

## Overview Consensus Statement

### FIRST INTERNATIONAL CONFERENCE ON CHEMOPREVENTION OF PROSTATE CANCER

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The First International Conference on Chemoprevention of Prostate Cancer was held in San Antonio, Texas, March 7–8, 2003. Conference attendees were selected based on their contributions to basic or clinical understanding of the chemoprevention of prostate cancer. The faculty included internationally recognized specialists in urology, oncology, epidemiology and biostatistics, pharmacology and drug development. The conference format combined brief scientific reports with extended periods of open discussion. At the end of the meeting participants summarized key information that was reviewed and discussed to formulate this consensus statement.

#### THE ROLE OF DIETARY COMPONENTS

A number of macronutrients and micronutrients and other dietary constituents have been or are currently being evaluated as potential chemopreventive agents. Attention has focused on dietary components because diet is believed to be one of the environmental factors that may help explain differences in the incidence of certain cancers by geographic location. However, to date much of the scientific evidence to support the value of most vitamins, trace elements or plant foods as chemopreventive agents in prostate cancer is relatively weak or inconclusive.

Two nutrients that have come under serious scrutiny as potential chemopreventive agents in prostate cancer are selenium and vitamin E. For example, there is considerable clinical evidence to support the potential value of selenium as an agent to prevent prostate cancer and the progression of high grade prostatic intraepithelial neoplasia to cancer. Findings from controlled studies of both of these micronutrients, suggest a potentially substantial impact on incidence and mortality. The ongoing Selenium and Vitamin E Cancer Prevention Trial should provide definitive evidence about the

value of these 2 nutrients in the prevention of prostate cancer.

Although there is some evidence from animal experimental models to suggest that various retinoids may have chemopreventive properties, these compounds have a high toxicity that makes them inappropriate for preventive interventions. To date, the only carotenoid that shows promise as a possible preventive agent for prostate cancer is lycopene. Well-designed clinical studies are needed to clarify any potential association between lycopene and prostate cancer risk.

For macronutrients a number of studies have suggested that there is an association between a high intake of dietary fat or certain high fat foods, such as red or processed meat, and prostate cancer. More work is needed to identify whether fat, other components of a high fat diet or effects of high fat foods, such as obesity, are etiologically relevant.

#### THE ROLE OF HORMONES

Given the important role of androgens in the development of prostate cancer, researchers are also investigating the effects of 5 $\alpha$ -reductase inhibitors, agents that suppress the conversion of testosterone to dihydrotestosterone. A large ongoing trial, the Prostate Cancer Prevention Trial, is investigating the value of finasteride, a 5 $\alpha$ -reductase inhibitor, in preventing prostate cancer. The results of this study were published subsequent to the date of the Chemoprevention Conference.<sup>1</sup>

#### THE ROLE OF INFLAMMATION OR INFECTION

As yet, there is no definitive proof that chronic or recurrent inflammation and/or infection has a role in prostate cancer although intraprostatic inflammation is common (eg asymptomatic prostatitis and proliferative inflammatory atrophy lesions). Epidemiological studies of sexually transmitted infections, prostatitis and now variants in genes involved in inflammation and response to infection suggest a role for chronic inflammation in the etiology of prostate cancer. However, additional well-designed research is needed to clarify

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the role of inflammation and infection in prostate carcinogenesis, and to determine if chronic intraprostatic inflammation is a potential target for chemopreventive efforts.

A number of mechanisms have been identified that could explain a link between inflammatory processes and the development of prostate cancer. One of these mechanisms is the induction of cyclooxygenase-2 (COX-2) in macrophages and epithelial cells. Studies have suggested that there is up-regulation of the COX-2 enzyme in proliferative inflammatory atrophy lesions compared with prostate tumor tissue and normal prostate tissue. Drugs that inhibit prostaglandin synthesis have been shown to induce apoptosis of prostate tumor cells. In addition, nonsteroidal anti-inflammatory drugs have been associated with lower incidence rates for colon and other types of cancer, although evidence regarding prostate cancer is mixed.

These observations have led to the evaluation of the selective COX-2 inhibitor rofecoxib in the prevention of prostate cancer in high risk patients. Exisulind, a derivative of the nonsteroidal anti-inflammatory drug sulindac that does not inhibit cyclooxygenase, is also under investigation as a potential chemopreventive agent in prostate cancer because it has been shown to delay the increase in prostate specific antigen in men at high risk for disease recurrence. It is possible that new research may identify COX independent mechanisms responsible for the chemopreventive activity of this class of drugs which will provide insight into new targets for agents with superior efficacy and safety.

#### THE ROLE OF GENETIC RESEARCH

Due in part to the long natural history of the disease, the identification of those men at highest risk for clinically significant prostate cancer is a major challenge. One approach to this problem is identifying men with a genetic predisposition to prostate cancer.

Some studies of prostate cancer risk have focused on genes that are involved in the regulation and metabolism of androgens, and the interactions between circulating androgens and the androgen receptor, which impact the development of normal and malignant cells in the prostate. Other studies have looked at genetic variations in the vitamin D receptor, which has an integral role in the antiproliferative effects of calcitriol. Currently, at least 1 polymorphism in the vitamin D receptor may predict the risk of prostate cancer in specific ethnic groups.

#### CHALLENGES IN CLINICAL TRIAL DESIGN

Large phase III studies may be planned as the next logical step following basic research and animal studies to clarify prostate carcinogenesis, epidemiological observations, smaller treatment trials and further analyses of other large cancer prevention trials. Identification of an appropriate study population is paramount in designing a study that is scientifically valid and feasible. The size of the study population is determined by the number of participants required to achieve statistically significant outcomes plus the estimated number of participants expected to die, be noncompliant with the treatment regimen and dropout or be otherwise lost to followup. In a prevention study it is also vital to select relevant and measurable primary and secondary end points.

As previously mentioned, prostate cancer may develop 20

or more years before it becomes clinically evident, and many prostate cancers remain latent over a life time. Therefore, it could require several decades before study participants reach an end point of clinically evident disease. There is increasing interest in developing new biomarkers that can be used in lieu of clinical disease as a primary end point.

Additional genetic polymorphisms must be identified, characterized and understood at the functional level. Combinations of single nucleotide polymorphisms of functional significance may identify a "bad genotype" that may convey an increased risk of cancer or an increased risk for more aggressive disease. Biomarkers based on these genetic polymorphisms that more accurately predict cancer risk may allow design of studies targeting a higher risk population. Studies that are smaller can be completed more quickly and at a lower cost.

#### OTHER ISSUES AND OPPORTUNITIES

Concern has been expressed about the possibility of inefficient use of limited research resources by duplication of studies. Investigators must share their areas of research interest and proposed studies with the research community. At times relevant studies are reported in journals that may not receive widespread international attention. One solution would be to establish a complete database, limited to reported negative side effects and evidence based proof of activity, for all potential strategies for prostate cancer prevention. Because of differences in requirements for conducting research in various countries, the large studies required to evaluate chemopreventive agents in prostate cancer may be more difficult to complete in Europe. However, individual countries in the European community could be valuable partners in multisite studies in conjunction with North American research centers.

Another area of interest is the value of data used to plan further research. Epidemiological studies need to be critically evaluated for their design, sample size and potential for bias. Possible agents for testing in chemoprevention studies should be those for which there is consistency in findings across epidemiological studies conducted using several different designs in a variety of populations and multiple methods of exposure assessment. Because chemoprevention studies typically require investment of substantial resources, epidemiological evidence may be used to prioritize those agents that merit large scale study.

How can findings in high risk patients be extrapolated to the general population? Will the use of molecularly targeted therapies of advanced malignancies translate to chemoprevention? Is predicting which man will have prostate cancer as important a strategy as identifying those men with prostate cancer who will die of the disease? In addition, it is important to consider interventions that may cross specialty barriers. A recommendation that not only reduces the risk of prostate cancer, but may also be of benefit in preventing other chronic diseases will be more powerful and effective in influencing public response.

#### REFERENCE

1. Thompson, I. M., Goodman, P. J., Tangen, C. M., Lucia, M. S., Miller, G. J., Ford, L. G. et al: The influence of finasteride on the development of prostate cancer. *N Engl J Med*, **349**: 215, 2003