

## Update on Cancer Prevention Research in the United States and China: The 2009 China—U.S. Forum on Frontiers of Cancer Research

Ann M. Bode<sup>1</sup>, Ya Cao<sup>2</sup>, and Zigang Dong<sup>1</sup>

### Abstract

Cancer is one of the major physical, social, and economic burdens and public health threats worldwide. Citizens everywhere face the challenge of dealing with the costs and devastation of this dreadful disease regardless of country of residence. In October 2009, a joint China—U.S. forum focusing on cancer prevention was held in Changsha, China. The goal of this timely joint conference was to provide a forum for the exchange of the most recent and relevant information on cancer control, translational cancer prevention research, and clinical trials in China and the United States. The scientifically driven symposium comprised didactic sessions that included discussions focused on identifying and validating effective chemopreventive agents and their molecular and cellular targets. A major highlight of the meeting was the participation of Chinese and American experts from Xiangya Medical School, Central South University and the Center for Health Policy and Management (China), and the National Institutes of Health (NIH, United States), who provided a unique insight into each country's public efforts and progress in cancer prevention. Participants clearly agreed that our current understanding of the many factors influencing cancer causation indicates that as much as two thirds or more of human cancers can be prevented. This perspective presents an overview of the progress being made in cancer prevention in China and the United States. *Cancer Prev Res*; 3(12); 1630–7. ©2010 AACR.

### Introduction

Cancer is one of the major physical, social, and economic burdens and public health threats worldwide. Citizens everywhere face the challenge of dealing with the costs and devastation of this dreadful disease regardless of country of residence. In October 2009, a joint China—U.S. forum focusing on cancer prevention was held in Changsha, China. The goal of this timely joint conference was to provide a forum for the exchange of the most recent and relevant information on cancer control, translational cancer prevention research, and clinical trials in China and the United States. The scientifically driven symposium comprised didactic sessions that included discussions focused on identifying and validating effective chemopreventive agents and their molecular and cellular targets. A major highlight of the meeting was the participation of Chinese and American experts from Xiangya Medical School, Central South University and the Center for Health Policy and Management (China), and the National Institutes of Health

(NIH, United States), who provided a unique insight into each country's public efforts and progress in cancer prevention. The United States and China have a history of cooperative collaboration. Since 1986, the NCI/NIH has worked with the Cancer Institute, Chinese Academy of Medical Sciences (CICAMS), and the Labor Protection Institute of Yunnan Tin Corporation (YTC) to conduct a number of different scientific studies among tin miners at the YTC, located in Gejiu, Yunnan Province, China, the largest tin industry site in Asia. Dr. Ping Hu (National Cancer Institute, National Institutes of Health) indicated that several studies have been initiated to identify early biomarkers and evaluate etiologic factors in tin miners in China (1).

The term *chemoprevention*, initially referred to as "chemoprophylaxis of carcinogenesis" (2), was coined in 1976 (3, 4). Chemoprevention is defined as the use of chemical agents, drugs, or dietary supplements to prevent disease (5). Many of the agents discussed in this meeting were compounds derived from natural sources and the new technologies being used to identify candidate molecules. Dr. Allan H. Conney (Susan Lehman Cullman Laboratory for Cancer Research, Department of Chemical Biology, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey) emphasized the fact that studies in migrant populations, changes in cancer incidence with time within the same country, and studies with identical twins indicate that environment and lifestyle are major players in the causation of human cancer. Cigarette smoking, diet, infectious agents and

**Authors' Affiliations:** <sup>1</sup>The Hormel Institute, University of Minnesota, Austin, Minnesota and <sup>2</sup>Xiangya Medical School, Central South University, Changsha, China

**Corresponding Author:** Zigang Dong, The Hormel Institute, University of Minnesota, Austin, MN 55912. Phone: 507-437-9600; Fax 507-437-9606; E-mail: zgdong@hi.umn.edu.

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obesity/inactivity are major factors that contribute to our cancer burden. Clearly, an urgent need exists for an increased emphasis on cancer prevention research. Current understanding of the many factors influencing cancer causation indicates that as much as two thirds or more of human cancers can be prevented. This perspective presents an overview of the progress being made in cancer prevention in China and the United States.

### Cancer prevention in China

The overriding theme from both American and Chinese participants was the importance of active prevention, early detection, and reasonable treatment as important principles in cancer prevention and treatment. Active prevention was defined as the enforcement of policies and measures to strictly control smoking, environmental hazards, dietary factors, and virus and bacterial infections. Many states in the United States have laws prohibiting tobacco use in restaurants and bars, universities and colleges, government buildings and other public areas. These types of policies are just beginning to be implemented in China. Early detection is recognized as an effective means to intervene in cancer development. To effectively diagnose cancer patients, before obvious symptoms are manifested requires advanced technical methods for targeting and effectively screening for specific cancers. Reasonable treatment suggests choosing appropriate surgery, chemotherapy, radiotherapy, immunotherapy, or alternative therapies based on the type, location, and development stage of the tumor and the patient's overall health.

As has been true in the United States in years past and currently, unhealthy lifestyles in China, including heavy smoking and poor diet combined with poor environmental practices leading to substantial pollution have contributed to a dramatic rise in chronic diseases such as cancer (6). The spectrum of cancer in the United States compared with China has been quite different in the past but now with economic changes, the disease pattern in China is becoming more similar to that observed in Western cultures. For example, with the advent of refrigeration and access to more fruits and vegetables, a decrease in stomach cancer is observed in both countries whereas gastrointestinal and breast cancers are increasing. The major exception is lung cancer associated with smoking, which appears to be decreasing in the West but increasing in China. The most common cancers in China include lung cancer, infection-induced cancers, such as hepatitis B virus (HBV) or HBV-induced liver cancer and human papillomavirus (HPV)-induced cervix cancers or *H. Pylori*-induced gastric cancers, cancers linked to being overweight and obesity, and those cancers associated with environmental pollution and occupation.

Dr. Ya Cao (Xiangya Medical School, Central South University, Changsha, China) described the China Cancer Prevention and Control Plan currently in place (2004–2010) includes the goals to (a) control tobacco use, (b) control HBV infection, (c) eliminate occupational and environmental hazards, (d) implement early screening

and intervention strategies, including providing the public with information and making people aware of warning signs. Screening and early therapies have been shown to be effective in early detection of nasopharyngeal, cervical, breast, gastric, and colorectal cancers. She indicated that process has been made in implementing the overall plan with funding from the Bill & Melinda Gates Foundation to establish a smoking control and research program mediated through the Chinese Medical Board. The Chinese government has initiated health screening to detect breast cancer and HPV for cervical cancer among the female rural population. In addition, a planned immunization program includes vaccinating against HBV to prevent liver cancer and screening for (prostate-specific antigen) PSA, ( $\alpha$ -feto-protein) AFP, and (carcinoembryonic antigen) CEA have also been included as part of routine health exams.

Even though progress has occurred, Dr. Feiyue Hu (Center for Health Policy and Management—Peking Union Medical College) indicated that China is currently in a period of social transformation, witnessing a rapid and unprecedented urbanization. The urbanization is associated with contradictions and problems in public health and hospital management for cancer prevention, early detection, diagnosis, and treatment. China is facing many challenges in cancer prevention for the general population, including accurate registration of cancer incidence and mortality and statistical analysis and evaluation of prognostic information.

The population with access to screening has increased over the last few years to include rural and poor Chinese because of the financial support from the Chinese government medical insurance, which plays a significant role in reducing cancer mortalities. However, Dr. Hu indicated that because institutionalization of the development, implementation, or effective monitoring and evaluation of prevention, early detection and the standard of diagnosis and treatment of cancer, the pertinence and feasibility of relevant supporting policies are not yet well justified. Furthermore, counterpart funds or detailed plans on personnel training for the existing national cancer prevention and control plan have not yet been made available. He suggested that at this point in time, the policies in place in the Chinese government do not mutually promote cancer research, epidemiological investigation and analysis, and the standard diagnosis and treatment of cancer. This is quite reminiscent of the history of cancer prevention progress and research in the United States and other Western countries. Historically, research efforts in Western countries have focused heavily on early detection and treatment, with less emphasis on environmental and lifestyle causes. Until recently in the United States, cancer prevention has not been typically viewed as a distinct strategy that can supplement early detection and treatment of cancer. The same appears to be true in China.

Dr. Hu believes that for China, the most important goal for cancer control is the appeal to promote research on the formulation of laws regarding cancer control and prevention. The belief is that this will provide evidence for

the development of badly needed policies and regulations for establishing national cancer screening and a registry system. This effort will initiate the legislative procedure to establish policies for budget allocation and professional training, promoting the incidence and mortality registration, and establishing and implementing the technical standards for the statistical analysis and evaluation of prognostic data. Furthermore, combined with the ongoing Chinese health system reform, the cancer prevention and treatment policies that are appropriate for China need to be formulated. The overall framework and priorities of cancer control for China entails (a) prevention and early detection, (b) equalization of medical services, (c) improving the quality of life of cancer patients, (d) promotion of cancer registration, and (e) promotion of research.

### Cancer prevention in the United States

In the United States, the 1990s and early 21st century marked the beginning of a heightened awareness of the effects of diet on health and especially more interest in cancer prevention and cancer prevention research. The NCI established the current NCI Division of Cancer Prevention (DCP) in October 1997 and its mission is to plan, direct, implement, and monitor cancer research and training that is focused on early detection, cancer risk, chemoprevention, and supportive care. NIH currently defines cancer prevention as the reduction of cancer death through the reduction of cancer incidence and suggests that cancer can be prevented by avoiding known risk factors such as carcinogens or smoking or by chemoprevention to reverse preneoplastic changes (see <http://www.cancer.gov/cancertopics/pdq/prevention/overview/healthprofessional>).

The association of tobacco, nutritional, and environmental factors with cancer has been realized in the United States for many years (7). Dr. Peter Greenwald (Director, NCI Division of Cancer Prevention, National Cancer Institute, National Institutes of Health) indicated that over the last few years, at the NIH, more research has focused on investigating the feasibility of reducing cancer risk by living a healthy lifestyle, and more recently, through medical approaches to cancer prevention (8). He indicated that attention has primarily focused on lung, breast, colorectal, and prostate cancers, which account for about one half of new cases of cancer worldwide each year. For lung cancer, an increasing number of countries, including the United States and China, are implementing public policies that discourage tobacco use through restrictions of its use in addition to research and randomized controlled trials for chemopreventive agents and antinicotine vaccines. Cancer deaths associated with obesity and overweight are reaching epidemic proportions in the Western world and especially in highly developed countries, an increase in caloric intake and lack of regular exercise have contributed to this epidemic (9, 10).

A number of cancer prevention trials have resulted in the identification of effective compounds for preventing breast and prostate cancers. These compounds include tamoxifen (11, 12) and raloxifene (13, 14) for breast cancer and

finasteride (15) and dutasteride (16) for prostate cancer. In contrast, dietary epidemiologic observations and animal studies for dietary factors from fruits and vegetables consistently suggest possible protection against various cancers; but in general, these findings have not yet been fully validated in randomized trials. In fact, results of most dietary intervention clinical trials have been somewhat disappointing. Most notably, the results of trials with  $\beta$ -carotene (17, 18) to prevent lung cancer or selenium (19) to prevent prostate cancer were a major setback to the role of nutrients in cancer prevention. On the other hand, some positive dietary (low fat) intervention studies are worth mentioning. For example, the Women's Intervention Study documented a 25% risk reduction for recurrence of stage I/II breast cancer (20) and the Women's Health Initiative documented a 40% reduction in the risk of developing ovarian cancer (21).

Colon cancer risk has been shown to be decreased in persons who took aspirin regularly (22) and celecoxib, a selective cyclooxygenase-2 (COX2) inhibitor, taken twice daily (400 mg) led to a significant reduction in the number of colorectal polyps (23). Unfortunately, the use of celecoxib has been associated with an increased risk of adverse cardiovascular effects (24). Notably, low doses of the anti-inflammatory sulindac and an investigational compound difluoromethylornithine (DFMO) prevented colon polyp recurrence by 70% and the recurrence of advanced adenomas by 92% in a recent phase III trial (25). These results clearly demonstrate the idea of combination prevention or therapy or convergent prevention and therapy, which will be discussed later in this perspective.

Dr. Levy Kopelovich (Division of Cancer Prevention, National Cancer Institute, National Institutes of Health) emphasized the critical importance of identifying potential cancer biomarkers for developing effective chemopreventive agents. The development of new drugs for cancer prevention is extremely difficult and time consuming (26, 27). Efficacy and off-target toxicity are major hurdles to overcome in the development process. The first step is drug identification and molecular targets followed by screening and verification *in vitro* and screening and efficacy studies *in vivo*. Toxicology studies must then be conducted before the drug can be moved into Phase 0 or Phase 1 clinical trials.

Dr. Vernon Steele (Division of Cancer Prevention, National Cancer Institute, National Institutes of Health) suggested that from the 20th century into the 21st century, the practice of medicine in the United States has shifted from (a) descriptive medicine to understanding mechanisms; (b) from empirical diagnosis to mechanism-based diagnosis; (c) from cancer grouped by organ site to subgrouping by molecular signature; and (d) from uniform, standardized treatment to personalized medicine; and finally from the idea of treating disease to preventing disease. Because the process of cancer development is usually long, the pathways involved can be suppressed, reversed, or retarded at various stages and thus the identification of the pathways involved in the process of cancer development is

crucial to block the process. The developing belief is that multiple pathways must be targeted for a limited period of time and different cancers might require a customized combination of prevention strategies to be successful (28, 29). In fact, according to Dr. Steele, combinations of drugs will provide multiple inhibitory mechanisms that might increase efficacy synergistically because single agents will not likely block heterogeneous cancers as has clearly been shown in clinical trials. In addition, combinations of drugs will likely require a lower dose of each compound thereby leading to lower toxicity and fewer adverse side effects. As indicated earlier, the positive results of the recent clinical trial with sulindac and DFMO for prevention of colon cancer strongly support these suggestions.

Historically, a relentless focus exclusively on early detection and treatment of cancer with less emphasis on its prevention has not been effective in eliminating this destructive disease. Early detection, treatment, and prevention must be combined to create a complete strategy for cancer control. We are seeing signs that this strategy is beginning to occur. Dr. Scott M. Lippman (The University of Texas MD Anderson Cancer Center) suggested that the greatest clinical benefit would come from the convergence of "early" cancer treatment and "late" cancer prevention. He indicated that early treatment will involve molecular tumor profiling to identify successfully treated patients who are at highest risk of reoccurrence, whereas late cancer prevention involves molecular profiling to identify micro-neoplasia/intraepithelial neoplasia (IEN) patients at highest risk of primary cancer. New molecular targeted agents combined with new technologies for screening provide unique opportunities for developing clinical trials that integrate treatment with prevention end points thus creating a convergence of prevention and therapy (30). This sharing of molecular targets provides a platform for convergent (treatment and prevention) drug development, which promises to accelerate the reduction of cancer burden (30). Dr. Peng Huang (Johns Hopkins University) discussed the advantages of designing clinical trials with multiple end points as opposed to single outcomes and introduced the idea of a new measure, the global treatment effect (GTE), to summarize a treatment's efficacy from multiple primary outcomes (31).

### Promising agents and targets

Much discussion centered on a number of promising agents being studied by various speakers at the joint China—U.S. symposium focusing on cancer prevention. Compared with many countries, including China, this was an area of research in which the United States has excelled. Clearly, carcinogenesis is a complex, multistage process that affects many genes and gene products, which are critical in the regulation of numerous cellular functions. The likelihood of finding a "magic bullet" or one compound that will cure cancer is probably not possible. Thus, focusing on the elucidation of numerous molecular targets and mechanisms in cancer development and prevention is critical (32, 33).

Dr. Young-Joon Surh (National Research Laboratory of Molecular Carcinogenesis & Chemoprevention, College of Pharmacy, Seoul National University) suggested that targeted modulation or restoration of the specific intracellular signaling pathways by use of phytochemicals offers a unique strategy for preventing abnormal cell proliferation and other malfunctions associated with multistage carcinogenesis (34). Research directed toward elucidating underlying molecular mechanisms of chemoprevention or chemoprotection with edible phytochemicals present in fruits, vegetables, spices, and herbs has recognized distinct redox-sensitive transcription factors and their upstream regulators as potential targets (35). Research findings from The Hormel Institute have shown that blocking certain cellular signals with natural small molecule inhibitors can decrease UV-induced skin carcinogenesis and other cancers (32, 33, 36–46).

Computer modeling and biological simulation is an extremely powerful technology that is beginning to be used extensively to predict interactions between small-molecule inhibitors (i.e., anticancer natural compounds) and cellular proteins. Dr. Ann M. Bode (The Hormel Institute) briefly described the idea of combining BlueGene/L super-computer technology with protein crystal structure determination and chemical library screening to identify the protein targets of natural anticancer compounds. This approach has been successful in identifying leukotriene A4 hydrolase (LTA4H) protein as a direct target of [6]-gingerol to prevent colon cancer in mice (36). In addition, the technology was successful in identifying kaempferol as a molecule that binds to the N-terminal (but not the C terminal) of ribosomal S6 kinase 2 (RSK2) to inhibit RSK2 activity and neoplastic cell transformation (47). Homology modeling of the NTD RSK2 and small-molecule docking, validated by mutagenesis experiments, clearly showed that Val82 and Lys100 are critical amino acids for kaempferol binding and RSK2 activity (47). Overall, combining super-computer technology with laboratory validation appears to be an excellent strategy for identifying small molecules and protein targets for chemopreventive or chemotherapeutic applications.

The idea of combining agents or using individual agents that target multiple pathways is rapidly gaining acceptance. Dr. Chung S. Yang (Department of Chemical Biology, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey) reported that using a tocopherol mixture that is rich in  $\gamma$ -tocopherol ( $\gamma$ -TmT: 57%  $\gamma$ -T) inhibited cancer formation and growth in various animal models much more effectively than isolated forms of tocopherol (48–52).

Colorectal cancer is a leading cause of cancer in the United States and increasing in China. Silibinin is a flavonolignan isolated from the seeds of milk thistle (*Silybum marianum*) and has been used clinically and as a dietary supplement against liver toxicity. Dr. Rajesh Agarwal (Department of Pharmaceutical Sciences, University of Colorado) reported on the effectiveness of silibinin in preventing colorectal cancer in various animal models by

inhibiting numerous pathways that control proliferation, inflammation, angiogenesis, and apoptosis (53–55). Dr. Chinthalapally V. Rao, Center for Chemoprevention and Drug Development, University of Oklahoma Health Sciences Center) reported that identifying proper combinatorial molecular targets and developing low-dose combinations of select small molecules might be a useful strategy to overcome unwanted side effects and could provide additive and synergistic efficacies for colon cancer prevention (56–59). The discussion of the advantage of using other agents, such as diallyl trisulfide (60, 61), phenethyl isothiocyanate (62), was led by Dr. S. Shivendra V. Singh (University of Pittsburgh Cancer Institute)

Another area in which the United States has made considerable progress is the identification of molecular and cellular targets critical in the skin carcinogenic process. Skin cancer is the most common cancer in the world and the major etiological factor of human skin cancer is exposure to sunlight (63). Dr. Zigang Dong (The Hormel Institute, University of Minnesota) reported progress in identifying new molecular targets for skin cancer. Genetic removal of the cannabinoid receptors 1/2 in mice results in a dramatic resistance to UVB-induced inflammation and a significant decrease in UVB-induced skin cancer (64). The transient receptor potential channel vanilloid subfamily 1 (TRPV1) is expressed highly in neuronal tissues, but is also expressed in the epidermis, dermal blood vessels, human keratinocytes, and other tissues. The absence of TRPV1 in mice results in a striking increase in skin carcinogenesis (65). UV light strongly activates many protein kinases including the MAP kinases JNK1/2, p38, and ERK1/2. JNK1-deficient mice develop more UV-induced tumors than JNK wild-type mice or JNK2-deficient mice (66–69).

Dr. J. DiGiovanni (MD Anderson Cancer Center) reported on the progress of their group in studying growth factor signaling pathways and especially work with signal transducer and activator of transcription 3 (Stat3) in skin cancer (70, 71). The activation of the PI3K/Akt/mTOR and the role of calorie restriction in modulating signaling through this pathway as part of its anti-tumor promoting effects were discussed (72). The insulin-like growth factor (IGF) system is clearly implicated in normal growth and development and its inhibition might be a promising therapy for cancer treatment (73–75). Dr. Douglas Yee (Masonic Cancer Center, University of Minnesota) emphasized the importance of this pathway and indicated that IGF1R signaling also cooperates with other known growth regulatory pathways such as EGFR/HER2, estrogen receptor, and integrins. Therefore, as new anti-IGF therapies emerge, attention to downstream signaling events needs careful consideration to identify predictive biomarkers and to define successful combination therapies (73–76).

The molecular events of AP-1 or NF- $\kappa$ B-dependent transcription and eIF4F-dependent translation in carcinogenesis have been a major focus of Dr. Nancy H. Colburn's (Laboratory of Cancer Prevention, Center for Cancer

Research, National Cancer Institute, National Institutes of Health) laboratory for a number of years and these were highlighted by Dr. Colburn (77–80). Activation of AP-1 and NF- $\kappa$ B is necessary to drive tumor promotion and tumor progression and Dr. Colburn's group has demonstrated that the preventive efficacy of the AP-1 blocker TAM67 now extends from skin to mammary and lung carcinogenesis. Pcd4 is a suppressor of translation, tumorigenesis, and invasion and inhibits tumor promoter induced transformation and AP-1. Dr. Colburn's group has now demonstrated that Pcd4 functions as a tumor suppressor *in vivo*, using transgenic overexpression and Pcd4 deletion in null mice (81). Pcd4 expression is lost during mouse and human carcinogenesis, with Pcd4 expression levels diagnostic for staging and prognostic for survival in human colon carcinogenesis.

Another interesting and relatively new target comprises the microRNAs. Dr. S.M. Zhuang's (School of Life Sciences, Sun Yat-sen University) laboratory has characterized the pathophysiologic role of miRNAs and their relevance to tumorigenesis based on clinical samples and both cell and animal models (82–84). They have shown that deregulated expression of miRNAs is common in hepatocellular carcinoma (HCC) and that miR-101 and -195, which are dramatically downregulated in the majority of HCC tissues, both significantly suppressed the ability of HCC cells to form colonies *in vitro* and to develop tumors in nude mice (82, 84). These data suggest that miRNAs may act as potential tumor suppressors and may represent new molecular targets for cancer therapy. The role of epigenetic changes in cancer development was also discussed in the context of their role in nasopharyngeal carcinoma (NPC), which is a prevalent tumor in southern China and Southeast Asia, particularly in the Cantonese population. As for other cancers, NPC involves multiple epigenetic alterations, such as promoter CpG methylation, leading to the disruption of critical tumor suppressor genes (TSGs). Dr. Q. Tao indicated that the frequent presence of epigenetic abnormalities in tumor cells could provide potential epigenetic biomarkers for molecular diagnosis and also a novel way to identify new TSGs. He suggested that using DNA methyltransferase and HDAC inhibitors, epigenetic inactivation of TSGs could be reversed and used as a new cancer therapy (85).

## Conclusions and Summary

Epidemiology and clinical evidence clearly indicate that factors, such as smoking, consumption of a poor diet (i.e., lack of fruit and vegetables, high fat intake) and obesity, are associated with an increased risk for cancer development. Most cancers are preventable and experts agreed that a strategy focusing more on cancer prevention and research to drive cancer prevention could reduce significantly the cost in the burden of cancer and lives lost both in the United States and in China. In addition, they agreed that combinations of agents with different mechanisms are likely to prevent more cancers and thus the key to success

in preventing cancer is to develop drugs with multiple mechanisms and/or use combinations for those at risk for cancer.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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