on one of
these mechanisms using surrogate endpoint modulation is a major objective of cancer chemoprevention drug development. Once modulation of the surrogate endpoint is validated as prevention of cancer, its subsequent use in a similar context (for example with different investigational drugs or at other target sites) may be facilitated.

**Summary and Recommendations.** The following brief statements summarize recommendations for future action in this area:

- identify and characterize cancer chemopreventive agents in dietary materials;
- explore effective uses of diet for the delivery of cancer chemopreventive agents;
- develop and use effective methods for the discovery of new cancer chemopreventive agents;
- establish bridging strategies for developing chemopreventive agents that are active in animal models;
- define biomarkers that are useful for assessing cancer chemopreventive agents;
- establish a firm basis for the characterization and use of cancer chemopreventive agents in combination;
- explore a variety of treatment/application methods to improve the therapeutic efficacy of cancer chemopreventive agents;
- reach consensus with the FDA regarding clinical evaluation criteria and market approval processes for chemopreventive agents.

**EDUCATIONAL AND SOCIETAL CONCERNS**

**Introduction.** Prevention of cancer is ultimately a problem for the entire society, because prevention involves many considerations beyond the immediate biology, diagnosis, and therapy of malignancy. However, various groups involved in the chemoprevention of cancer have looked at this problem in a widely divergent manner, which has impeded progress. As described above, several chemopreventive agents have now proven effective in human subjects. It is therefore time for a coordinated effort among patient advocacy groups, practicing general physicians and oncologists, biomedical researchers, the pharmaceutical industry, cancer funding agencies (both federal and private), and regulatory agencies such as the FDA to achieve the goal of cancer prevention. Previous sections of this Report have dealt with specific areas of basic science, clinical research, and drug development necessary to facilitate the prevention of cancer. In this section, some of the broader, nontechnical, educational, and societal problems that have impeded progress in the past will be considered, along with specific recommendations for the future.

**Education.** Educational and conceptual issues are significant obstacles to chemoprevention of cancer. This is true both for the public and for physicians and researchers. In contrast to the intensive and successful educational effort that has occurred in the prevention of cardiovascular disease, the importance of the multistage nature of the development of invasive cancer is not generally recognized. Both practicing oncologists and the general public are still encumbered with an archaic nomenclature that fails to recognize that cancer is not a single event; rather, it is a disease process. The disease process is carcinogenesis, not invasive or symptomatic cancer (128). By failing to emphasize the importance of controlling carcinogenesis in its earliest stages with adequate preventive measures, attention and resources have been shifted to finding cures for advanced invasive and metastatic disease. Although it is intuitively obvious that it is easier to fix a piece of machinery when only a few components are broken, this intuition has been ignored in dealing with the process of carcinogenesis. By waiting to treat neoplastic disease until it is invasive, one waits until a large number of genes and their resultant products are dysfunctional; unfortunately, such damage is difficult to repair.

Another fundamental problem is a lack of adequate understanding of the concept of risk and, as a corollary to this, a misperception of the word, “healthy.” Ultimately, everyone has some finite risk for development of disease. This risk may be so low that from a pragmatic viewpoint, it is not worthwhile to consider any preventive intervention. However, as the degree of risk of disease increases, so does the benefit associated with intervention increase, if one can devise a safe and effective preventive regimen. Changes in lifestyle may be sufficient prevention for some people. However, if significant genetic and cytological risk factors are known to be present, then the possibility of chemoprevention needs to be considered. There is a need to develop a sophisticated algorithm for estimating risk for each type of cancer in specific individuals, based on all the known risk factors for that particular cancer. Prospective candidates for chemoprevention can then be stratified, and active intervention can be considered for those at highest risk. This strategy has been successfully used in the large trial that recently demonstrated the effectiveness of tamoxifen in prevention of breast cancer (21, 129).

In discussions of risk reduction, the important distinction between relative risk and absolute risk reduction should be made (130). A chemopreventive agent may provide the same relative benefit for high- and average-risk individuals (e.g., a 20% reduction in mortality). However, when relative benefits are the same, the absolute benefit (the actual number of premature deaths averted) will be much greater for the high-risk individuals simply because their absolute risk was so much higher at the start. Still, even for interventions that produce impressive results (e.g., tamoxifen for breast cancer), the majority of individuals in the intervention might not be expected to benefit. Further effort is needed to educate both physicians and the public about the various factors that contribute to risk of disease and how best to frame and individualize the probability of benefit associated with the intervention. The public needs to understand that the presence of asymptomatic precursor lesions such as marked dysplasia is associated with increased risk, although in absolute terms that risk may be small. At the same time, the public should be informed when chemoprevention offers the possibility of decreasing such risk.

Above all, absence of clinical signs and symptoms does not guarantee that one is indeed totally healthy. In cardiovascular medicine, the public has been taught that elevated blood pressure and cholesterol are significant risk factors, even in the absence of symptoms. In turn, the use of such biomarkers has identified individuals at-risk, who are candidates for active chemoprevention. The use of chemopreventive agents resulting in lowered blood pressure and cholesterol levels is generally conceded to provide a major health benefit. Clearly, this general strategy has been both effective and accepted in cardiovascular medicine. Similar preventive approaches now need to be applied in the field of oncology, as markers of increased cancer risk that are amenable to chemopreventive intervention are discovered (131).

Another area that needs intensified educational effort is the interface between chemoprevention and genetic testing. In spite of the remarkable scientific advances in our understanding of genetic susceptibility, there are concerns about the widespread application of genetic testing. These concerns include fears of stigmatization, loss of confidentiality, loss of insurability, and loss of future employability. Safeguards must be developed to protect patients from these concerns. At the same time, genetic testing can provide essential information about disease susceptibility and risk that will be highly beneficial. In the future, it will be important to couple genetic testing for susceptibility with information to patients about the benefits of chemoprevention, so that the impact of “bad news” can be cushioned by the hope that a preventive drug might offer. Much has been written about the potential adverse psychological effects of genetic testing (132, 133);
for some, cancer chemoprevention can provide a strategy that helps to deal with this problem.

The Need to Expand the Interest of Physicians and Researchers in Prevention. A lack of emphasis by physicians and researchers on cancer prevention is an additional obstacle. In general, prevention of disease is not emphasized in the curricula of most American medical schools, and few physicians choose this area for a career. This has led to a shortage of personnel trained in disease prevention and specifically in chemoprevention, as well as a lack of both clinical and basic science trainees for the future, further perpetuating this unsatisfactory situation. The root causes are many. In the past, effective agents for prevention of cancer were not available, so prevention was regarded as a “public health” area, rather than a focus for basic scientific or clinical investigation. In addition, new information about the benefits of chemopreventive agents has not been widely disseminated. Chemoprevention has been viewed by some clinicians as a threat to established patterns of practice. Furthermore, although health insurance companies provide reimbursement for the therapy of invasive cancer, this is often not the case for the treatment of premalignant lesions.

The above scenario needs to be corrected. Chemoprevention needs to assume its rightful place in the curricula of medical schools, in residency and fellowship training programs, and in the training of Ph.D. scientists. With new advances in molecular and cell biology, major opportunities now exist for careers in basic research related to chemoprevention, and funding for training in both the basic science and clinical investigation aspects of this field needs to be increased. Advances in basic science are the driving force for new pharmacological approaches to the prevention of cancer, as well as other diseases. The intellectual excitement of participating in these efforts should stimulate the recruitment and training of a new generation of physicians and laboratory scientists dedicated to careers in disease prevention. Clearly, it will be essential to provide major incremental financial and institutional resources to achieve these goals.

Concerns of the Pharmaceutical Industry. As noted in a previous section, clinical trials of agents for chemoprevention are exceptionally difficult to perform because of their long duration, the large number of patients involved, the problem of developing meaningful endpoints (other than cancer incidence and mortality), and the resulting high costs of these trials. In the pharmaceutical industry, patents on a new drug may expire before definitive evidence of preventive efficacy is obtained. In addition, there is widespread concern about potential, unforeseen hazardous side effects of chemopreventive agents, especially when they are administered over many years. Such concerns in turn raise further worry about possible legal liability, especially when a new preventive drug is given to asymptomatic individuals, who perceive themselves as “healthy.” Similar concerns existed before new agents, such as the statins, were developed to prevent cardiovascular disease by lowering cholesterol levels. In spite of these concerns, the pharmaceutical industry made an immense investment in the development and clinical assessment of statins. These products are now widely used as effective agents to prevent cardiovascular disease, and they have been a major source of revenue to the pharmaceutical industry.

A similar commitment to develop new drugs for chemoprevention of cancer now needs to be made by the pharmaceutical industry. This effort should involve not only the industry itself but also leaders in academic medicine and federal institutions, as well as the concerned public, particularly individuals with a high risk of developing cancer. Given the long time that it takes to screen and validate a new chemopreventive drug, the possibility of developing new legislation to extend the duration of patent protection specifically for preventive agents should be considered. Such legislation would eliminate the possibility that the patent for a preventive drug might expire before the drug could be marketed. Also, a societal strategy to provide liability insurance against extremely rare, untoward events that might occur from the use of preventive agents is needed. It is unlikely that pharmacological agents for cancer prevention that are totally free of risk during long-term use will ever be discovered. However, if new drugs show a significant benefit in reducing cancer incidence, and the occurrence of untoward effects is exceptionally rare, then it is in society’s best interest to encourage the use of such agents. Further discussion among the pharmaceutical and insurance industries, academics, legislators, and the public should be encouraged to create a climate that will favor the development and use of drugs for chemoprevention.

All of these concerns will be compounded with the development of combination chemoprevention, i.e., the use of multiple agents with different mechanisms of action to prevent cancer. There is considerable evidence from animal experimentation that combinations of agents can be more effective than single agents for the prevention of cancer. As discussed earlier in this Report, basic research has shown that most cancers result from damage to multiple genes. Therefore, it is likely that multiple agents will be needed to repair and contain this damage. Because clinical trials of this concept are now imperative, there is a need to establish an environment of corporate cooperation among the various pharmaceutical companies that have proprietary interests in each component of a combination regimen.

Funding. A significant increase in funding is critical if we are to achieve the above-described goals in cancer chemoprevention. Historically, chemoprevention research has not been a popular area for funding from either government or private philanthropic sources. Instead, the emphasis has been on the treatment of established, often advanced, cancers. Thus, the NCI still promotes and funds many more projects in cancer chemotherapy than in chemoprevention. There is a similar imbalance in the efforts of most of this nation’s cancer centers and training programs. In chemoprevention, there are special needs for increased funding to train young investigators (both basic and clinical) and for the support of clinical trials, which are uniquely expensive. Particular emphasis should also be given to funding the development of novel biomarkers and intermediate endpoints and their validation and use as surrogate endpoints in chemoprevention trials. Thus, the availability of biomarkers such as elevated blood pressure or elevated serum cholesterol and other lipids as useful predictors of stroke or myocardial infarction has greatly accelerated the introduction of new drugs for chemoprevention of cardiovascular disease.

Role of Advocacy Groups and the Government. As mentioned above, there is a major need for better communication between the academic medical community, the pharmaceutical industry, and the appropriate branches of government that deal with the prevention of cancer in our society. Previous sections have made suggestions that involve regulatory agencies such as the FDA, funding agencies such as the NCI, or the legislative branch of government. In this regard, advocacy groups, representing the needs and concerns of citizens with respect to cancer prevention, can also play an important role. Advocacy groups have a unique capacity to articulate their concerns about prevention of cancer, to educate and influence public opinion, and to influence government action for the benefit of society. In the past, cancer advocacy groups have rightfully focused most of their activities on the immediate and critical problems of research and patient care related to advanced cancer. These endeavors continue to be a major concern. However, in view of the promising advances in cancer chemoprevention, advocacy groups now have an excellent opportu-
SUMMARY AND RECOMMENDATIONS

The incidence and mortality rates for most of the common forms of cancer are still unacceptably high. This stark fact in itself is a strong argument for further research, both basic and clinical, to prevent cancer. The new science of chemoprevention, defined as the use of pharmacological or natural agents to inhibit the development of invasive cancer, has been established as a promising new strategy to achieve this goal. In the area of basic science, immense advances in the understanding of the molecular and cellular biology of the process of carcinogenesis (the development of cancer) now provide a rational basis for further progress in cancer chemoprevention. Clinical studies have validated the use of new drugs both for prevention of first cancers (primary prevention), as well as for prevention of new cancers in patients who have had surgery for removal of a malignancy (secondary prevention). The development of new and better drugs for chemoprevention remains a principal need. Toward this goal, it is essential to understand the molecular and cellular mechanism of action of such drugs, as well as to develop accurate biomarkers to assess their efficacy. The introduction of new drugs for chemoprevention will require new cooperative efforts among the academic community, the pharmaceutical industry, and government agencies such as the NCI and FDA. The implementation of chemoprevention also requires that important societal concerns be addressed. These include concerns about genetic testing, confidentiality of medical data, and the appropriateness of treating people who are free of symptomatic disease. A major educational effort involving patient advocacy groups, as well as the pharmaceutical industry, the government, and the academic community, will be required to achieve the promise of widespread chemoprevention.

Finally, the development of chemoprevention as both a basic and a clinical science will require a major increase in funding and institutional resources, if we are to achieve these goals. There is a compelling need for funding to attract young professionals, both M.D.s and Ph.D.s, to choose a career in this field. There is a specific major need for further funding for clinical trials of new chemopreventive agents. “Proof of principle” for chemoprevention as a practical approach to the control of cancer now exists. The challenge now is to increase our efforts to achieve the worldwide benefit that would result from the prevention of cancer.

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Appendix

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