Cancer Prevention Research in China

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Abstract

While cancer incidence and mortality rates in the United States and some European countries have started to decrease, those in developing countries are increasing. China, the most populous developing country, is facing a serious challenge from cancer. Cancer incidence has been increasing for decades, and cancer is the leading cause of death in China. In 2012, the cancer incidence was 174.0 per 100,000 and the cancer mortality was 122.2 per 100,000 in China. In addition to the still-prevalent traditional Chinese cancers of the stomach, liver, esophagus, cervix and nasopharynx, incidence of “Western” cancers such those of the lung, breast and colorectum have increased alarmingly in recent years. These increases are likely due to the lifestyle and environmental changes associated with rapid economic development and population aging. More importantly, a large portion of these cancers are preventable. Researchers in China have made important contributions to cancer prevention research, especially in the traditional Chinese cancers. More cancer prevention research and measures, especially on the major emerging cancers, are urgently needed. This review article highlights some of the past achievements and present needs in cancer prevention research in China, and suggests important areas for future studies.
A. Introduction

In the 1970s, China had made major strides in studying the mortality and etiology of different types of cancer in the country, and this information was made known to the biomedical communities in the Western world in the 1978 book Cancer in China, edited by Kaplan and Tsuchitani (1). This book reported the etiology, prevention, diagnosis and treatment of major cancers in China. The detailed description of the massive Chinese national cancer survey was published in the well-known China Cancer Map in 1980 (2). Interestingly, there were several noted high incidence areas of major cancers in China. The populations in these high-risk areas (Figure 1) provided unique opportunities to study the etiology and prevention of esophageal, stomach, liver, lung, nasopharyngeal and cervical cancers, and some of the research achievement on these cancers are highlighted in this article.

China has experienced miraculous socioeconomic development during the past decades, and the average lifespan of the Chinese people has been prolonged from 67.77 years in 1981 to 74.83 years in 2010. Rapid industrialization and urbanization in China have brought tremendous changes in lifestyle and environment. These changes, together with an aging population, significantly contribute to the increase in the incidence and mortality of different types of cancer in China. While the mortalities of gastric, esophageal and cervical cancers have shown a trend of decrease, the mortalities caused by lung, colorectal and breast cancers have been increasing (3). The pattern of changes in the age standardized mortality rates of the top 10 cancers is shown in Figure 2 (4). While the age standardized mortality rates of lung cancer increased markedly, those of colorectal and breast cancer only increased slightly. The overall cancer incidence rose significantly in the more developed eastern China and large cities; in the previous high incidence areas such as Qidong and Linzhou (for liver and esophageal cancers, respective), the decrease in
traditional cancer was accompanied by the increase of modern cancers (Supplemental Table 1). Again, population aging contributed to this increase. For example, from 1988-1992 to 2004, the annual raw incidence rates for breast cancer in Shanghai increased by 57%, but the age adjusted rates only increased by 17% (Supplemental Table 2). Overall, cancer incidence and mortality rates are increasing, and cancer has become the leading cause of death in China since 2011 (5). In 2012, the cancer incidence rate was 174.0 per 100,000 and death rate was 122.2 per 100,000. New annual cancer cases and deaths were 3.065 and 2.206 millions in China, accounting for 21.75% and 26.90% of world cancer cases and deaths, respectively (6). It should be noted that the health impact of environmental and lifestyle changes on cancer needs 10 to 40 years to emerge; it is expected to overlap with the peak of population aging to cause even more serious health problems.

Based on the rapid increase in the number of cigarette smokers in China in the 1980s, an enormous rise in lung cancer incidence was predicted; unfortunately, this prediction has been proven to be correct (7, 8). An increase in breast cancer incidence could also be predicted based on a younger age of menarche, late age of first birth and the “one-child” family planning policy. What was not expected was the rapid rise in the incidence of colorectal cancers, possibly due to changes in lifestyle and dietary patterns. This rapid increase in cancer incidence rates of these cancers reflects a lack of effective approaches for cancer prevention and control.

This article reviews the research achievements on cancer etiology and prevention in the high risk areas for esophageal, gastric, liver, lung, nasopharyngeal and cervical cancers. It also discusses current activities and research needs in the prevention of major cancers in China. Based on the results and experiences gained from the studies in China and other countries, we
suggest ideas for enhancing cancer prevention in China. We hope that this article will stimulate further discussions on effective approaches for the prevention of cancer.

B. Cancer Prevention Studies in High Risk Areas of Traditional Chinese Cancers

China had conducted some community based cancer prevention measures in the past. For example, in the 1970s, there were the well-publicized “Five Preventive Measures” for the prevention and control of esophageal cancer in Linxian (now named Linzhou City) in Henan Province: 1) Prevention of mold contamination, which was thought to produce carcinogens; 2) Removal of nitrosamines and their precursors from food; 3) Elimination of undesirable eating habits; 4) Use of molybdenum fertilizer, which decreased nitrite and nitrate contents and increased vitamin C levels in crops; and 5) Treatment of precancerous lesions (1, 9).

After the normalization of the diplomatic relationship between China and the United States, several well organized joint US-China collaborative cancer research projects were conducted to study the etiology and prevention of esophageal/gastric cardia, gastric, liver, lung, nasopharyngeal and cervical cancers. The following are some studies on cancer prevention by nutrients, antibiotics, vaccination and environmental intervention, as well as by early detection and treatment.

1. Etiology and nutrition intervention studies of esophageal/gastric cardia cancer in Linxian

In the 1960s and 1970s, Chinese investigators carried out extensive studies on esophageal squamous cell carcinoma (ESCC) in high incidence areas around the Taihang mountain range of Henan, Hebei and Shanxi, especially in Linxian of Henan Province. One of the co-authors (J. Li) has worked on cancer epidemiology, etiology and prevention studies since 1972. Another co-author (C.S. Yang) from the United States visited China in 1979 and started collaborative
research on esophageal cancer. The leading etiological factors, as summarized at that time, were nitrosamines and nitrosamides, preformed or formed endogenously from precursors (nitrite from drinking water and amines or amides from moldy food). Mycotoxins from moldy food and polycyclic hydrocarbons from stoves for cooking and room heating were also suspected etiological factors (8). However, evidence supporting these hypotheses is still insufficient.

Another line of studies indicated micronutrient deficiencies (or insufficiencies), and that this factor could render the Linxian population more susceptible to carcinogenesis in the esophagus and gastric cardia. Micronutrient insufficiencies were long suspected and were indicated in a nutrition assessment in 1980 that was based on blood vitamin levels and nutrient availability calculated from the records of food production (crops were produced collectively) (10). Based on the results, the possibility of a nutritional intervention trial in Linxian was discussed. In the 1980s, while J. Li was a visiting scientist at the US National Cancer Institute (NCI), several collaborative contracts for epidemiology and intervention studies in China were signed between the Cancer Institute of the Chinese Academy of Medical Sciences (CICAMS) and NCI. Among them, the largest and most comprehensive one was the Linxian Nutrition Intervention Trials (LNIT). After long discussions among Chinese and American scientists, the final design used four groups of nutrients: A) retinol, zinc; B) riboflavin, niacin; C) ascorbate, molybdenum; and D) α-tocopherol, β-carotene, selenium in a factorial design with eight groups: placebo, AB, AC, BC, AD, BD, CD, ABCD. The study involved 29,584 adults (aged 40 to 69) who were given supplementations as daily pills for 63 months (1985 to 1991). There were 2,127 deaths during the trial period; 32% were due to esophageal and gastric cancer. Supplementation with a combination of α-tocopherol/β-carotene/selenium was found to decrease mortality due to gastric (mainly gastric cardia) cancer by 21% and total cancer mortality by 13% (11). Nested
case-control studies showed that the blood levels of $\alpha$-tocopherol and selenium were low and inversely associated with gastroesophageal cancer risk (12, 13). Results from a 10-year follow-up also showed that the protective effects of the combination of $\alpha$-tocopherol/$\beta$-carotene/selenium on gastric cardia cancer still persisted. A preventive effect of this nutrient combination against ESCC was observed in subjects with enrollment ages younger than 55 years old, but not in those older than 55 years (14). It is possible that the intervention was effective in younger subjects because they had lower grade or no precancerous lesions, while the older subjects had more severe lesions. This is consistent with the result of a parallel trial on subjects with esophageal dysplasia, showing that supplementation with multiple micronutrients did not produce a significant beneficial effect (15). Studies in a rat model also demonstrated that insufficiencies in vitamin E and selenium enhanced methylbenzyl nitrosamine-induced esophageal carcinogenesis, and supplementation with these nutrients at the early stage (but not the late stage) of carcinogenesis had a protective effect (16).

The concept that chemoprevention is more effective in patients with less severe precancerous lesions was also demonstrated in another study in Linxian. In a randomized, placebo-controlled ESCC precancerous trial with selenomethionine and celecoxib for 10 months, selenomethionine improved squamous histology in 115 patients with mild dysplasia, but not in 125 patients with severe dysplasia (17). Celecoxib had no effect on the squamous histology.

The lowering of esophageal and gastric cardia cancer death rate by supplementation of a combination of $\alpha$-tocopherol/$\beta$-carotene/selenium in LNIT suggests that a low antioxidant status was a risk factor of this cancer. A low antioxidant nutrition status could make the upper gastrointestinal epithelial tissues more prone to inflammation. Inflammation of the esophagus (esophagitis) was reported to widely occur in this population (9). A suspected low dietary
methionine and choline (methyl donors) status may also make the subjects prone to epigenetic changes such as the silencing of tumor suppressor and receptor genes by promoter hypermethylation (18). This population intervention trial also provided opportunities for follow-up studies to investigate the progression of the disease and to identify intermediate end-points (biomarkers) and preventive agents for gastroesophageal cancer (19). Today, the esophageal cancer incidence and mortality rates in Linzhou (previously named Linxian) have been significantly decreased (by approximately 50% from the 1970s) (20). The primary reason for this decrease is attributed to the improvement of living standards, resulting in the improvement of the nutritional status and reduction of causative factors (which have not been identified).

2. Studies on etiology and prevention of gastric cancer in Linqu County

Gastric cancer (GC) is the second most common cancer worldwide and also in China. There is a substantial geographic variation in GC mortality within China. In the late 1970s, Linqu County, a poor mountainous and hilly rural region in the Shandong Province, was identified in a nationwide survey to be one of the areas of highest GC incidence and mortality rate in the world. In 1973 to 1975, the mortality rates were 55 and 19 per 100,000 (Chinese age standard) for males and females, respectively, accounting for 42% of total cancer deaths in Linqu. In 1983, a collaborative population-based case-control study was initiated to explore the possible etiology of this cancer (21). Daily consumption of sour pancakes, a popular fermented local food, was associated with a 30% increase in GC risk. Risks of GC were increased by 2- to 3-fold among persons with prior chronic gastritis or gastric ulcers, by 80% among those with a family member who had GC, by 50% among men who smoked one or more packs of cigarettes per day, by 40% among those who preferred salted foods, and by 50% among those in families with moldy grains in storage. In contrast, the risks tended to decrease with increased...
consumption of fresh vegetables and fruit. This protective effect was more pronounced for vegetables; those in the highest quartile of intake had <50% of the risk of those in the lowest. A dose-response pattern was found for the protective effects of allium vegetables (garlic, onions and Chinese chives) (21).

GC is generally thought to evolve from a series of precancerous lesions in the gastric mucosa over a long period of time. Beginning in 1989, a study of gastric precancerous lesions was launched in Linqu County (22). A total of 3,433 residents, aged 35–64 years, were enrolled in an endoscopic survey, in which biopsies were taken from seven standard locations: four from the antrum, one from the angulus and two from the body. Of 3,433 subjects, only 2% had normal gastric mucosa or superficial gastritis (SG), while 98% had chronic atrophic gastritis (CAG), 33% had intestinal metaplasia (IM) and 20% had gastric dysplasia. The highest prevalence of gastric dysplasia was found along the lesser curvature of the stomach, especially in the angulus or antrum. Follow-up gastroscopy with biopsy was carried out in 2,628 subjects who had baseline information of histopathology in 1994. Compared to subjects with SG/mild CAG at baseline, the odds ratios (OR) for GC in 1999 in subjects with deep IM, with mild gastric dysplasia or with moderate/severe gastric dysplasia were 17.4, 25.8 or 104.2, respectively (23). The site of distribution of GC was similar to that of the precancerous lesions. These results strongly support the concept that GC develops from the progression of precancerous lesions.

In addition to the smoking and dietary factors mentioned above, *Helicobacter pylori* infection is also an important etiological factor. Among the population screened in 1989 to 1990, 72% were positive for *H. pylori*, and the infection was associated with gastric pathology (24). The OR (with SG as baseline) for mild CAG, severe CAG, IM, and gastric dysplasia were 1.3, 5.9, 3.5 and 3.6, respectively. Subsequently, a prospective follow-up study confirmed that
the presence of *H. pylori* at baseline was associated with an increased risk of dysplasia or GC (OR = 1.8), and that the risk of progression was decreased by 80% among subjects with baseline ascorbic acid levels in the highest tertile vs. the lowest tertile. To investigate the modes of *H. pylori* transmission in rural China, a familial aggregation study among 100 children aged 3 to 12 years and 289 adults aged 35 to 64 years was conducted in a village in Linqu in 1994. In families with at least one infected parent, 85% of children were *H. pylori* positive, while in families with both parents uninfected, only 22% of children were *H. pylori* positive (OR = 30.4) (25). These findings suggest that *H. pylori* infection is acquired during early childhood through transmission from parents to children.

Linqu is one of the first sites for studying the effect of *H. pylori* eradication on GC prevention. In late 1995, a total of 3,411 subjects were randomized to study the effects of anti-*H. pylori* drugs, aged garlic preparation and α-tocopherol/selenium on GC in a 2×2×2 factorial trial design (26). The intervention resulted in a 40% reduction in the prevalence of severe CAG, IM and dysplasia as well as favourable effects on GC (OR=0.60). The clearest effect was shown to be due to *H. pylori* eradication. A 15-year follow-up of this cohort showed that *H. pylori* eradication could reduce GC incidence (OR=0.61) (27). A recent subgroup analysis indicated that the elimination of *H. pylori* can reduce GC incidence in older participants and in those with advanced baseline histopathology (28). From 2002 to 2006, another randomized, placebo-controlled trial was conducted in Linqu to study the effects of *H. pylori* eradication and a cyclooxygenase-2 inhibitor (Celecoxib) in a 2×2 factorial design with 1,024 participants (29). The proportion of regression of precancerous gastric lesions was significantly higher in the anti-*H. pylori* treatment group than in the placebo control group. The results also supported the conclusion that eradication of *H. pylori* can reduce the incidence of GC. To generate more
convincing results to support an approach for community-based eradication, a large intervention trial was initiated in 2011. A total of 184,786 residents aged 25 to 54 from 980 villages of Linqu were enrolled. The villages were randomized to anti-\textit{H. pylori} treatment or placebo control group. The \textit{H. pylori} positive subjects in the treatment villages received a 10-day quadruple anti-\textit{H. pylori} treatment (omeprazole 20 mg bid, tetracycline 750 mg tid, metronidazole 400 mg tid, and bismuth citrate 300 mg bid) and those in the control villages received a placebo. The participants will be followed for 7 to 10 years in order to assess the impact of \textit{H. pylori} eradication on incidence and mortality rates of GC.

Efforts have been made to detect GC in the early stages. In 2012 to 2013, 3,018 residents aged 40-69 of Linqu County were screened by endoscopy and 38 (1.26\%) cases of GC were detected. Among those GC cases, 78.95\% were at early stages. This screening program has been extended to 110 counties nationwide. Studies on molecular epidemiology were also conducted in Linqu by analyzing the polymorphism of carcinogen-metabolizing genes, inflammation genes and DNA repair genes. This large volume of information helps us to understand the interactions between environmental and host factors in the etiology of GC.

In conclusion, the Linqu studies clearly document the step-wise histopathological progression of gastric precursor to GC. \textit{H. pylori} infection, unhealthy diet and cigarette smoking are major risk factors for GC. Early detection and intervention are promising approaches for reducing the mortality of GC.

3. Liver cancer prevention studies in Qidong on hepatitis B virus and aflatoxin

Qidong City (formerly known as Qidong County), located at the easternmost part of Jiangsu province and adjacent to Shanghai, was well-known for its high incidence of liver cancer due to aflatoxin exposure and endemic hepatitis B virus (HBV) infection. A retrospective survey
of all-death causes for the period of 1958-1971 showed a high prevalence of liver cancer in Qidong, with mortality rates of 20.45 and 49.02 per 100,000 in 1958 and 1971, respectively (30). A population-based cancer registration system was then established, which enabled subsequent studies of cancer patterns, lifestyles and effects of intervention (30).

Evidence from extensive epidemiological research in Qidong has demonstrated that infection with HBV and aflatoxins in corn are the two major risk factors of primary liver cancer (PLC). In 1976, a prospective cohort was established to study the development of PLC by chronic carriers of HBsAg. Results showed that the relative risks of PLC development of carriers were 11.70 to 13.69 times higher than non-carriers, with the highest rate being found in males (31). A close relationship between aflatoxin contamination in foods and the development of PLC was verified in many investigations. In an earlier study (32), the geographic distribution of warm and humid “mold producing days”, which produced “mildewed corn”, was correlated with the mortality due to PLC. The induction of liver cancer by mildewed corn (containing aflatoxin B1) in ducks was demonstrated in the 1970s (33).

Preventive measures against the major risk factors in the Qidong area have hence been taken. A large-scale controlled clinical trial on hepatitis B vaccination involving about 80,000 newborns was initiated in 1983, before hepatitis B vaccines became commercially available in China. The result of the 5 year pilot study showed that the HBsAg positive rate was 2.52%-3.08% in children vaccinated with recombinant vaccine, as compared with 12.5% in the non-vaccinated controls. Thus, a 75% protective efficacy against hepatitis B infection was observed (34). The final evaluation of vaccine efficacy against liver cancer is being conducted through the population-based cancer registration.
Control of aflatoxin contamination was an important prevention strategy for PLC. Due to the economic development since the 1980s, rice has gradually replaced corn as the staple food in Qidong. This change has led to a gradual reduction of aflatoxin intake in Qidong. For example, the median levels of aflatoxin–albumin adducts from local residents declined from 19.3 pg/mg albumin in 1989, to 3.6, 2.3 and 1.4 pg/mg in 1995, 1999 and 2003, respectively, and to non-detectable levels (<0.5 pg/mg) in 2009 and 2012 (35). It is worth noting that aflatoxin exposure and HBV infection have significant synergistic effect on PLC risk, and a rapid decline of PLC mortality rate was observed in Qidong following the decrease in dietary aflatoxin, even before the protective effect of HBV vaccination took place (35).

Screening based on $\alpha$-fetoprotein and HBsAg has been an effective approach in finding PLC patients and is still a key strategy of secondary prevention (36). A recent study in a cohort of HBsAg carriers screened for $\alpha$-fetoprotein and with B ultrasound scan found that screening could detect PLC in an asymptomatic stage that helps treatment (Chen JG, unpublished data). In chemoprevention, several classes of prevention agents were examined in randomized clinical trials for the purpose of reducing the harmful effects of aflatoxins, throughout a series of China-US collaborative studies, in Qidong: 1) oral administration of oltipraz, an inducer of enzymes that detoxify carcinogens, resulted in a 2.6-fold increase in urinary excretion of a detoxification metabolite aflatoxin–mercapturic acid (37); 2) oral administration of chlorophyllin led to an overall 55% reduction in median urinary levels of aflatoxin–$N^7$-guanine adducts (38); and 3) supplementation with broccoli sprouts produced an inverse association between urinary excretion of glucoraphanin metabolites and aflatoxin-$N^7$-guanine adducts (39).

After four decades of efforts of cancer prevention and control in Qidong, the PLC incidence rate has decreased from 63.20 to 37.09 per 100,000 (30). Furthermore, birth cohort
analysis showed that there has been a 60-75% decline in incidence/mortality rates from PLC in Qidong younger residents (30, 36). The experience in Qidong shows that preventive measures, such as reducing dietary aflatoxin exposures and vaccination against HBV, can reduce PLC incidence and mortality.

4. Studies on lung cancer and indoor pollution in Xunwei

The lung cancer mortality rates in Xuanwei County of Yunnan Province were found to be among the highest in China in the first national causes of death survey (1973-1975). In particular, lung cancer of females, with an annual age-adjusted lung cancer mortality rate of 25.3/100,000, was significantly higher than the national rate (3.3/100,000). The reasons for this high lung cancer mortality were not understood at that time. To identify the risk factors and to develop effective primary prevention strategies, scientists from the Institute of Environmental Health and Engineering, the Chinese Academy of Preventive Medicine and US Environmental Protection Agency, in collaboration with local medical investigators, carried out many epidemiological and toxicological studies.

Xuanwei residents have traditionally burned coal or wood in unvented indoor fire pits, which generated large amounts of airborne particulate matter, benzo[a]pyrene, and other noxious compounds. These are believed to be the most important contributing factors for lung cancer in Xuanwei (40-42). In recent decades, most Xuanwei residents have changed from fire pits to stoves with chimneys, partly because they can afford it, and partly due to health education. Residents have generally changed stoves at their own expense, though the government offered a small one-time subsidy of ¥10 (about $5 at that time) in 1976 to assist with stove improvement. Anecdotal evidence suggests that some residents did not change their stoves until they had already developed respiratory symptoms; sometimes, they made the changes based on their
physician's advice. Levels of indoor air pollution during burning with chimneys were $<35\%$ of those during unvented burning (43).

Xuanwei’s and other studies indicate that stove improvements can substantially reduce the levels of indoor air pollution and eventually reduce lung cancer incidence (43). Reduction of lung cancer incidence became unequivocal about 10 years after stove improvement (43). Comparative analysis showed that risk for lung cancer after stove improvement was significantly decreased, showing relative risk of 0.59 in men and 0.54 in women. The study clearly showed that the reduction of indoor pollution decreased lung cancer risk, and it may do the same in other areas as well.

5. **Field and laboratory studies on nasopharyngeal carcinoma**

Nasopharyngeal carcinoma (NPC) is uniquely prevalent in southern China and Southeast Asia. For example, in the Cantonese population, the peak incidence rate of NPC was 20-30 cases per 100,000. In the last few decades, incidence and mortality of NPC among Chinese in some areas of China and Asia have gradually declined (44, 45). China will have an estimated 36,080 new cases and 22,558 deaths of NPC in 2015 (46).

Studies conducted in China suggested that NPC is caused by the combined effects of Epstein-Barr virus (EBV) infections (especially early-life infection), environmental exposures and genetic factors (47, 48). More recently, 2 cohort and 8 case–control studies (49) further support the association between EBV and NPC. Epidemiological studies also suggested intake of Cantonese-style soft-salted fish and other putrefied/preserved foods, tobacco smoking and alcohol consumption as strong environmental risk factors (50). Salted fish, suspected to contain carcinogenic nitrosamines, was shown experimentally to produce NPC in rodents (51). Recent studies also confirmed that both cigarette smoking and elevated levels of the VCA (viral capsid antigen) - IgA antibody were associated with NPC risk and that smoking appeared to activate
EBV (52). Exposure to traditional herbal medicines, fumes, smoke, and wood dust, and burning incense has also been suggested as risk factors (47). On the other hand, frequent consumption of fresh fruits and vegetables, especially during childhood, has been associated with a lower risk of NPC (53). These studies indicate that smoking cessation together with EBV control may be the most important approach for the prevention of NPC.

Family history of NPC also increases the risk of NPC (54). Over 10% of NPC cases exhibited the tendency of familial aggregation. People with human leukocyte antigen (HLA) A*0207 or B*4601 had an increased risk of developing NPC (55). Familial linkage and genome-wide association studies suggested several candidate NPC susceptibility genes or loci, including DNA repair gene variants (e.g. RAD51-L1) (56), 4p15.1-q12, 3p21.3, 5p13-15 (3), TNFRSF19 (13q12), MDS1-EVI1 (3q26) and the CDKN2A-CDKN2B gene cluster (9p21) (57). Recently, the mutational landscapes by whole-exome and targeted deep sequencing revealed a distinct mutational signature. This integrated analysis showed enrichment of genetic lesions, including ERBB-PI3K signaling and autophagosome machinery (58). This genetic information may help the development of approaches for prevention and early detection of NPC, and also for exploring new therapies for NPC.

 Searches for genes conferring susceptibility to NPC have focused on the human leukocyte antigen (HLA) genes. These genes encode proteins required for the presentation of foreign antigens, including viral peptides, to the immune system for targeted lysis. Latent membrane protein 1 (LMP1), an oncogene that is encoded by EBV, plays a key role in the development of NPC (59), and the detailed oncogenic pathway has been elucidated (60). LMP1 was also found to inhibit p53-mediated cell cycle arrest and apoptosis (56) and to increase glycolysis by upregulating the expression of HK2, which plays a key role in NPC metabolic reprogramming.
In the latest NPC-SVM classification, LMP1 was identified as a marker for predicting survival in NPC (62). Recently, Ya Cao’s lab successfully developed a DNAzyme (DZ1) that was engineered to specifically bind and cleave LMP1 mRNA, which inhibited tumor cell proliferation and enhanced radiosensitivity of NPC (63). EBV infection can also cause epigenetic changes; a specific CpG island methylation phenotype (CIMP) of NPC was identified.

In endemic areas, screening has been the most promising tool to improve the early detection rate and to eventually reduce mortality from NPC. Currently, serum EBV DNA copy number is used for screening and early diagnosis of NPC in high-risk populations (63). The plasma EBV DNA load may improve the accuracy of diagnosing NPC in high-risk individuals (64). Combined fibrinogen and EBV DNA data have been shown to improve prognostic prediction in advanced-stage NPC disease (65). A large-scale retrospective and prospective cohort study demonstrated that both EBV and high sensitivity C-reactive protein (hs-CRP) were positively correlated with poor disease free survival, distant metastasis-free survival, and overall survival for NPC patients; their combined effect provided prognostic information (66). Moreover, the plasma EBV DNA clearance rate can serve as a novel prognostic marker of NPC metastasis or recurrence (59). Elevated levels of antibodies against EBV in the lytic phase are important predictive markers for NPC risk (57). Recently, two EBV-related serologic antibody-based (EBV VCA/IgA and EBNA1/IgA) enzyme-linked immunosorbent assays were used in the initial phase of a randomized trial in Southern China (67). EBV microRNAs, which are present at functional levels in NPC tissues and in serum of NPC patients (68), could be developed as a quantitative serum-based screening assay for NPC in the future.

6. Cervical cancer prevention in high incidence areas
Cervical Cancer is the fourth most common cancer of women worldwide. An estimated 528,000 new cases and 266,000 deaths of cervical cancer occur annually, among which 85% occur in developing countries including China (69). Human papilloma virus (HPV) infection is a major risk factor. Therefore, screening for HPV infection is an important approach for cervical cancer prevention. Some of the population studies in China are discussed below:

a. Population-based cervical cancer screening studies: There have been over 20 population-based cervical cancer screening trials conducted in China since 1999. Liquid-based cytology (LBC), HPV DNA testing and visual inspection with acetic acid/lugol’s iodine (VIA/VILI) were clinically evaluated. HPV co-testing with LBC was demonstrated as an optimal strategy for cervical cancer screening, and VIA/VILI was found to be an alternative method for primary screening in areas with limited resources. Consequently, HPV testing was demonstrated to be the most effective technology for cervical cancer screening in China (70).

b. Implementation of population-based cervical cancer screening program: The Cancer Foundation of China (CFC) established the Chinese National Cervical Cancer Consortium to provide technical support, and the nationwide campaign for fighting against cervical cancer was gradually developed. Because of this excellent work, WHO cited China as an example of a “Top-Down” cancer control planning process in their guide for translating knowledge to action (71).

In 2005, two national demonstration sites for early detection and treatment of cervical cancer were established by CFC: Shenzhen - a prosperous neighbor of Hong Kong and Xiangyuan – a poor county in North China. Thereafter, with support from the central government, screening sites have been further expanded nationwide to 43 sites in 31 provinces in 2008. From 2009 to 2011, the central government launched the National Free Cervical Cancer...
Screening Program for 10 million rural women in 221 counties. The ambitious program not only significantly expanded the coverage of screening, but also added cytology into the VIA-based screening method. Since 2012, the National Screening Program has expanded to 1,140 counties to cover 10 million rural women annually (72).

c. HPV prophylactic vaccine: Although both quadrivalent and bivalent HPV prophylactic vaccines are recommended by WHO and have been approved in more than 140 countries and areas, they are not presently available in China. Chinese FDA regulations require all pharmaceutical companies seeking to license their products in China to conduct clinical trials in mainland China. In 2008, Chinese investigators started Phase III clinical trials of both vaccines and are still waiting for the efficacy endpoint data. Additionally, a Chinese domestic HPV prophylactic vaccine targeting HPV16 and 18 started its Phase III clinical trials in 2012 and is expected to obtain the results in 2016.

In summary, HPV vaccination and screening has been demonstrated to reduce the risk for cervical cancer. More research is needed to improve the vaccination and screening procedures as well as to decrease the cost for their use in the at-risk population in China.

C. Research Needs in the Prevention of Major Cancers in China

As described in previous sections, researchers in China have made significant advancement in research on the epidemiology, etiology and prevention of the traditional Chinese cancers of the liver, stomach, esophagus, cervix and nasopharyngus. The research results will help to continuously reduce the incidence of these cancers. On the other hand, with the soaring increase in incidence of lung, colorectal and breast cancers, more research is needed on cancer prevention. Primary prevention in the elimination of the causative factors would have the largest impact on public health. Some of these and other preventive approaches are discussed in the following sections.
1. **Lung cancer prevention**

Lung cancer has become a prominent cancer in China in the past 3 decades. During the period of 1988 to 2005, there was an average annual increase of 1.63% (1.3% in men and 2.34% in women) in lung cancer incidence rate (73). There were 652,842 newly diagnosed lung cancer cases (36.1/100,000, 21.3% of all cancer incidence) and 597,182 deaths due to lung cancer (32.5/100,000, 27.1% of all cancer deaths) in 2012 in China (46). Lung cancer has been the number one cause of death since 2008 (74). The World Health Organization estimates that the annual lung cancer mortality rate in China may reach 1 million by 2025 (75). The lung cancer incidence rates in two large cities are generally higher than rural area; however, the rural area of Qidong is an exception, with recent lung cancer incidence rates comparable to those in Shanghai (Supplemental Table 3).

The most prominent risk factor of lung cancer is cigarette smoking (including second-hand smoking). Tobacco use prevalence in China was 63% in men in 1984, and the prevalence of smoking in men reached its peak of 66.9% in 1996 (76-78). The 2010 Global Adults Tobacco Survey (GATS) reported that in China 288 million adult men (52.9%) and 12.6 million adult women (2.4%) smoked at the time of the survey (79). More than 70% of the population are regularly exposed to second-hand smoking. It was estimated that in China tobacco smoking was responsible for 214,528 and 24,694 deaths from lung cancer among men and women, respectively, which account for 75% and 18% of the lung cancer deaths, respectively (80). An emerging risk factor for lung cancer in China is air pollution, which was classified as carcinogenic to humans (Group 1) by WHO (46, 81). More than half of the lung cancer deaths were estimated to be attributable to ambient PM$_{2.5}$ in China and other East Asian countries (82). There was also a strong evidence of lung cancer associated with exposure to indoor air pollution among women in China (81).
Although frequent consumption of vegetables and fruits may lower lung cancer risk (83), the most effective way to prevent cancer is tobacco control (84) and decrease in air pollution (discussed in Section D). In addition to lung cancer, both smoking and air pollution also cause other diseases, such as cardiovascular diseases (84). The importance of lung cancer screening and early detection has been long recognized, but effective screening methods were not available. In recent years, low dose spiral computed tomography (LDCT) has shown promising results and related guidelines for screening have been developed in the United States (85, 86). A demonstration program of population-based lung cancer screening was initiated in China (87) and it will provide opportunities to explore the feasibility of LDCT lung cancer screening in the Chinese setting.

2. Colorectal cancer prevention

The colorectal cancer (CRC) rate also increased markedly during the past 2 decades. During the period of 1988-1992 to 2009, the raw CRC incidence rates were more than doubled in big cities and rural areas (Supplemental Table 3). For example, in Shanghai the rates in males increased from 27.1 to 64.7 (expressed as number per 100,000), but the world age-standardized rate (WASR) stayed at around 20. However, in Beijing the WASR increased from 14.0 to 20.5. In Qidong and Linzhou, the raw rates (and WASR) increased from 10.2 (9.6) to 25.6 (15.5) and from 3.2 (3.4) to 13.3 (11.6), respectively. The incidence rates for females were similar to those for males. The mortality rates (WASR) were roughly half of the incidence rates in both big cities and rural areas.

The increase in CRC is likely due to dietary and lifestyle changes such as increased meat and calorie intake as well as decreased physical activity (83). The increased consumption of alcohol and tobacco may also contribute to the rise in CRC incidence rate. The obvious preventive measure is diet and lifestyle modification (discussed in Section D). Another approach
is chemoprevention. The evidence of colon cancer prevention by aspirin in observational epidemiology, randomized clinical trials and large cohort studies in North America and Europe has been studied extensively (88-94). It appears that at least 3 years of aspirin use is required to reduce the cancer risk, and aspirin use for 5 years or longer decreases cancer mortality. Gastrointestinal bleeding is a common and serious problem (91), but the benefits outweigh the harms (94). In light of these findings and the affordability of aspirin, the use of aspirin for CRC prevention warrants careful investigation, especially on the issue of gastrointestinal bleeding in the Chinese population. Recommendation or guidelines for screening have been suggested (Supplemental Table 4), but they are only followed in certain areas or hospitals. The possible application of the recently developed Multi-Target Stool DNA Test (MT-sDNA) (approved by the US FDA) in China warrants investigation.

3. Breast cancer prevention

During the past 2 decades, breast cancer incidence rates increased tremendously in China, in both big cities and rural areas. For example, the raw incidence rates (and WASR) in Shanghai were more than doubled from 35.0 (26.5) in 1988-1992 to 73.6 (38.7) in 2009 (Supplemental Table 2). For the same time period, the incidence rates increased from 12.8 (11.2) to 38.7 (13.1) in Qidong, and from 4.1 (5.1) to 23.3 (17.6) in Linzhou. The mortality rates (WASR) in Beijing and Shanghai were approximately 20-30%, and in Qidong and Linzhou were 25-66%, those of the incidence rates, reflecting the difference in medical treatment.

The known risk factors for breast cancer are younger ages of menarche and rising body weight in postmenopausal women; both factors are related to increased coloric intake and decreased physical activity. In China, the “one child” family planning policy and delay in childbirth are also important factors. In addition to the general diet/lifestyle guidelines on cancer prevention (discussed in Section D), other preventive measures need to be studied. For example,
whether soybean (containing genistein) consumption starting at an early age can decrease the risk of breast cancer may be any interesting topic to study. Chinese investigators may learn from the research experience of Western scientists on selective estrogen receptor modulators (SERMs) (95, 96), and consider the suitability for use these agents in high risk individuals in China. Recommendation or guidelines for screening have been suggested (Supplemental Table 4), but they are only followed in some areas or hospitals.

4. Anti-\textit{H. Pylori} and vaccination approaches to prevent stomach, cervical and other cancers

In China, the incidence rates of GC have decreased in big cities, but they remain high in rural areas (72.82 and 34.02 per 100,000 for males and females, respectively), possibly due to the higher frequency of \textit{H. Pylori} infection in rural areas. As shown by the studies in Linqu and elsewhere (21-23), \textit{H. pylori} eradication is an effective approach to reduce the risk of GC. It is estimated that an effective \textit{H. pylori} eradication program in the rural areas of China could reduce the GC risk by 20-40%. This could prevent 120,000-150,000 new GC cases per year. More translational research is needed before large population-based programs are launched. To identify and treat those infected with high virulence \textit{H. pylori} should be a top priority. Predictive models of individual susceptibility and potential biomarkers in response to \textit{H. pylori} infection need further investigation. Detecting \textit{H. pylori} and treating those with both precancerous gastric lesions and \textit{H. pylori} infection will increase the cost-effectiveness in a combined primary and secondary prevention strategy. A possible association between \textit{H. pylori} infection and lung cancer has been suggested (97), and it would be interesting to study this association in China.

\textit{HPV} prophylactic vaccination and screening for \textit{HPV} infection have been shown to be effective in preventing cervical cancer. It is estimated that such approaches would reduce 54,558 new cervical cancer cases annually in China (98). Vaccinating young adolescents and screening
middle-aged women should be the most effective approach. Demonstration projects with combined HPV vaccination and cervical cancer screening should be established in selected areas of China. With optimization from the demonstration projects, optimized anti-HPV programs can be expanded to the whole nation. A recent meta-analysis showed an association between HPV infection and ESCC in the Chinese population (99). This topic, however, has been controversial and remains to be further investigated.

HBV vaccination is a mature approach for liver cancer prevention and should be extended to uncovered populations. Vaccination against EBV could be an effective approach for preventing NPC. More research is needed in vaccine development and related mechanistic studies.

5. Basic chemoprevention research

Chemoprevention refers to the strategy to prevent, delay or reverse the development of cancer by using natural or synthetic chemicals (100, 101). Some chemopreventive agents such as SERMs, aspirin, and cyclooxygenase-2 selective inhibitors have been shown to be clinically effective (88, 95, 96, 102-104). Investigators in China may learn from the experience of Western scientists about the successes and pitfalls in the development of these agents. Nevertheless, the effectiveness of many nutrients and laboratory chemopreventive agents has not been demonstrated in humans, and there are even severe criticisms about the cancer chemoprevention approach (105). We believe that chemoprevention is a promising field that needs more research. Many of the negative results in human trials were due to a lack of understanding of the nature of cancer development and the biological activities of the preventive agents. Using the modern “precision medicine” concept from cancer therapy by targeting the driver genes to treat
premalignant lesions for cancer prevention is an interesting idea, and it will need long term research before fruition.

In the development of cancer chemopreventive agents, several considerations are needed: 1) efficacy, 2) safety - minimal side effects, 3) cost of the agent, and 4) acceptability of the agent by populations at risk. Based on these considerations, repurposing commonly used drugs, such as aspirin, for cancer chemoprevention has been considered a practical approach. Another example is the current studies on the repurposing of metformin, which is a biguanide drug most widely prescribed for type 2 diabetes. Metformin use has been associated with a decreased risk of specific cancers including prostate, colon, liver, pancreas and breast cancers (106). Metformin is now being evaluated prospectively for possible prevention of different types of cancer. An interesting possibility is to use a combination of metformin and aspirin for the prevention of pancreatic cancer (107) and other cancers.

Repurposing traditional Chinese medicine for cancer prevention is an attractive idea, especially in China. This is an area that Chinese scientists could make a unique contribution. Many herbal preparations that possess appropriate anti-inflammatory activities may be good candidates for the prevention of inflammation-associated cancer. Inflammation is known to promote the development of colon, liver and other types of cancer (108). Systematic studies on the traditional herbal preparations or isolated active constituents are needed. These require the collaboration among scientists with expertise in traditional Chinese medicine, natural product chemistry, laboratory cancer prevention studies and clinical cancer prevention trials.

6. Studies on dietary and lifestyle factors

The approach of using the National Nutritional Survey data to study cancer etiology in China has yielded much information in the past (109) and should be continued. China, with its
diverse dietary habits and social economic status, provides many opportunities for studies; some are as follows:

a. Nutritional deficiencies: Even though the living standards in China have risen in the past 30 years, deficiencies or insufficiencies in nutrients such as iron, selenium, calcium and vitamin D are still common. Lower nutritional status in certain micronutrients may significantly increase cancer risk. For example, in the Shanghai Women’s Health Study (1997-2000) and the Shanghai Men’s Health Study (2002-2006), intake of dietary or supplemental vitamin E was inversely associated with liver cancer risk (110). The nutritional statuses of different populations in China need to be studied, and measures to remedy the deficiencies should be developed. This is an important issue in China, even though research on nutrition and cancer is currently not a major topic of interest in the United States because of the disappointing results of several large scale trials (105, 111). These trials were mostly conducted in populations that already had sufficient intake of the nutrients being studied.

b. Dietary carcinogens: Although fungal and bacterial contamination of food has decreased, it is still a problem. Research is also needed on the carcinogens present in some of the traditional foods, such as salt- and nitrate-processed meat and fish and in adulterated foods.

c. Prevention against environmental carcinogens: Air pollution is a serious problem that increases the occurrence of respiratory diseases, lung cancer, cardiovascular diseases and other diseases (81). 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 significantly impact the qualities of food supplies and increase the cancer burden of the exposed populations (112, 113). These provide challenges and opportunities for cancer prevention research. There are also ample opportunities for establishing new cohorts for study with respect to the new risk factors.
associated with the new dietary patterns and the serious problems of air, water and soil pollution. Although the fundamental solution is to minimize these populations, research efforts are needed on the remediation and improvement of water and food quality. Another possible preventive measure is to use a dietary approach to reduce the damage in the exposed individuals. It has been shown that calcium supplementation can reduce the absorption and toxicity of lead and cadmium (114) and that vitamin E may reduce cancer risk (115). A broccoli sprout preparation (which activates, cytoprotective enzymes) has been shown to enhance the detoxification of airborne pollutants in a trial in Qidong (116). It would be interesting to explore whether supplementation with broccoli sprouts, tocopherols or other agents can reduce the severity of respiratory diseases or markers for lung carcinogenesis.

d. Dietary and lifestyle modifications: There are many dietary and lifestyle recommendations for cancer prevention. However, the recommendations by the American Institute for Cancer Research/World Cancer Research Fund (83) appear to be the most practical. A modified version of the recommendations is shown in Table 1. These recommendations are based on strong epidemiological data and they can also prevent other chronic diseases. The recommendation of “Choose mostly plant-based foods” for cancer prevention is consistent with the traditional Chinese dietary pattern, which mainly comprises of plant-based foods. People in China are also faced with problems of obesity and diabetes, which increases the risk for many types of cancer (117). The recommendations of “be physically active” and “maintain a healthy body weight” are also appropriated. Of course, tobacco cessation is of prominent importance. Research should be conducted on how to reverse the trend of increasing consumption of meat, refined grains and sugar, and on how to increase physical activity and quit smoking. Chinese scientists can take
advantage of the experience of the Western countries and develop practical approaches for China.

D. Recommendations

1. Primary and secondary cancer prevention

The results from China and other parts of the world clearly demonstrated that primary prevention by eliminating causative factors is the most effective approach to reduce cancer burden. This is not an easy task and requires the combined efforts of the government and industry to reduce environmental pollution. More importantly, it requires the general public to choose healthy diets and lifestyles and to influence the government to improve the environment and establish effective tobacco control policies. Though considered difficult, these efforts would provide the greatest benefit not only in the prevention of cancer, but also in preventing cardiovascular and other diseases.

Through the efforts of many scientists and physicians and after years of debate, the first draft of the National Tobacco Control Regulation has recently been released by the State Council of China, which prohibits smoking in all indoor public places (118). More and more provinces and cities are taking corresponding legislative action on tobacco control (119). Some of the efforts leading to this positive step include large-scale smoke-free campaigns (84, 120, 121) and health education campaigns. It will not be easy for China to rapidly reduce tobacco consumption and clean up the environment, but citizens shall be made aware of these issues and attempt their best to improve the situation. Vaccination and screening for HPV and other virus are also important for primary and secondary cancer prevention. Cancer researchers are in a pivotal position to contribute to these efforts by conducting research: to improve our understanding about environmental, dietary and lifestyle factors that affect cancer risk; on effective ways of
behavior modifications; and on better approaches for early detection and treatment of precancerous lesions.

2. **Increase research collaboration and strengthen scientific societies and non-government organizations**

   The examples described in Section C illustrate the importance of international collaborations. It is also important to increase the collaborations among scientists in China. Frequent informal cancer prevention workshops would help to facilitate such interactions. More interactions among laboratory researchers, epidemiologists and clinicians in the spirit of mutual respect will lead to fruitful collaborations to advance the field of cancer prevention. It is important to strengthen the activities of academic organizations and scientific societies in providing forums for scientific discussions and policy advocacy in cancer prevention. The government should also encourage voluntary non-governmental organizations to initiate and promote cancer prevention activities in society. The successful campaign on smoking cessation, as promoted by the American Cancer Society, is a good example of this.

3. **Establish governmental cancer prevention policies and increase funding for research**

   The importance of cancer prevention is well-recognized and emphasized by WHO. In long-term cancer control planning, the Chinese government also emphasized the strategy of prevention and early stage disease control. The Chinese government has sponsored several large- and small-scale screening programs for the early detection of cervical, breast, and other cancers, as well as HBV vaccination programs. However, more efforts are needed. We would like to make the following suggestions:

   a. *To establish cancer prevention as a priority in health care and in biomedical research:* The “prevention first” strategy needs to be enforced by practical policies, such as the government-
sponsored national urban and rural medical insurance programs. Funds should be provided to support eradication of risk factors such as H. Pylori, HPV and HBV as part of the governmental health care budget. In terms of institutional organization, a strong branch of cancer prevention should be established in the Chinese National Cancer Center. Similarly, strong cancer prevention units should be established at the provincial level and at large medical centers. A close collaboration of these units with the China Center for Disease Control would greatly facilitate activities in cancer prevention and control.

b. *To invest more resources in cancer prevention research and its translation to the population*: Certain percentages of tax income from tobacco and industries that cause pollution (such as the coal and petroleum industry) should be earmarked for cancer prevention and control. The Natural Science Foundation of China (NSFC) and other funding agencies should increase their support to basic cancer prevention research, early screening and long-term population intervention studies.

c. *To enhance health education in the school curriculum and public media*: The government should provide teaching materials for disease prevention to be taught in the primary, middle and high schools. The government may also require television and radio stations to include at least 5-10 minutes of health education messages in their programs per day.

In conclusion, significant progresses in cancer prevention research and measures have been made in China. However, the country faces an alarming increase in cancer burden due to environmental, dietary and lifestyle factors; most of these cancers are preventable through effective intervention. More research efforts are needed in developing effective approaches for the prevention of cancer. We hope our suggestions will stimulate more discussions in this area.
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Legends

Figure 1: The highest mortality regions of common cancers in China identified in 1973-1975 National Population Death Cause Survey.

Figure 2: Trends of Age-Standardized Death Rates from Common Cancers over 1980-2013 in China. A, males; B, females. Data extracted from Reference 4.
**Table 1: Guidelines for Cancer Prevention**

- Choose mostly plant-based foods, limit red meat and avoid processed meat (*eat whole grains, vegetables, fruits, legumes, nuts and fish*).
- Be physically active every day and maintain at a healthy body weight.
- Do not smoke or chew tobacco

Modified from Reference (83).
Figures 2A

Trends of Age-Standardized Death Rates for Common Cancers over 1980-2013 in China (Male)*

Figures 2B

Trends of Age-Standardized Death Rates for Common Cancers over 1980-2013 in China (Female)*

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