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Invited Review

Chemo/Dietary prevention of cancer: perspectives in China

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Abstract

Cancer is a major disease worldwide and different approaches are needed for its prevention. Previous laboratory and clinical studies suggest that cancer can be prevented by chemicals, including those from the diet. Furthermore, epidemiological studies have suggested that deficiencies in certain nutrients can increase the risk of some cancers. In this article on chemo/dietary prevention, examples will be given to illustrate the effectiveness of chemopreventive agents in the prevention of breast, colon and prostate cancers in high-risk populations and the possible side effects of these agents. The potential usefulness of dietary approaches in cancer prevention and the reasons for some of the failed trials will be discussed. Lessons learned from these studies can be used to design more relevant research projects and develop effective measures for cancer prevention in the future. The development of effective chemopreventive agents, the use of nutrient supplements in deficient or carcinogen-exposed populations, and the importance of cohort studies will be discussed in the context of the current socioeconomic situation in China. More discussions are needed on how we can influence society to pay more attention to cancer prevention research and measures.

Keywords: cancer chemoprevention, dietary, intervention

INTRODUCTION

Cancer is a major threat to human health. According to the World Health Organization (WHO), cancer deaths will rise to 11.5 million worldwide by 2030. Most of the increase in cancer burden occurs in developing countries. China, which has a large population base, experienced the largest increase in cancer deaths in recent years. In addition to the traditional Chinese cancers of the stomach, esophagus, liver and nasopharyngus, the "Western Cancers" of the colon, breast and lung drastically increased. Since the genetics of the population has not changed, the rapid elevation in cancer rate is likely due to environmental factors such as cigarette smoking, excessive intake of meat/fat/calories, decreased intake of whole grains and other plant-based food, and decreased physical activity. Understanding the etiology of these cancers provides the basis for their

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prevention. According to the WHO, about 40% of human cancers are preventable. A good example in cancer prevention is the decrease of cancer incidence and mortality in the United States of America in recent years due to smoking cessation, early detection and treatment and other cancer preventive measures.

DIFFERENT APPROACHES OF CANCER PREVENTION

In the 1970s in China, there were the famous ''Five Preventive Measures'' for the prevention of esophageal cancer in Linxian (now named Linzhou): 1) The use of molybdenum fertilizer, which decreased nitrite and nitrate contents and increased vitamin C levels in crops; 2) Prevention of mold contamination, which was thought to produce carcinogens; 3) Removal of nitrosamines and their precursors; 4) Elimination of undesirable eating habits; 5) Treatment of precancerous lesions[1]. Indeed, the removal of cancer-causing substances from our diet and environment, if it can be accomplished, is the best approach for cancer prevention; good examples are smoking cessation, prevention of aflatoxin contamination of corn and peanuts, and avoidance of salted fish and nitrite-preserved meat. Viral and bacterial infections have also been recognized as major causative factors for certain cancers; prevention or elimination of such infection would reduce cancer incidence. Successful examples are the use of antibiotics to eliminate *Helicobacter pylori* for gastric cancer prevention, vaccination against hepatitis B virus to prevent liver cancer, and vaccination against human papilloma virus to prevent cervical cancer. Early detection has also been shown to be an effective preventive approach for certain cancers. For example, polypectomy (removal of polyps) during colonoscopy has been shown to significantly reduce the occurrence of colorectal carcinoma. The major emphasis of this article is on chemo/dietary prevention of cancer.

More than forty years ago, Dr. Lee Wattenberg discussed cancer preventive substances, and used the expression ''chemoprophylaxis of carcinogenesis''[2]. Subsequently, Dr. Michael Sporn coined the term ''chemoprevention''[3]. Their pioneer work suggests that cancer can be prevented by chemicals, including those in our diet. Furthermore, epidemiological studies have suggested that deficiencies in certain micronutrients can increase the risk of some types of cancer. Such types of cancer, in theory, could be prevented by dietary or nutritional approaches. The term ''dietary prevention of cancer'' also includes the avoidance of dietary factors that can induce cancer (such as aflatoxin and nitrosamines) or promote cancer development (such as the over-consumption of animal-based food and calories). In fact, obesity has been recognized as a significant risk factor for endometrial, gallbladder, thyroid, breast, colon, pancreatic and other cancers[4].

SUCCESSFUL EXAMPLES OF CHEMOPREVENTIVE AGENTS FOR HIGH RISK POPULATIONS

The scientific basis for chemoprevention is that the development of most epithelial cancers involves a series of genetic and epigenetic alterations over a rather long period of time, from 10 to 40 years[5]. If effective and safe drugs can be used to arrest or reverse these carcinogenic effects, cancer can be prevented. Among the most well studied drugs are the selective estrogen receptor modulators (SERMs), such as tamoxifen and raloxifene, for the prevention of breast cancer in high-risk populations[6,7]. These compounds, which are effective for the prevention of estrogen receptor-positive breast cancer, have been approved in the U.S. for breast cancer prevention. However, the use of these drugs, even by women at high risk for breast cancer, has been limited because of cardiovascular events and other side effects. To reduce the side effects, clinical trials have been conducted to use lower doses, less frequent dosing, hydroalcoholic gel for topical application and low-dose tamoxifen in combination with fenretinide.

The androgen analogs, finasteride and dustasteride[8], have been shown to reduce the occurrence of prostate cancer in men at risk. A study in Italy has also demonstrated the prostate cancer preventive activity of green tea polyphenols. In this double-blind, phase II trial in Italy, 30 men with high-grade prostate intraepithelial neoplasia (PIN) were given 600 mg of green tea catechins daily for 12 months[9]. Only 1 patient developed prostate cancer, whereas 9 of the 30 patients with high-grade PIN in the placebo group developed prostate cancer (statistically significant). This result is very exciting and needs to be confirmed in studies with a larger number of subjects.

Inflammation is known to promote cancer development, especially colon cancer[10]. Colon cancer prevention by non-steroidal anti-inflammatory drugs (NSAIDs) has been extensively studied. The strong evidence of colon cancer prevention by aspirin as well as its side effects in causing gastrointestinal bleeding in some individuals have been studied extensively[11–16]. Early epidemiological studies have suggested that aspirin intake is associated with a lower incidence of colorectal cancer (CRC). In 5 randomized clinical trials

in more than 3,000 subjects with a prior history of adenoma or CRC, intake of aspirin (doses ranged of 81–325 mg daily) showed significantly reduced risk for the recurrence of colon adenoma. In two large cohort studies: the Nurses′ Health Study and the Health Professional Follow-Up Study, starting in 1980 and 1986, respectively, information on diet aspirin use, tobacco use, BMI and other information were taken. In these studies, regular aspirin use for more than 10 years was found to reduce the risk of CRC by more than 30%. Further studies also indicated that aspirin use in this cohort also significantly reduced CRC-specific mortality. However, aspirin use was found to have a dose dependent increase in gastrointestinal bleeding, showing a relative risk of 1.59 in groups using 6–14 standard tablets of aspirin per week[14]. The US Preventive Service Task Force recommended against routine use of aspirin or NSAIDs to prevent CRC in average risk individuals in 2007. However, recent studies revealed more beneficial effects of aspirin use. For example, a new study suggests that aspirin intake not only reduces the risk of CRC but also other cancers[15,16]. In the two large cohort studies mentioned above, aspirin was found to be more effective in individuals with low expression of 15-hydroxyprostaglandin dehydrogenase[12]. Regular aspirin use was found to reduce the risk and mortality in patients with tumors overexpressing cyclooxygenase (COX)-2 and reduced CRC-induced mortality within patients with tumors expressing mutant PIK3CA. In the light of these findings, the use of aspirin for CRC prevention in certain populations may be considered. Aspirin is an inhibitor of both COX-1 and -2. To avoid the side effects due to inhibition of COX-1, many selective COX-2-inhibitors have been developed for the treatment of pain associated arthritis. Such drugs have also been studied for colon cancer prevention. For example, celecoxib (400 mg/day) was studied in individuals who have a history of adenomas in two trials, with treatment and follow-up for 3 years[17,18]. Celecoxib treatment was shown to significantly reduce the relative risk of adenoma recurrence and advanced adenocarcinoma incidence. However, these two trials had to be terminated early because of cardiovascular events. Other related ‘‘-coxib’’ COX-2 inhibitors have also been shown to have similar cardiovascular toxicity, with a higher risk in patients with pre-existing cardiovascular risk factors. Because of this concern, two COX-2 inhibitors, rofecoxib and valdecoxib, were withdrawn from the market. A risk and benefit analysis indicated that the risk of celecoxib for inducing cardiovascular events outweighs its beneficial effect for the prevention of colorectal cancer[19]. Some researchers believe that drugs such as celecoxib can still be used to prevent colon cancer by individuals who are at high risk for this cancer but at low risk for cardiovascular diseases. Another approach is to use these drugs at low doses in combination with another class of drugs. A successful example is the use of sulindac in combination with a low dose difluoromethylornithine in a trial for preventing the progression of adenomas[20].

LESSONS LEARNED FROM NUTRITIONAL INTERVENTION STUDIES

There is a large number of studies that suggest that deficiencies in micronutrients increase the risk of certain epithelial cancers. An earlier large-scale intervention study to examine this idea is the China-U.S. Cooperative Nutritional Intervention Trial in Linxian, which was initiated in the early 1980s. The study, using an 8-group design with 29,584 subjects in the general population (>40 years old), showed that supplementation for 63 months with a combination of α-tocopherol, β-carotene and selenium decreased mortality due to gastric (mainly cardia) cancer by 20% and total cancer mortality by 13%[21]. The result is consistent with the results of the nested case-control studies, which showed that the blood levels of α-tocopherol and selenium were inversely associated with cancer risk[22,23]. The results for a 10-year follow-up showed that the protective effects of the combination of α-tocopherol/β-carotene/selenium on gastric cardia cancer sustained, and the protective effects of this nutrient combination was observed in subjects younger than 55 years old (but not in those older than 55 years) when they were enrolled in the study[24]. Studies in a rat model also demonstrated that deficiencies in vitamin E and selenium enhanced methylbenzylnitrosamine-induced esophageal carcinogenesis, and supplementation of these nutrients at the early stage (but not the late stage) of carcinogenesis had a protective effect[25].

In the 1980s, β-carotene was lauded as a very promising chemopreventive agent, based mainly on epidemiological studies on the lower cancer risk associated with vegetable and fruit consumption[26]. The hypothesis that β-carotene can prevent lung cancer was tested in Finnish smokers in the α-Tocopherol and β-Carotene (ATBC) study in the 1980s[27]. Surprisingly, increased lung cancer incidence was observed in the β-carotene group after an average of 4.5 years of supplementation. Some consider this study a failure; however, many interesting observations were made subsequently in this cohort, resulting in more than 180 publications. For example, supplementation with α-tocopheryl acetate

(50 mg/day), in a secondary end-point analysis, was found to reduce the incidence of prostate cancer by 45% in a secondary endpoint analysis of the ABTC study[28].

The decrease of prostate cancer risk by α-tocopherol supplementation in the ATBC study, along with a similar effect of selenium supplementation in the Nutritional Prevention Trial[29] provided a strong rationale for the Selenium and Vitamin E Cancer Prevention Trial (SELECT)[30]. In this large multicenter trial in North America, men over 50 years of age were given daily supplementation with 400 mg of all-rac-α-tocopheryl acetate and 200 μg selenium (as L-selenomethionine) in a 2 × 2 sign for an average of 5.5 years. The result was very disappointing in that the supplementation did not prevent prostate or other cancers. In a follow-up (for 7–12 years) of this study, supplementation with α-tocopherol acetate actually increased the risk for prostate cancer (hazard ratio of 1.17)[31]. A possible interpretation of the lack of cancer preventive effect of α-T is that the supplementation of a nutrient to a population that is already adequate in this nutrient may not produce any beneficial effects. It is also possible that some of these subjects already had preneoplastic lesions when entering the trial, and supplementation with high doses of α-T promoted prostate cancer development. The exact reasons for these negative results from the SELECT and other trials[30–33] are not known. Nevertheless, the disappointing outcome of these large-scale trials reflects our insufficient understanding of the biological activities of tocopherols and points to the need for systematic studies of the disease-preventive activities of the different forms of tocopherols.

Although epidemiological studies have suggested cancer prevention by certain nutrients, most intervention trials failed to demonstrate a beneficial effect[34]. Some possible reasons are as follows:

1. *The subjects already had sufficient amounts of the intervening nutrients*. This may explain the results of the SELECT[30]. The mean baseline median plasma level of α-T was 12.5 μg/mL and of serum selenium was 135 ng/mL, indicating the sufficiency of these nutrients. It was demonstrated in the Nutritional Prevention of Cancer Trial that a beneficial effect of selenium supplementation was observed in individuals with low levels, but not with high levels, of baseline serum levels of selenium[29,35].
2. *The doses of intervening agents were too high or too low*. To avoid using dosages that would be too low, many studies tended to use high doses. In the case of the SELECT, the supplementation of α-tocopheryl acetate at a daily dose of 400 mg might have been too high. It actually decreased plasma γ-T levels by 50%[30]. If γ-T plays a role in prostate cancer prevention, its decrease could result in the increase of prostate cancer risk[36,37].
3. *The intervention started too late in individuals that already had precancerous lesions*. For example, it has been reported that in rats, supplementation with folic acid at an early stage of carcinogenesis decreased colon carcinogenesis, whereas supplementation at a late stage enhanced colon carcinogenesis[38]. The later phenomenon is also consistent with the results of a human trial on colon cancer[39]. Similar interpretation may also apply to the results of the SELECT (30, 31) and the Linxian Nutritional Intervention Trial[24].
4. *The intervening agents do not possess cancer preventive activity in the population studied*. In some cases, the existing epidemiological association of cancer prevention was due to other factors, rather than the hypothesized nutrient. This mistake was actually made in the 1980s, in the design of the ATBC study[27].

A recent report on the large-scale Physicians Health Study Randomized Controlled Trial II showed that men taking multivitamins had a significant reduction in the incidence of total cancer[40]. The effect is considered to be modest, but this result is significant in demonstrating the preventive effect in a well-nourished population and even in individuals with a history of cancer. These results are not consistent with Points 1 and 3 as discussed above. Research on nutrition and cancer prevention is a rather complicated field. It is possible that many of the inconsistent observations in human studies were due to the lack of power to detect a protective effect in some studies or due to chances for positive results when multiple endpoints were analyzed.

THE USEFULNESS AND LIMITATIONS OF LABORATORY STUDIES

Laboratory studies can provide the experimental basis for human cancer prevention studies as well as the molecular interpretation for results obtained from observational epidemiological studies or clinical trials. Here, we use our studies on tocopherols as an example to illustrate this point. Previous cancer prevention studies in different animal models, mainly with α-T, have obtained inconsistent results (review[37]). On the other hand, recent studies from our research team at Rutgers University have demonstrated the inhibition of cancer formation and growth in the lung, colon, mammary gland and prostate by a tocopherol mixture that is rich in γ-T (named γ-TmT) (review[37]). γ-TmT is a by-pro-

duct in the distillation of vegetable oil and usually contains (per g) 130 mg α-T, 15 mg β-T, 568 mg γ-T, and 243 mg δ-T. We further demonstrated that δ-T was more active than γ-T in inhibiting cancer cell growth in cultures, in human lung cancer H1299 tumorigenesis in a xenograft model in nude mice, and in colon carcinogenesis in rats induced by azoxymethane, whereas α-T was ineffective in these models. Takahashi *et al*. also demonstrated that γ-T (0.01% in the diet), but not α-T, decreased the number of adenocarcinomas in the ventral lobe in the ''transgenic rat for adenocarcinoma of prostate'' model[36]. Based on the aforementioned laboratory and epidemiological studies, we hypothesize that, at the nutritional levels, all forms of vitamin E are cancer preventive. At the supra-nutritional levels, γ-T and δ-T are cancer preventive, but α-T is not cancer preventive[37]. This hypothesis needs to be tested in human cancer prevention trials.

Phytochemicals from food, beverages and medicinal plants have been studied extensively as cancer preventive agents in numerous laboratories worldwide. Many mechanisms of cancer prevention have been proposed, mainly from studies based in cell lines. However, the cancer preventive activities of these phytochemicals in humans are uncertain. Here, we use our studies on green tea to illustrate the usefulness and limitation of laboratory studies. Tea, made from the leaves of plant *Camellia sinesis*, is a common beverage in China and many other countries. The cancer preventive activities of green tea extracts, tea polyphenols and (-)-epigallocatechin-3-gallate (EGCG) have been demonstrated in many animal models (review[41]). These studies used chemically-induced and genetic models for lung, oral, esophageal, stomach, small intestinal, colorectal and prostate cancers, and showed the broad cancer preventive activities of tea or tea constituents when they are administered in the drinking water or diet. In contrast to the strong evidence for the cancer preventive activity of tea constituents in animal models, results from epidemiological studies have been inconsistent concerning the cancer preventive effect of tea consumption in humans (review[42]). The different results between animal and human studies are likely to be due to the lower quantities of tea consumption by humans as compared to the doses used in animal studies. In animal studies, the doses of tea preparations and the experimental conditions are set to maximize the opportunity to detect a cancer preventive effect. Because of these reasons, caution needs to be applied when extrapolating results from laboratory studies to humans. Without considering the relevance of the experimental system and the bioavailability of phytochemicals, extrapolation of results from studies *in vitro* to animals and humans can be misleading.

DEVELOPMENT OF NEW CHEMOPREVENTIVE AGENTS

During the past 25 years, many laboratories have conducted research with the purpose of discovering and developing cancer chemopreventive agents. However, very few agents have been proven to be useful in practical application. In the development of cancer chemopreventive agents, several considerations are needed: 1) efficacy, 2) safety - minimal side effects, 3) costs of the agents, and 4) acceptability of the agent by populations at risk. Based on these considerations, repurposing existing commonly used drugs, such as NSAIDs, for cancer chemoprevention has been considered a promising approach. Some new studies on the repurposing of metformin is another example.

Metformin, a biguanide compound, is the most widely prescribed drug to treat hyperglycemia in individuals with type 2 diabetes. Recently, metformin use has been associated with a decreased risk of specific cancers, including prostate, colon, liver, pancreas, and breast cancers[43–46]. Furthermore, a retrospective study of diabetic patients with pancreatic cancer revealed an improved survival rate of 32% for patients using metformin[47]. A meta-analysis of nine observational studies (6 cohort, and 3 case-control), however, showed a trend but not a significant association between metformin and the risk of developing pancreatic cancer[48], indicating a significant heterogeneity in clinical studies on the relationship between metformin use and pancreatic cancer risk. Metformin is now being evaluated prospectively for possible prevention of different types of cancers. An interesting possibility is to use a combination of metformin and aspirin for the prevention of pancreatic cancer[49]. Although epidemiological data concerning aspirin use and pancreatic cancer have been inconsistent, a case-control study showed that aspirin use is associated with lower risk of developing pancreatic cancer[50]. Recent laboratory results also suggest that metformin and aspirin synergistically induced cell death in pancreatic cancer cells associated with down-regulation of Bcl-2 and Mcl-1 through the STAT3 pathway (unpublished results from X-L. Tan, Rutgers University).

To improve the delivery of chemopreventive agents, they may be incorporated into solid-lipid nanoparticles[51]. These nanoparticles can be prepared with stearic acid using a hot melt, oil-in-water emulsion technique. The resulting nanoparticles consist of a solid-lipid core and are stabilized by surfactants. These types of nanoparticles have been reported to be stable and suitable for oral delivery[52]. A recent study by Grandhi *et al.*[53]

has demonstrated the high efficacy of the combination of aspirin and curcumin in such nanoparticles for the prevention of pancreatic cancer in an animal model. The solid-lipid nanoparticles have been reported to be absorbed through the lymphatic system and then enter the systemic circulation, hence passing gastrointestinal metabolism[54]. The toxicity profile of this type of nanoparticles needs to be systematically studied.

Repurposing traditional medicine for cancer prevention is another interesting idea. Many herbal preparations that possess appropriate anti-inflammatory activities may be good candidates for the prevention of inflammation-associated cancer. This group of agents also includes food, such as bitter melon. Systematic research, including animal and human studies on the traditional herbal preparation or isolated active constituents, is needed before a claim can be made.

Because of the disappointing results in intervention trials with nutrients and other isolated natural compounds, some investigators have been advocating a ''whole food'' approach or ''green chemoprevention''[55]. Interesting results have been obtained with green tea extracts, berry powders, tomato paste, broccoli sprouts, and other food preparations.

DIETARY APPROACHES FOR CANCER PREVENTION IN CHINA

Although the development of effective chemopreventive agents is a worthwhile goal and these agents may help individuals at high risk, a good understanding of the relationship between diet and cancer would impact cancer prevention for the general population. China, with her diverse dietary habits and social economic status, provides many interesting and challenging opportunities for studying cancer prevention. Some are as follows:

1. *Nutritional deficiencies:* Even though China has made great strides in economic development in the past 30 years and raised the living standard of the people, nutritional deficiencies are still common, such as in iron, selenium, calcium. Marginal deficiencies in some nutrients may significantly increase cancer risk. For example, in the Shanghai Women's Health Study from 1997 to 2000 and the Shanghai Men's Health Study from 2002 to 2006, intake of dietary or supplemental vitamin E was inversely associated with liver cancer risk[56]. It is possible that this association may not be due to vitamin E alone; however, the results illustrate the importance of diet and nutrition in affecting cancer occurrence. The nutritional status of different populations in China needs to be studied, and measures to remedy the situation need to be developed. This is an important issue in cancer prevention in China, even though nutrition and cancer is not a hot topic for research in the U.S. because of the disappointing results of several large scale trials, mostly in populations that already had sufficient amounts of the nutrients studied.
2. *Dietary and environmental carcinogens* Whereas the traditional fungal and bacterial contamination of food is still a problem, increased water and air pollution due to rapid economic development is becoming an alarming problem in China. The well-publicized pollution of water and soil by heavy metals, such as cadmium, chromium, lead and arsenic, as well as the misuse of pesticides, could significantly impact the qualities of food supplies and increase the cancer burden of the exposed populations. Air pollution is another serious issue that increases the occurrence of respiratory diseases, lung cancer, cardiovascular diseases and other diseases. Although the fundamental solution is to minimize these populations, efforts are needed to assess the real and perceived risks. In dietary prevention, one aspect is to avoid consumption of contaminated food and water. Another aspect is to use a dietary approach to protect individuals who have been or are being exposed to the above toxins. China has many of such populations, such as inhabitants in the Huai River region, which provide unique opportunities for studies. It has been shown that calcium supplementation can reduce the absorption and blood levels of lead and cadmium, and vitamin E may reduce cancer risk in smokers. Further research along this line should be pursued. For example, we could explore whether supplementation with tocopherols or broccoli sprouts (which activate cytoprotective enzymes) can reduce the severeness of respiratory diseases or incidence of lung cancer.
3. *Use and misuse of dietary supplements* Supplementation with a certain vitamin or trace element to populations that are deficient in this nutrient should provide beneficial effects. Taking fish oil pills has also shown beneficial effects in some individuals. The business of nutritional and dietary supplements is booming. This is good because people are willing to buy and take pills to improve their health. However, the usefulness of the popular supplements in preventing cancer and other diseases is an open question[34]. Most of the information circulated in public press and used in promoting these products was extrapolated from studies in cell lines or rodents or from small human trials in subjects with a particular situation, and the results may not be

applicable to the general population. Possible contamination of these supplements with toxic substances, such as heavy metals and pesticides, is also a concern.

4. *Food selection, dietary habits and behavior modification* Many dietary constituents, plant derived materials, and "whole food" products have been demonstrated to have cancer preventive activities in laboratory studies and small human trials, and the list is becoming longer. Although research in this area of chemoprevention is worthwhile, the recommendation to "choose mostly plant foods, limit red meat and avoid processed meat" for cancer prevention by the American Institute for Cancer Research – World Cancer Research Fund[57] may have a larger impact on public health. Whole grains, vegetables, fruits, spices, tea, coffee, and practically all plants contain substances that may be shown to have "cancer preventive" activities in some experimental systems. These substances, of course, include fiber. The above dietary recommendation is consistent with the traditional Chinese dietary pattern, which mainly comprises plant-based food. China is in a stage of dietary transition. Overcoming the misconception that "refined grains and meat are better" and 'Western food such as hamburgers and fried chicken will make you healthier" is an important issue to tackle; it requires education and behavior modification. Similarly, behavior modifications for the avoidance of overeating, excessive drinking, and tobacco products are also of great importance for cancer prevention.

SUGGESTIONS

Previous research in laboratories and in human populations has demonstrated that cancer is preventable and continued efforts on cancer prevention research are needed. In chemo/dietary prevention, additional research in the following areas is recommended for China:

1. Laboratory and clinical studies to identify efficacious chemopreventive drugs for high risk populations.
2. Cohort studies to monitor and identify populations that are deficient in certain nutrients or populations that have been exposed to known carcinogens; developing effective nutritional and dietary approaches to reduce their cancer risk.
3. Laboratory studies in support of the above human studies. This includes development of better methods for nutritional assessment and measurement of exposure markers, preclinical studies to determine the effectiveness of the intervention agents, and biomarkers for the effects of intervention.

We hope society and the government can recognize and support this area of research. Translating the research results to cancer prevention measures requires more effort from society and the government in promoting health education and establishing policies to encourage healthful behavior. These are big challenges, but are doable. Taking the smoking cessation movement in the U.S. as an example, public education, legislation and taxation definitely helped. The contributions of non-governmental organizations such as the American Cancer Society are also important to the success of this behavioral modification. Most importantly, individual citizens should believe they can make a difference in reducing their own cancer risk and the overall cancer burden of the country.

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