## Editorial

# The Chemoprevention of Cancer: Directions for the Future

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### Current Status

The decade of the 1990s is witnessing an endorsement of the science of preventing cancer by chemical means. This represents a significant departure from the emphasis on therapeutic strategies which characterized research efforts in the 1970s and 1980s. Already more than 100,000 subjects have been involved in chemoprevention trials, and in 1992 the NSABP[1] launched the largest nationwide chemoprevention trial ever designed, the BCPT, using the drug tamoxifen to prevent breast cancer in healthy high risk women. An even larger study involving 18,000 men to prevent prostate cancer is in the final planning stages.

As is always the case with new scientific advances, there are historical reasons that chemoprevention is being embraced and supported by national health care policy makers at the current time. With the development of more sophisticated biochemical and technological tools, and advances in the molecular genetics of cancer, scientists have gained a more precise understanding of the process of carcinogenesis and are identifying early, potentially modifiable premalignant biochemical changes. At the same time, epidemiological studies have provided an appreciation of the role of dietary micronutrients in cancer risk and their potential for inhibiting the progression of precancerous lesions. Just as important as the progress made at the biological level is the experience of limited success in finding curative therapeutic strategies for cancer, with a subsequent shift in focus to a search for preventive approaches.

In view of the limited cancer research budget and the national health care crisis, much forethought and planning should accompany our chemoprevention program so as to minimize the costs and maximize the information obtained. The clinical trial experience of the last 20 years has taught us many valuable lessons which can be used in the design and implementation of chemoprevention trials. However, chemoprevention studies have several unique features which distinguish them from therapeutic trials and call for new strategies and approaches. We are at a crucial point in time for reflection on the key questions which pertain to the future of the chemoprevention of cancer.

### How Does Chemoprevention Relate to Oncology as We Know It?

The use of chemical agents to prevent the initiating and/or promoting events in the carcinogenic process completes a triad of prevention strategies for cancer control, which also includes the elimination or avoidance of carcinogens in the environment (*e.g.*, smoking cessation or low fat diets), and screening and early detection of cancer. It is a multidisciplinary effort which draws heavily on a basic understanding of the biology of cancer causation and development. Not only does an understanding of the carcinogenic process provide clues for the chemical modification of these events, but also by learning how chemopreventive agents alter the natural history of precancerous lesions we gain new insights into the process of carcinogenesis itself.

Agents with cancer preventive potential, both synthetic as well as natural, are being developed much in the same way as cancer chemotherapeutic drugs have been, with increasingly complex design phases. The initiative to date has been taken by the medical oncology community, borrowing heavily from its clinical trial experience. However, the unique features of dealing with healthy asymptomatic populations who are being asked to comply with a drug regimen for a long duration (usually 5 or more years) for an unknown benefit have identified the need for involvement of other scientific disciplines to create new research and analytic designs, to explore ways to maximize compliance, and to evaluate the quality of life issues generated by the trial experience.

### Who Will Participate in Chemoprevention Trials?

The relationship between basic tumor biology and mechanisms of chemoprevention indirectly determines the appropriate candidates for participation in chemoprevention trials. Data from both animal models and human cancer suggest that the induction of neoplasia is a multistep process, requiring an initiation phase and a prolonged promotion phase during which there are multiple opportunities for both progression and inhibition of the process. Our understanding of the molecular and cellular systems which regulate growth and proliferation forms the basis for exploring sites of both tumorigenesis and chemoprevention. These insights in turn allow for identification of individuals who, by virtue of having a genetic predisposition, an exposure history, or a personal history of a cancerous or precancerous lesion, have either manifest or have the potential to manifest a defined growth abnormality toward which a chemopreventive agent may be targeted. Appropriate candidates for most chemoprevention trials, then, will be individuals who have defined risk factors for a cancer which has a significant impact on morbidity and mortality, and in which early intervention is likely to affect outcome. Risk profiles may be based on genetic factors, lifestyle and environmental exposures, a history of a precursor lesion, or some combination of these. The more precise our methods for determining risk status, the more efficient will be our prevention trials. The current NSABP Breast Cancer Prevention Trial uses a mathematical model combining family history, reproductive history, and a history of benign breast disease to estimate lifetime risk for breast cancer and to determine eligibility for the trial (1).

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[1] The abbreviations used are: NSABP, National Surgical Adjuvant Breast and Bowel Project; BCPT, Breast Cancer Prevention Trial.

Targeting high risk individuals for chemoprevention trials increases their efficiency in terms of sample size and duration by maximizing outcome events. This approach, however, limits the generalizability of the results to the population at large, whose risk/benefit ratio may be very different from that of the study population. In addition to the definition of population risk characteristics which are deliberately built into the study design, other uncontrolled lifestyle factors tend to bias participation in these studies. The underrepresentation of ethnic minority groups in most prevention trials, for example, has been attributed to cultural differences in health beliefs and attitudes, as well as socioeconomic barriers, and has resulted in uncertainty about the significance of study findings for these groups. While policy makers have voiced concern about this situation, the intensive outreach efforts which will be needed in future trials to capture these special populations will be very costly and will require a special commitment from funding sources.

The increasing sophistication of cancer chemoprevention trials has resulted in another potential barrier to participation by representative target groups, the consent form. Concern about the exposure of healthy at-risk populations to potentially harmful chemicals has resulted in the creation of consent forms the length and technicality of which limit their comprehension and make truly "informed" consent a privilege of only the highly educated. Much of the complexity of consent forms is dictated by the legal community, the language of which often appears equivocal to the layperson. A compromise whereby individuals can be truly informed about the risks and benefits of their participation in a trial in language which is clear and straightforward without sacrificing content must be achieved.

## What Are the Appropriate Outcomes for Chemoprevention Trials?

The ultimate goal of cancer chemoprevention is to prevent new cancers and thus reduce cancer mortality. However, cancer endpoints are relatively rare, take a long time to occur, and need large sample sizes to achieve statistical power and significance. Even when high risk populations are chosen to increase the yield of cancer events, these trials are long and costly and subject to contamination by drop-ins, dropouts, and other secular trends.

The use of intermediate markers as predictors of subsequent cancer occurrence, which requires less time, fewer subjects, and costs less money, is gaining increasing acceptance, particularly in the early phases of drug development. Cellular, biochemical, and molecular changes which represent early signals of carcinogenic transformation and growth can provide opportunities to more efficiently evaluate the effectiveness of new drugs on tumor inhibition. Effective intermediate markers ideally have differential expression in normal and high risk sites, manifest a correlation between degree of change and stage of carcinogenesis, can be measured in a reproducible way, and can be altered by chemopreventive agents. Several such candidate markers exist, including genomic markers, proliferation indices, and differential markers, but most remain largely unvalidated (2).

The primary role for intermediate markers will be in the intermediate stages of developing large-scale phase III chemoprevention studies, where panels of markers representing different stages in the carcinogenic process can be identified and evaluated. Ultimately, however, disease outcomes, both incidence and mortality, must be evaluated in order to justify the transfer of a chemopreventive approach for a particular cancer to the public health arena. These studies will require large sample sizes, long periods of follow-up, and expensive budgets. The classical drug development approach used for cancer chemotherapy agents is very effective at characterizing acute toxic reactions to drugs given for defined, usually relatively short-term schedules, but is inappropriate for drugs given in low doses to healthy individuals over long periods of time. Therefore, assessment of long-term treatment sequelae must be built into subsequent phase II and III trials to adequately describe the full spectrum of toxicities associated with the long-term use of chemopreventive agents.

A seriously overlooked outcome measure in cancer chemoprevention trials is adherence. Most of the energy devoted to issues of adherence to date have concentrated on how to measure adherence, not how to promote it. The incorporation of a run-in period prior to randomization eliminates those who have compliance problems from the outset, leaving the more highly motivated to begin the trial. However, little is known about long-term compliance after the initial glow of interest and motivation fades or is displaced by newer, more pressing concerns. The high recidivism rates observed in programs targeted toward other preventive behaviors, such as smoking cessation and weight loss, suggest a short "prevention attention span" in most individuals, and indicate a need for a proactive promotion of adherence strategies.

The last decade has witnessed a growing appreciation of the importance of other alternate endpoints in clinical research, and the inclusion of quality of life measures in clinical trials has gained wide acceptance, at least at the conceptual level. Attention to functional, psychological, and social outcomes are especially important when testing unknown therapies for prevention in healthy, asymptomatic individuals. An extensive quality of life measurement tool has been fully integrated into the Tamoxifen Breast Cancer Prevention Trial. The challenge in the future will be to decide how to use this information to weigh the relative quality of life costs and benefits in comparison to the demonstrated effectiveness of the chemoprevention agent being tested.

Finally, sophisticated cost analyses are needed so that public policy decisions regarding the widespread adoption of chemoprevention programs are fiscally as well as scientifically sound.

## Who Should Conduct Chemoprevention Trials?

There is an emerging trend for large-scale chemoprevention trials to be conducted through the collaborative group mechanism. There are many strengths to this approach. Collaborative groups already understand how to do clinical trials and have the organizational infrastructure for collecting, handling, and analyzing data in place. In addition to clinicians, there is strong representation from basic scientists interested in tumor biology, intermediate markers, and prognostic factors. Participation by behavioral scientists with special expertise in issues of recruitment and compliance is increasing. The major weakness of the collaborative groups with regard to chemoprevention trials is their lack of access to healthy populations. Active membership in collaborative groups has traditionally been restricted to oncology subspecialists who diagnose and treat cancer patients. To conduct cancer chemoprevention trials, collaborative groups will have to expand their research base to affiliate in some capacity with primary care practitioners. There is actually a model for this type of expansion in the Community Clinical

Oncology Program, which affiliates community oncologists with academic centers to conduct clinical trials. A similar program whereby primary care practitioners can affiliate either directly or through oncology practices with collaborative groups for participation in chemoprevention trials is needed. Most primary care physicians lack confidence in their behavior modification and health promotion skills and have expressed a need for support in implementing cancer control activities in the office setting (3). To effectively include primary care practitioners in chemoprevention research, they must be given the skills and resources necessary to prepare their staff and to educate their patients for participation in preventive trials. The involvement of non-physician medical staff in the implementation of chemoprevention trials is equally important. The extensive time and labor demands generated by the unique recruitment and compliance challenges of prevention trials require a team approach, with participation at all levels by nurses, physicians, health educators, and data managers, to be feasible.

Reimbursement issues also need to be addressed to remove the cost barriers from both potential participants in these trials and their primary care providers. Many of the required physician visits and tests in the BCPT, for example, will not be covered by insurers and will either have to be paid out of pocket by the women participating in the trial or will be financial losses to the participating physicians and institutions. While much lip service is being given to disease prevention by politicians involved in the reform of health care in this country, it remains to be seen how much actual support for the development and testing of preventive strategies will emerge.

## How Should Chemoprevention Trials Be Developed?

The National Cancer Institute has called for the same scientific rigor in prevention trials as is customary in therapeutic clinical trials and has called for a step-wise process of development from basic science research to hypothesis generation, methods development, and controlled clinical trials.

In 1982 the National Cancer Institute established the Chemoprevention Branch of the Division of Cancer Prevention and Control to: (*a*) identify, through animal studies, and on the basis of epidemiological observations, agents with efficacy in preventing carcinogenesis; (*b*) test the efficacy and safety profiles of these agents in animal models; and (*c*) implement clinical trials in human populations (4). Natural and synthetic compounds which block both initiation and promotion of the carcinogenic process are screened and studied. Design of these studies is based on the model developed for testing new chemotherapeutic agents and includes a phase I stage in which pharmacokinetics and toxicity are the main endpoints, followed by limited phase II and III studies modeled after classical cancer clinical trials, usually testing a single agent with a single end-organ outcome measure.

While the experience in chemotherapy drug development provides a valuable model for the early phases of developing chemopreventive compounds, the unique features of chemoprevention trials have inspired some innovative study designs. Eligibility for chemoprevention trials is determined not by a disease state, as in traditional clinical trials, but by a risk profile, which may be very complex as in the Gail model used in the BCPT. Statistical designs must consider attrition from "drop-ins" as well as "drop-outs" especially in trials of natural products which may be available outside the medical care system. As the agents being studied in chemoprevention trials are generally non-toxic, they can often be given in combination rather than as single agents. Factorial designs which allow for studying two distinct research questions simultaneously with a very marginal cost increase are ideally suited for chemoprevention trials, where multiple independent outcomes are of interest.

## Toward a Chemoprevention Consortium

Large-scale, costly chemoprevention trials, such as the BCPT, cannot be repeated over and over with minor variations as has been the custom with chemotherapy trials in the past. Pilot studies are particularly important in chemoprevention studies to address the following issues: (*a*) drug development through phase I pharmacokinetic and toxicity studies; (*b*) validation of intermediate endpoints for different tumor models; (*c*) recruitment and adherence strategies for targeted populations; (*d*) consideration of ethical and legal implications of the trial; and (*e*) development of training materials and workshops for the uniform implementation and conduct of the trial.

The pilot work needed to prepare for a large-scale efficacy trial requires input from many disciplines working in collaboration. The kinds of expertise needed for all of these dimensions do not exist in any one institution or even in any one collaborative group. Planners of the BCPT, the first chemoprevention trial of this magnitude, have, for example, called upon advise and input from a diverse group of consultants from many sources.

The future success of chemoprevention would seem to be best served by the formation of consortia where scientists from diverse backgrounds and disciplines could collaborate rather than compete to maximize both the success of the trials as well as the scientific knowledge gained from each. Individuals with shared interests in a particular area related to chemoprevention would share experiences and pool ideas in the preparatory phases of large trials. By laying the groundwork for the scientific and logistic aspects of new trials, the final products would represent the best strategies possible. Among the tasks of such consortia could be, for instance, the creation and validation of risk assessment profiles for determining eligibility criteria, the development of common approaches to recruitment and adherence in targeted population groups, a consensus on the most appropriate quality of life outcome measures for chemoprevention trials, and the standardization of toxicity scoring for agents such as the retinoids and other micronutrients. Centralized specimen banks for the collection, storage, and evaluation of preneoplastic tissues and biomarkers could be set up and supervised by such consortia and would permit ancillary research to be more efficient and productive. Participation by practitioners from diverse practice settings would ensure that implementation strategies would be more realistic and would encourage more widespread participation. Input from health care planners would facilitate the ultimate transfer of findings from chemoprevention studies to the public health arena. Ancillary studies to address secondary objectives, such as age and gender differences in compliance with pill taking, could be designed to cross several studies.

It would seem that the expertise represented by the membership of the American Society of Preventive Oncology provides an excellent opportunity to take the lead in the formation of a chemoprevention consortium. The chemoprevention subcommittee of the American Society of Pre-

ventive Oncology has already begun to tackle some of the unique challenges posed by chemoprevention research, and since disease prevention assumes a position of priority in the national health care plan, is in a strong position to organize and guide the membership in this direction.

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