REVIEW

Aetiology of Cancer in Asia

Sohee Park[1], Jisuk Bae[2], Byung-Ho Nam[1], Keun-Young Yoo[2]*

Abstract

    Cancer has become the leading cause of death in many Asian countries. There is an increasing trend in breast, prostate and colon cancers, which are considered as typical of economically developed countries. Although breast and prostate cancer rates are still lower than in western countries, they are particularly rapidly increasing. In this paper, we review recently published literature to identify important etiologic factors affecting the cancer risk in Asian populations. Infectious agents such as *Helicobacter pylori*, hepatitis B and C viruses, , and human papillomavirus were shown to be associated with elevated risks of stomach, liver and cervical cancer, respectively. Tobacco smoking was shown to be significantly associated with higher lung cancer risk and moderately increased all cancer risk. Excessive alcohol drinking appeared to increase the risk of colorectal cancer in Japanese and breast cancer in the Korean population. Betel nut chewing was associated with higher risk of oral and esophageal cancer. In terms of diet, various studies have demonstrated that high caloric and fat intake was associated with breast cancer risk, salted food intake with stomach cancer, aflatoxin B1 with liver cancer, and low fruits and vegetables intake with breast and lung cancer. Environmental exposure to indoor and outdoor air pollution, arsenic, radon, asbestos and second hand smoke was shown to increase the lung cancer risk. Reproductive factors such as late age at first childbirth, early menarche, late menopause, oral contraceptive intake, and short duration of lifetime lactation were shown to be associated with breast and/or colorectal cancer. Cancer has clearly become an emerging health threat in Asia and cancer control programs should be actively implemented and evaluated in this region. Various strategies for cancer control have been developed in some Asian countries, including the set-up of national cancer registries, cancer screening programs, education programs for health behavior change, eradication of *Helicobacter pylori* and vaccination for hepatitis B and C viruses, and human papilloma virus high risk forms. However, more attention should also be paid to low- and medium-resource Asian countries where cancer incidence rates are high, but neither intensive research on cancer for planning effective cancer control programs, nor easy implementation of such programs are available, due to limited financial resources.

Key Words: Asia - cancer - etiology - risk factors

Introduction

Trends in cancer incidence and mortality

    Cancer is becoming a serious health threat in many Asian countries and it has become the leading cause of death in Asian Pacific countries such as Japan and Korea. Most commonly diagnosed cancers in Asia are in the order of lung, breast, colon and rectum, and the leading causes of cancer deaths are lung, stomach and liver. In year 2000, there were over 3 million new cancer cases and over 2 million cancer deaths in Asia and projections suggest that the number of new cancer cases in Asia will increase to 7.1 million by year 2020 if existing prevention and management strategies remain unchanged (Mackay et al., 2006).

    There is an increasing trend in breast, prostate and colon cancer, which are regarded as the cancer of economically developed countries (Yang et al., 2004). Although breast and prostate cancer rates are still lower in Asian countries than in western countries, the rates have been increasing rapidly (Figure 1a, 1b). Age-standardized prostate cancer mortality rates showed an apparent increase ranging from 50% in Thailand to 260% in Korea over the last several decades (Sim et al., 2005). Colon cancer incidence rates in Asia have gradually caught up with the rates of western countries (Figure 1c). In particular, there was a rapid increasing trend in both incidence and mortality from colorectal cancer in Japan from 1960 to 1990, where the per capita consumption of meat and animal fat showed an apparent increase during this period (Yiu et al., 2004; Bosetti et al., 2005). Although this correlation of national data does not provide evidence

[1]*Cancer Registration and Biostatistics Branch, National Cancer Control Research Institute, National Cancer Center, Goyang, Korea,* [2]*Department of Preventive Medicine, Catholic University of Daegu, Daegu, Korea,* [2]*Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, Korea* *For correspondence: kyyoo@plaza.snu.ac.kr*

for a causal relationship, it motivates the hypothesis that increased risk of colorectal cancer may be attributable to a change in diet. The incidence and mortality rates of stomach and liver cancer are very high in Japan, Korea and China, but stomach cancer rates have been steadily decreasing and liver cancer rates have recently begun to decrease (Ngoan et al., 2002; Chen et al., 2006). Lung cancer is the leading cancer-killer in Asia and specifically the lung cancer incidences in women have been increasing in Japan.

In this paper, we review recently published literature to identify important etiologic factors affecting the cancer risk in Asia, but since this topic covers large literature, the references we cite here are not exhaustive.

Etiologic Factors for Cancer

1) Infectious Agents

Helicobacter pylori (HP), hepatitis B virus (HBV), hepatitis C virus (HCV), and human papilloma virus (HPV) are important risk factors for the development of gastric, liver, and uterine cervical cancer in Asia.

Helicobacter pylori (HP) and gastric cancer

The International Agency for Research on Cancer (IARC) classified Helicobacter pylori (HP) as a group 1 human carcinogen for gastric cancer in 1994. The infection rates of HP in the world population is approximately fifty percent, and in Asian countries these rates are considerably high (Prinz et al., 2006). In 2001, the Helicobacter and Cancer Collaborative Group (Helicobacter, 2001) conducted a pooled analysis on the association between HP seropositivity and gastric cancer risk in 12 nested case-control studies within prospective cohorts. Four out of these 12 studies were from Asian countries including Japan, China (2 studies) and Taiwan, and of these the Chinese and Taiwanese studies showed risks of less than 2.0, which were lower than the overall pooled risk estimate of 2.36.

A nested case-control study in Korea revealed that there was no direct association between HP and gastric cancer risk (OR=1.06, 95% CI: 0.80–1.40) (Shin et al., 2005). It has been suggested that factors other than HP infection could explain the diversity of gastric cancer incidence in Asian region. Azuma (2004) investigated the distribution of CagA strain, and classified two major CagA subtypes, namely the East Asian and the Western type (Azuma, 2004). The prevalence of the East Asian CagA-positive strain was shown to be associated with the high mortality rates of gastric cancer in Asia. A Korean study on the association between HP and gastric cancer by the virulence factors (CagA and VagA) further suggested that CagA seropositivity was significantly associated with a higher risk of gastric cancer among HP-infected subjects (OR=3.57, 95% CI: 1.05–12.14) (Gwack et al., 2006).

Although there is an inconsistency, there is an abundance of epidemiological evidence suggesting that HP eradication is able to reduce the risk of gastric cancer, especially among subjects without atrophic gastritis or intestinal metaplasia (Malfertheiner et al., 2005).
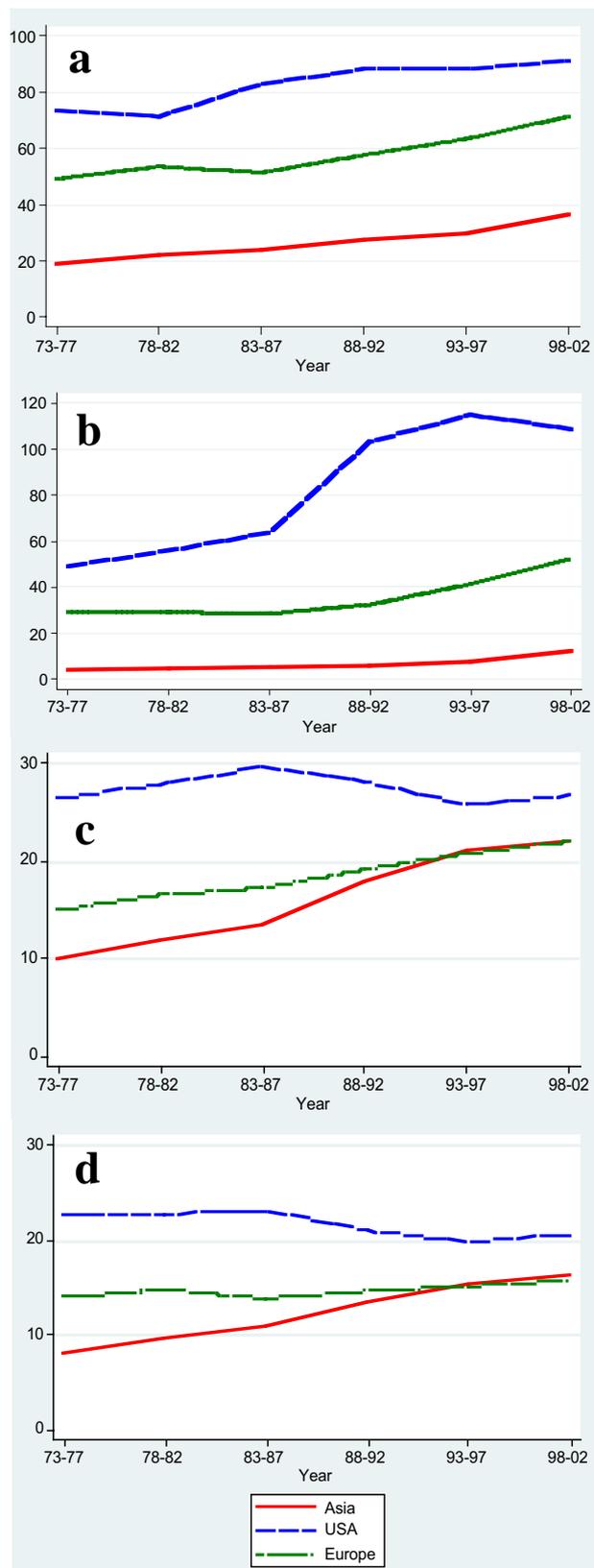
Figure 1. Trends of Cancer Incidence Rates in Asia, USA and Europe: a) Breast cancer; b) Prostate cancer; c) Colon cancer (male); d) Colon cancer (female) *Data derived from Cancer Incidence in Five Continents, Volumes IV – IX

Hepatitis B virus (HBV), hepatitis C virus (HCV) and liver cancer

Chronic infection with HBV and/or HCV is a well-

known risk factor for hepatocellular carcinoma (HCC) (Tsukuma et al., 2005). HBV and HCV carriers are at 20-fold and 25-fold higher risk of liver cancer than non-carriers, respectively. However, only small fractions of chronic HBV carriers are expected to develop HCC in their lifetime. The inter-individual variation in the risk and age at onset of HCC among chronic HBV carriers can be attributed to the variability in aflatoxin exposures and lifestyle factors such as alcohol consumption and cigarette smoking (Srivatanakul et al., 2004).

Although chronic HBV infection is a major cause of HCC, there is wide variation in the proportion of HCC attributable to HBV (Muir, 1996). A number of studies have implicated that HCV infection is an important risk factor for HCC. In addition, co-infection of HCV and HBV have been reported to have an additive effect on the risk of HCC (Tsai et al., 1997).

Liver flukes and liver cancer

Liver flukes such as *Clonorchis sinensis* (CS) and *Opisthorchis viverrini* (OV) have been suggested as the risk factors for liver cancer including cholangiocarcinoma (CCA) and hepatocellular carcinoma (HCC). As for CCA, the variation in geographical distribution is related to the infestation rate of liver flukes; the incidence of CCA is relatively high in Indochina countries such as Thailand, an endemic area for OV and Far East Asia, an endemic area for CS (Srivatanakul et al., 2004).

It has been known that the role of liver flukes in carcinogenesis is related to chronic inflammation induced by prolonged infestation. Preventive strategies such as the intake of cooked fish and hygienic caution should be implemented to reduce the risk of CCA in the endemic areas of liver flukes.

Human papillomavirus (HPV) and cervical cancer

Uterine cervical cancer is the second most frequently diagnosed female cancer worldwide and the persistent infection with a high risk "oncogenic" type of HPV is a well-established risk factor for invasive cervical cancer. An international comparison study showed that there was large variation in the overall and age-specific HPV prevalence rates across countries. There is a high prevalence of HPV in Asia, especially in India and China (Moore et al., 2004; Franceschi et al., 2006). An effective HPV vaccination program for pre-adolescent girls may reduce mortality from cervical cancer by 80%, however, high cost of vaccine, poor awareness of linkage between HPV infection and cervical cancer, and social stigmatizing for a sexually transmitted disease are barriers to be overcome (Lee et al., 2007).

2) Lifestyle

Potential explanations for large geographic differences in cancer incidences may be due to genetics or lifestyle and environment. For example, adaptation of "western" lifestyle which is a combination of decreased parity, delayed childbearing, early menarche, high total caloric or fat intake and sedentary life pattern has been considered as the primary reason for increasing trends of cancer in breast, colon, rectum and prostate in Asian countries. An international comparison has shown that the breast cancer incidence rates have markedly increased in Asian countries. "Westernized" lifestyle changes in fertility and diet have been hypothesized as an explanation for these increases (Althuis et al., 2005). Several migration studies have further supported this hypothesis in breast cancer (Ziegler et al., 1993; Stanford et al., 1995; Pike et al., 2002). Some risk factors related to lifestyle such as smoking have shown consistent results in various studies conducted in Asian populations but several factors showed weaker evidence as discussed below.

Smoking and alcohol

Smoking is a primary lifestyle-related, avoidable risk factor for cancer. International ecological studies showed that countries with high cigarette consumption had higher lung cancer incidence rates (Kobayashi et al., 2000). Moore and Tsuda (2002) have intensively reviewed the smoking-related research in Asian-Pacific countries (Moore et al., 2002). The association of cigarette smoking with cancer risk appears to differ by cancer sites and gender. There are recently published series of systematic review on smoking and cancer risk based on cohort and case-control studies in Japan (Inoue et al., 2005; Mizoue et al., 2006; Nagata et al., 2006; Wakai et al., 2006). The authors reported that there is convincing evidence that current tobacco smoking moderately increases the risk of total cancer (about 1.5 times). In lung cancer, smoking was a strong risk factor (OR=4.39 in men; OR=2.79 in women) (Yamaguchi et al., 2000). However, the effect of smoking on other cancers is not conclusive. Smoking was reported as a possible risk factor for breast cancer (Nagata et al., 2006), but not enough evidence showed for the risk of colorectal and liver cancer (Mizoue et al., 2006; Tanaka et al., 2006). Korean and Japanese studies showed similar results with elevated risk of lung cancer for current smokers (RR=4.0 in men; RR=2.2 in women) (Jee et al., 2004). Jee et al (2004) reported that smoking was also associated with an elevated risk for other cancers such as esophagus, stomach, pancreas, larynx, bladder and leukemia.

Second hand smoke was reported to moderately increase the risk of lung cancer incidence and mortality. In the Shanghai women's health study, high proportion of study participants (83.1%) were exposed to second hand smoke from their husbands, at work and from family members in early life. Non-smoking women who were exposed to second hand smoke showed moderately higher risk of lung cancer mortality than those unexposed (HR=1.79) (Wen et al., 2006).

Excessive alcohol drinking is another avoidable risk factor for cancer. A meta-analysis in Japan reported that even moderate drinkers (<46 g/day) had a higher risk of colorectal cancer and this finding was different from a pooled analysis of studies in Western countries (Mizoue et al., 2006). Alcohol drinking also increased the breast cancer risk in Koreans (Yoo et al., 2006).

Along with tobacco smoke and alcohol consumption, betel nut chewing which is very common in South-East Asia, was also identified as human carcinogens by the

International Agency for Research of Cancer (IARC). A Taiwanese study reported that those who chewed betel nut with a piece of betel inflorescence or swallowed betel-quid juice had a significantly higher risk of esophageal cancer (OR=4.2 and 3.3, respectively). Betel nut chewing plays a relevant role in the development of esophageal squamous cell carcinoma, and interacts with smoking and alcohol drinking (Wu et al., 2006). The betel nut chewers had an increased risk of esophageal cancer ranging from 2.4 to 27.4 times that of non-chewers in India, depending on different combinations of betel nut chewing pattern (Phukan et al., 2001). On the contrary, a review article in mainland China has reported that the prevalence of oral cancer among betel quid chewers was low (0.02% to 0.05%) in Hunan and Hainan, while the betel quid chewing was very common in these provinces. They suggested that betel quid chewing habits differ across geographic areas, which may affect the magnitude of associated cancer risk (Zhang et al., 2007). A cancer incidence study in Pakistan also identified 'smokeless tobacco use' as a potential risk factor for oral and pharyngeal cancer (Bhurgri et al., 2003).

Dietary factors

There have been tremendous reports on food or nutrients and their association with cancer risk. High total caloric and fat consumption was reported to increase the risk of breast and colorectal cancer. Some Asian diet may play a protective role in cancer risk and these have been more intensively studied recently.

High total caloric and fat intake: Red meat and animal fat consumption was found to increase the breast caner risk in a number of epidemiological studies in Asia (OR=3.84 in Malaysia; OR=5.1 in Taiwan; OR=8.47 in Indonesia; OR=2.9 in China) (Yuan et al., 1995; Wakai et al., 2000; Lee et al., 2005; Kamarudin et al., 2006). High red meat or animal fat intake are also associated with the risk of colorectal cancer (OR=1.5~2.2) (Seow et al., 2002; Chiu et al., 2003). The amount of fat intake may differ by various cooking methods. Deep-frying is known to increase the fat content in the food. Furthermore, a case-control study conducted in Philippines showed an associated risk of breast cancer with the consumption food boiled in coconut milk in their adolescence (OR=2.78), and this was thought to be due to high total caloric and animal fat contents in coconut milk (Kotsopoulos et al., 2006).

Low fruit and vegetable intake: Although some inconsistencies were found, epidemiologic studies showed that low consumption of fruits and vegetables is associated with cancer risk in Asian countries. High consumption of Chinese white turnips, dark yellow-orange or green vegetables and fruits was shown to reduce the breast cancer risk (ORs ranging from 0.65 to 0.79 for highest quartile group) (Hirose et al., 2003; Malin et al., 2003; Sauvaget et al., 2003). Studies also reported its association with lung cancer risk. After controlling for smoking and occupational exposures, people with low yellow and light green vegetables were at a higher risk of lung cancer in southern China and Hong Kong (OR=2.26, 2.39) (Forman et al., 1992). However, population-based cohort studies in Japan found no association between lung cancer and

fruits and vegetables (Liu et al., 2004). A case-control study in India reported that prostate cancer risk can be reduced in men with high fruits and vegetables consumption (OR=0.4) (Sunny, 2005). On the other hand, the association with colorectal cancer risk has been inconsistently reported (Sato et al., 2005).

High Salt Intake and gastric cancer: Higher intake of salt and salted food is known to increase the risk of gastric cancer and the prevalence of HP infection (Correa, 1992; Tsugane et al., 1993; Tsugane et al., 2004; Tsugane, 2005). Besides their effect on HP infection, salt and salted food also acts synergistically to promote the development of gastric cancer.

Aflatoxin B1 (AFB1) and Liver Cancer: Although chronic HBV infection has been well documented as the most important risk factor for HCC, dietary exposure of AFB1 has been implicated as another major cause. The AFB1 binding to DNA may be a critical step in hepatocarcinogenesis. The extent of the AFB1 binding to DNA may depend on various endogenous factors and concurrent exposure to other environmental agents such as alcohol drinking and cigarette smoking (Yu et al., 1996). A synergistic interaction between AFB1 exposure and HBV infection on HCC risk also has been reported in several epidemiological studies (Chen et al., 2001). HBV infection may affect AFB1 adduct formation through alteration of AFB1 metabolism. On the other hand, the immunosuppressive actions of AFB1 may modulate HBV infection. Food safety procedures to control AFB1 contamination could offer strategies for lowering HCC rates in Asia.

Soy intake and green tea consumption (protective): Soy intake and green tea consumption represent protective Asian diet that has drawn much attention recently. Soybeans are a rich source of isoflavones and a main type of plant estrogens. Epidemiological studies showed significant associations between high soy intake and the reduced risk of breast cancer (OR=0.46 for highest quartile group) (Yamamoto et al., 2003; Hirose et al., 2005). There has been an attention in soy product which may, in part, give an explanation for large international differences in breast cancer incidence rates. However, this protective effect of soy intake was questioned by Wu et al (1998) when they found the effect was weakened in US-born Asian Americans compared to non-US-born Asian Americans. It was suspected that soy intake may be a marker of other factors associated with the degree of westernization that are causally associated with the breast cancer risk (Wu et al., 1998; Wu et al., 2000). In relation to the colorectal cancer risk, animal studies have shown that soyfoods and isoflavones inhibited the formation of aberrant crypt foci, however the findings from epidemiologic studies have not been consistent (Toyomura et al., 2002). Further evaluation will be needed for the conclusive protective effect of soybeans.

Green tea has a number of compounds, including polyphenols, that have chemopreventive properties, and in vivo and animal studies have reported its preventing role from cancer. While animal studies have shown the protective effect of polyphenols in green tea, there is large variation among the results from epidemiological studies.

High green tea consumption was associated with the reduced risk of breast cancer in Chinese women (OR=0.59~0.87) and Japanese-American women (OR=0.53) (Wu et al., 2003; Zhang et al., 2006) but not in Japanese women (Suzuki et al., 2004). A Japanese case-control study reported a significant protective effect for stomach (OR=0.69) and rectal cancer (OR=0.46) (Inoue et al., 2001). However, no association was found for prostate cancer (Kikuchi et al., 2006). A recent meta-analysis reported that the evidence for a protective effect of green tea on colorectal cancer risk was insufficient in epidemiological studies (Sun et al., 2006). The role of green tea in chemoprevention should be evaluated further in humans.

Physical inactivity

Low physical activity has shown to be linked to a significantly increased risk of breast and colorectal cancer in numerous studies. A Japanese study has reported a significantly reduced risk of female breast cancer among those with high physical activities (Hirose et al., 2003). Other studies also have suggested that regular and frequent physical activity over a long time period were associated with lower risk of colon cancer in Chinese (OR= 0.52) (Hou et al., 2004) and with distal colon and rectal cancer in Japanese (OR=0.5~0.7) (Isomura et al., 2006). Weaker evidence was reported in prostate, lung and endometrial cancers and there was insufficient evidence for other sites of cancer (Kruk et al., 2006). There are limitations in studying the effect of physical activity because the methods are various in the assessment of physical activity including its frequency, duration and intensity. Nonetheless, animal and experimental studies strongly support the decreased risk of breast and colon cancer. In relation to physical activity, obesity is a major public health problem worldwide. In Asian countries with accelerated economic growth, less physical activity along with diet change towards high caloric and fat intake has increased the prevalence of obesity.

Sexual behavior

Age at first intercourse, lifetime number of sexual partners and high parity were found to be important factors for invasive cervical cancer, especially through oncogenic HPV infection, in many Asian countries (Chichareon et al., 1998; Hsieh et al., 1999; Thomas et al., 2001; de Boer et al., 2006; Kanato et al., 2006). Besides the risk caused by their own sexual behavior, women's risk of developing cervical cancer is also attributable to the sexual behavior of male sex partners. Women whose husbands had multiple sex partners were at a significantly higher risk of HPV infection and cervical cancer (OR=1.42, China) (Zhao et al., 2006). A study of massage parlor and a brothel in Bangkok, Thailand, revealed that the risk of invasive cervical cancer in monogamous women was associated with their husband's lifetime visits to prostitutes (OR=3.2, for >280 visits vs. none) and suggested that commercial sex workers in Bangkok serve as reservoirs of oncogenic HPV and cervical cancer for monogamous Thai women (Thomas et al., 2001). Furthermore, sexual behavior of young and unmarried women tend to be more risky, in terms of having unprotected intercourse and having multiple sexual partners, hence more attention will be needed to educate the teenagers (Kanato et al., 2006).

3) Reproductive Factors

Late age at first child birth, early menarche, late menopause, oral contraceptive intake, and shorter duration of lifetime lactation are known to increase the risk of breast cancer. Epidemiological studies have shown consistent results in these risk factors in many Asian countries (Yoo et al., 1992; Zheng et al., 2000; Lee et al., 2003; Kamarudin et al., 2006; Sim et al., 2006; Yoo et al., 2006). One interesting note is that the breast cancer patients are relatively younger and age-specific breast cancer rates show somewhat different patterns in Asian countries compared to those in western countries. For example, there is an inverted U-shape risk of breast cancer with age in Korea, showing a steep increase until forties and a slow decrease in later ages (Yoo et al., 2002).

Some studies suggested that reproductive factors are also associated with colorectal cancer risk in Japanese (Yoo et al., 1999; Tamakoshi et al., 2004). Such reproductive factors include menstrual regularity, early menarche, late age at menopause, first pregnancy, and number of abortions. It was hypothesized that reproductive events may affect the carcinogenesis in the large bowl through hepatic function and bile acid formation. However, the results have been rather inconsistent in other studies, hence evaluation will be needed to make a firm conclusion.

In contrast to breast cancer, early age at first child birth was found to increase the risk of cervical cancer (Guo et al., 1994). In addition, women with multiple parities were at higher risk of cervical cancer than nulliparous women. A hospital-based case-control study in India showed that early age at first marriage was a single independent risk factor for cervical cancer. This study also suggested that the rapidity of multiple pregnancies was a more important factor than the parity itself in increasing the cervical cancer risk (Mukherjee et al., 1994).

4) Environmental Carcinogens

With rapid industrialization and economic development, the air quality has worsened in Asian countries and outdoor air pollution has become a concern. For instance, the levels of polycyclic aromatic hydrocarbons (PAHs), well-established human carcinogens, are high in major cities in Asia, compared to western countries. Although not conclusive, studies have reported there exists an association between outdoor air pollution and cancer risk, mortality and other health problems (Chen et al., 2004). Besides outdoor air pollution, indoor air pollution is known to elevate the risk of lung cancer. In rural areas of China, coal stove has been commonly used for heating or deep-fry cooking in a house with poor ventilation. Studies in northeast China showed that there was a two-fold elevated risk of lung cancer for those involved in smoky outdoor environments, long use

of coal-burning stoves and high indoor air pollution. (Xu et al., 1989; Wu-Williams et al., 1990). Similarly, compared to using unprocessed biomass (crop residues, wood, sticks, and twigs), using coal for heating and cooking was linked to an elevated risk of lung cancer (OR=1.29) among residents in the rural area of China (Kleinerman et al., 2002).

Arsenic exposure has also been associated with cancer. Data from an arseniasis-endemic area of Taiwan suggested that high mortality rates from bladder and lung cancer were observed in highly arsenic-exposed villages, with significant dose-response relationship. In China, a three-fold increased risk of lung cancer was reported in smelter workers that were exposed to inorganic arsenic (Wu-Williams et al., 1990). Liver cancer mortality also appeared to be associated with arsenic exposure (Morales et al., 2000).

Radon and asbestos are other known environmental factors to elevate the risk of lung cancer. Miners were intensively studied to show a significant association between radon and lung cancer. Residential radon exposure also appears to be able to increase lung cancer risk, as shown for example in studies in China (Wang et al., 2002; Lubin et al., 2004) and Pakistan (Matiullah et al., 2003).

Prevention Measures

Many Asian countries are rapidly reaching an aging or aged society and we expect more cancer cases occurring in the future. Moreover, cancers of "westernized" lifestyle, such as breast, prostate and colon cancers, are significantly increasing in Asian countries, and this implies that so-called "protective Asian lifestyle" involving healthy diet and more physical activity may no longer exist. In addition, better diagnosis will only increase the number of newly diagnosed cancer cases further in Asia and cancer will become an emerging health threat in this part of the world.

Various strategies for cancer control have been developed in Asia, including the set-up of national cancer

Table 1. Cervical Cancer Incidence Rates (ASR) in Asia Compared with the USA, Australia and Europe

Country	1973-77	1978-82	1983-87	1988-92	1993-97	1998-2002
Asia						
China	29.0	14.4	9.4	6.9	5.4	5.6
Japan	17.3	15.4	11.8	8.8	7.3	6.7
Singapore	17.6	16.5	16.3	15.2	14.1	10.6
Thailand	NA	NA	25.7	26.5	25.9	23.8
India	NA	18.7	28.4	24.9	21.9	18.2
Philippines	NA	NA	26.4	22.7	22.9	19.8
USA	11.4	9.4	8.7	8.9	8.0	7.5
Europe						
France	NA	15.0	12.1	10.0	8.4	7.3
UK	10.4	11.9	13.0	12.3	9.4	7.3
Oceania						
Australia	12.5	10.6	10.7	9.9	8.1	6.0

Data derived from Cancer Incidence in Five Continents, Volumes IV – IX

registries, cancer screening program, education program for health behavior change, eradication of HP and the vaccination for HBV, HCV and HPV.

1) Cancer Screening

As a "secondary prevention" of cancer, early detection for cancer cases through screening program is important. Many studies in Asia have shown the effectiveness of cancer screening in reducing cancer mortality rates. To control high stomach cancer incidences in Japan, mass screening program was introduced in 1960 and there was substantial evidence showing that the screening program played an important role in reducing the gastric cancer mortality rates (Tsubono et al., 2000). Since 1982, Japan has begun a national cancer screening program in the cancer of stomach, lung, colon, rectum, breast and cervix. The Korean government began to implement a national cancer-screening program in 1999, which covers the same five cancer sites as in Japan.

In Asian countries, there is a large concern in two major female cancers: breast and cervical cancer. Cervical cancer is the second in importance in developing Asian countries, with high incidence rates, whereas the importance is in the seventh in developed countries (Parkin et al., 2005). By applying routine Pap smear tests, the incidence of invasive cervical cancer has decreased in the developed countries for last fifty years. However, cervical cancer screening has not been established in many Asian countries and the incidence and mortality rates remain still high. Although showing decreasing trends in China and Japan, the cervical cancer incidence rates have been high in Thailand, India and Philippines, which are about 3 times the rates of the USA, Europe or Australia (Table 1). In less developed countries, the cost-effectiveness of screening program has been questioned and the implementation of screening program has been difficult because of the cost. A population-based simulation model using the case data of Thailand demonstrated that well-organized screening programs can reduce cervical cancer deaths in less developed countries at relatively low costs (Mandelblatt et al., 2002). Furthermore, as important as setting up cancer screening programs, appropriate health education is also essential to arrive at the successful secondary prevention, as supported by a report in Thai females (Wiwanitkit, 2006). The cervical cancer program has not been established in other Asian countries such as India and Indonesia (Schapiro et al., 1996; Murthy et al., 2005).

2) Vaccination

Hepatocellular carcinoma (HCC) takes a large part as a cause of deaths in Asian men. Chronic HB infection, a well-known risk factor for HCC, can be approximately 90% preventable with HB vaccination. The global immunization strategy is carried out based on the generally accepted assumption that prevention of the HB-carrier state with vaccine will prevent the disease. National vaccination against HB has been implemented in Taiwan, Thailand, Malaysia, Singapore, Korea and China.

Table 2. List of Etiologic Factors for Cancer in Asia

Etiologic factors	Cancer sites
Infectious Agents	
Helicobacter pylori	Stomach
Hepatitis B virus	Liver
Hepatitis C virus	Liver
Liver flukes	Bile Duct
Human papilloma virus	Uterine Cervix
Lifestyle	
Smoking	Lung
Betel nut chewing	Oral, Esophagus
Alcohol drinking	Breast, Colorectum
Physical inactivity	Breast, Colorectum, Prostate, Lung
Diet	
High caloric/fat intake	Breast
Salted food intake	Stomach
Aflatoxin B1	Liver
Low fruit and vegetables	Breast, Lung
Soy products (protective)	Breast, Colorectum
Green tea (protective)	Breast, Colorectum
Environment	
Outdoor air pollution	Lung
Indoor air pollution	Lung
Arsenic	Lung, Liver
Radon	Lung
Asbestos	Lung
Second hand smoke	Lung
Reproductive Factor	
Late age at first child birth	Breast, Colorectum
Early menarche	Breast, Colorectum
Late menopause	Breast, Colorectum
Oral contraceptive intake	Breast
Short duration of lactation	Breast
Menstral regularity	Colorectum
Number of abortion	Colorectum
Multiple parity	Cervix
Number of sexual partners	Cervix
Sexual behavior of partner(s)	Cervix

In Taiwan, a nationwide HB vaccination program has launched in 1984, and this program has shown to be very successful in preventing HCC (Lee et al., 2003; Su et al., 2007). There was a significant decrease in both the chronic HBV carrier rates and HCC incidence rates among birth cohorts born after the implementation of vaccination program (Chang et al., 1997). Mongolia began implementing HB vaccination program in 1991 and Malaysia began the expanded program of immunization in 1989, which showed a dramatic impact in school children. A follow-up study observed a steady decline of HBV surface antigen prevalence rate from 2.5% among children born in 1985 to 0.4% among children born in 1996 (Ng et al., 2005). HB vaccination program was the most effective in preventing vertical transmission of HB, thus reducing the risk of liver cancer.

As part of preventing cervical cancer, HPV vaccination is now being introduced in Asia. It is still at its early stage, however many population-based trials are being conducted to study the cost-effectiveness of HPV vaccination. Lastly, vaccination for HP infection may contribute to the reduction of stomach cancer. Although the eradication of HP is considered for reducing gastric cancer incidence, its effectiveness is questioned since a large proportion of Asian population is infected, yet only a relatively small proportion will develop stomach cancer.

3) Health education

For changeable lifestyle risk factors of cancer, education for promoting the healthy lifestyle will be essential. For example, public health policymakers should make an effort to promote the smoking cessation, physical activity and healthy diet such as high consumption of fruits and vegetables, less consumption of salty food and red meat, and reduced alcohol consumption. It is a high priority that risky sexual behavior should be warned agaisnt as well.

As an effort to reduce smoking prevalence, for instance, a national health policy against smoking can be developed through raising cigarette price, putting warning label on cigarette cases, banning tobacco smoking at public places and running smoking cessation clinics. Such programs will effectively reduce the incidence and mortality from lung cancer, although the effect of these policies will be seen after a significant number of years. Studies have shown an inverse dose-response relationship between the duration of smoking cessation and lung cancer risk, however the risk of former smokers may never reach as low as that of non-smokers. Thus, in addition to making an effort to promote the smoking cessation, educating adolescents not to start smoking will clearly be very important.

Conclusions

In this paper, we have reviewed the etiologic factors of cancer that are more likely to be modifiable, as summarized in Table 2. There is also a rapidly evolving research area, namely the molecular cancer epidemiology, which searches for the genetic variations that are associated with the cancer risk. Some genetic variants such as BRCA1 against the risk of breast and ovarian cancer have been already identified. Further studies are underway to investigate the genetic markers and the gene-gene and gene-environment interactions in their impact on cancer risk. Then the prevention strategy for cancer will have to be modified to reflect these future findings.

Cancer has clearly become an emerging health threat in Asia and cancer control programs should be actively implemented and evaluated in this region. Furthermore, much attention should be paid to poor Asian countries with high cancer incidence rates, where neither intensive research on cancer for planning effective cancer control programs is available, nor the implementation of such programs are easily possible due to very limited financial resources.

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References

Althuis MD, Dozier JM, Anderson WF, Devesa SS, Brinton LA (2005). Global trends in breast cancer incidence and mortality 1973-1997. *Int J Epidemiol*, **34**, 405-12.

Azuma T (2004). *Helicobacter pylori* CagA protein variation associated with gastric cancer in Asia. *J Gastroenterol*, **39**, 97-103.

Bhurgri Y, Bhurgri A, Hussainy AS, et al. (2003). Cancer of the oral cavity and pharynx in Karachi--identification of potential risk factors. *Asian Pac J Cancer Prev*, **4**, 125-30.

Bosetti C, Malvezzi M, Chatenoud L, et al (2005). Trends in colorectal cancer mortality in Japan, 1970-2000. *Int J Cancer*, **113**, 339-41.

Chang MH, Chen CJ, Lai MS, et al. (1997). Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. *N Engl J Med*, **336**, 1855-9.

Chen B, Hong C, Kan H (2004). Exposures and health outcomes from outdoor air pollutants in China. *Toxicology*, **198**, 291-300.

Chen J-G, Zhu J, Parkin DM, et al (2006). Trends in the incidence of cancer in Qidong, China, 1978-2002. *Int J Cancer*, **119**, 1447-54.

Chen SY, Chen CJ, Chou SR, et al. (2001). Association of aflatoxin B(1)-albumin adduct levels with hepatitis B surface antigen status among adolescents in Taiwan. *Cancer Epidemiol Biomarkers Prev*, **10**, 1223-6.

Chichareon S, Herrero R, Munoz N, et al (1998). Risk factors for cervical cancer in Thailand: a case-control study. *J Natl Cancer Inst*, **90**, 50-7.

Chiu BC, Ji BT, Dai Q, et al (2003). Dietary factors and risk of colon cancer in Shanghai, China. *Cancer Epidemiol Biomarkers Prev*, **12**, 201-8.

Correa P (1992). Diet modification and gastric cancer prevention. *J Natl Cancer Inst Monogr*, **12**, 75-8.

de Boer MA, Vet JN, Aziz MF, et al (2006). Human papillomavirus type 18 and other risk factors for cervical cancer in Jakarta, Indonesia. *Int J Gynecol Cancer*, **16**, 1809-14.

Forman MR, Yao SX, Graubard BI, et al (1992). The effect of dietary intake of fruits and vegetables on the odds ratio of lung cancer among Yunnan tin miners. *Int J Epidemiol*, **21**, 437-41.

Franceschi S, Herrero R, Clifford GM, et al (2006). Variations in the age-specific curves of human papillomavirus prevalence in women worldwide. *Int J Cancer*, **119**, 2677-84.

Guo WD, Hsing AW, Li JY, et al (1994). Correlation of cervical cancer mortality with reproductive and dietary factors, and serum markers in China. *Int J Epidemiol*, **23**, 1127-32.

Gwack J, Shin A, Kim CS, et al (2006). CagA-producing *Helicobacter pylori* and increased risk of gastric cancer: a nested case-control study in Korea. *Br J Cancer*, **95**, 639-41.

Helicobacter and Cancer Collaborative Group (2001). Gastric cancer and Helicobacter pylori: a combined analysis of 12 case control studies nested within prospective cohorts. *Gut*, **49**, 347-53.

Hirose K, Hamajima N, Takezaki T, Miura S, Tajima K (2003). Physical exercise reduces risk of breast cancer in Japanese women. *Cancer Sci*, **94**, 193-9.

Hirose K, Imaeda N, Tokudome Y, et al. (2005). Soybean products and reduction of breast cancer risk: a case-control study in Japan. *Br J Cancer*, **93**, 15-22.

Hirose K, Takezaki T, Hamajima N, Miura S, Tajima K (2003). Dietary factors protective against breast cancer in Japanese

premenopausal and postmenopausal women. *Int J Cancer*, **107**, 276-82.

Hou L, Ji BT, Blair A, et al (2004). Commuting physical activity and risk of colon cancer in Shanghai, China. *Am J Epidemiol*, **160**, 860-7.

Hsieh CY, You SL, Kao CL, Chen CJ (1999). Reproductive and infectious risk factors for invasive cervical cancer in Taiwan. *Anticancer Res*, **19**, 4495-500.

Inoue M, Tajima K, Mizutani M, et al. (2001). Regular consumption of green tea and the risk of breast cancer recurrence: follow-up study from the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC), Japan. *Cancer Lett*, **167**, 175-82.

Inoue M, Tsuji I, Wakai K, et al. (2005). Evaluation based on systematic review of epidemiological evidence among Japanese populations: tobacco smoking and total cancer risk. *Jpn J Clin Oncol*, **35**, 404-11.

Isomura K, Kono S, Moore MA, et al (2006). Physical activity and colorectal cancer: the Fukuoka Colorectal Cancer Study. *Cancer Sci*, **97**, 1099-104.

Jee SH, Samet JM, Ohrr H, Kim JH, Kim IS (2004). Smoking and cancer risk in Korean men and women. *Cancer Causes Control*, **15**, 341-8.

Kamarudin R, Shah SA, Hidayah N (2006). Lifestyle factors and breast cancer: a case-control study in Kuala Lumpur, Malaysia. *Asian Pac J Cancer Prev*, **7**, 51-4.

Kanato M, Saranrittichai K (2006). Early experience of sexual intercourse--a risk factor for cervical cancer requiring specific intervention for teenagers. *Asian Pac J Cancer Prev*, **7**, 151-3.

Kikuchi N, Ohmori K, Shimazu T, et al (2006). No association between green tea and prostate cancer risk in Japanese men: the Ohsaki Cohort Study. *Br J Cancer*, **95**, 371-3.

Kleinerman RA, Wang Z, Wang L, et al. (2002). Lung cancer and indoor exposure to coal and biomass in rural China. *J Occup Environ Med*, **44**, 338-44.

Kobayashi YM, Moore MA (2000). Tobacco smoking in the Asian Pacific - the scope of the problem. *Asian Pac J Cancer Prev*, **1**, 73-6.

Kotsopoulos J, Liede A, De Matsuda ML, Sun P, Narod SA (2006). Method of cooking and risk of breast cancer in the Philippines. *Cancer Causes Control*, **17**, 341-8.

Kruk J, Aboul-Enein HY (2006). Physical activity in the prevention of cancer. *Asian Pac J Cancer Prev*, **7**, 11-21.

Lee CL, Hsieh KS, Ko YC (2003). Trends in the incidence of hepatocellular carcinoma in boys and girls in Taiwan after large-scale hepatitis B vaccination. *Cancer Epidemiol Biomarkers Prev*, **12**, 57-9.

Lee MM, Chang IY, Horng CF, et al. (2005). Breast cancer and dietary factors in Taiwanese women. *Cancer Causes Control*, **16**, 929-37.

Lee PW, Kwan TT, Tam KF, et al (2007). Beliefs about cervical cancer and human papillomavirus (HPV) and acceptability of HPV vaccination among Chinese women in Hong Kong. *Prev Med*, **45**, 130-4.

Lee SY, Kim MT, Kim SW, Song MS, Yoon SJ (2003). Effect of lifetime lactation on breast cancer risk: a Korean women's cohort study. *Int J Cancer*, **105**, 390-3.

Liu Y, Sobue T, Otani T, Tsugane S (2004). Vegetables, fruit consumption and risk of lung cancer among middle-aged Japanese men and women: JPHC study. *Cancer Causes Control*, **15**, 349-57.

Lubin JH, Wang ZY, Boice JD Jr, et al (2004). Risk of lung cancer and residential radon in China: pooled results of two studies. *Int J Cancer*, **109**, 132-7.

Mackay J, Jemal A, Lee N, Parkin D, Eds. (2006). The Cancer Atlas. Atlanta, American Cancer Society.

Malfertheiner P, Sipponen P, Naumann M, et al (2005). *Helicobacter pylori* eradication has the potential to prevent gastric cancer: a state-of-the-art critique. *Am J Gastroenterol*, **100**, 2100-15.

Malin AS, Qi D, Shu XO, et al. (2003). Intake of fruits, vegetables and selected micronutrients in relation to the risk of breast cancer. *Int J Cancer*, **105**, 413-8.

Mandelblatt JS, Lawrence WF, Gaffikin L, et al (2002). Costs and benefits of different strategies to screen for cervical cancer in less-developed countries. *J Natl Cancer Inst*, **94**, 1469-83.

Matiullah AA, Rehman S, Mirza ML (2003). Indoor radon levels and lung cancer risk estimates in seven cities of the Bahawalpur Division, Pakistan. *Radiat Prot Dosimetry*, **107**, 269-76.

Mizoue T, Inoue M, Tanaka K, et al. (2006). Tobacco smoking and colorectal cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. *Jpn J Clin Oncol*, **36**, 25-39.

Mizoue T, Tanaka K, Tsuji I, et al (2006). Alcohol drinking and colorectal cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. *Jpn J Clin Oncol*, **36**, 582-97.

Moore MA, Tajima K (2004). Cervical cancer in the asian pacific-epidemiology, screening and treatment. *Asian Pac J Cancer Prev*, **5**, 349-61.

Moore MA, Tsuda H (2002). Smoking-related research in the Asian-Pacific countries. *Asian Pac J Cancer Prev*, **3**, 291-304.

Morales KH, Ryan L, Kuo TL, Wu MM, Chen CJ (2000). Risk of internal cancers from arsenic in drinking water. *Environ Health Perspect*, **108**, 655-61.

Muir CS (1996). Epidemiology of cancer in ethnic groups. *Br J Cancer*, **29**, S12-6.

Mukherjee BN, Sengupta S, Chaudhuri S, Biswas LN, Maiti P (1994). A case-control study of reproductive risk factors associated with cervical cancer. *Int J Cancer*, **59**, 476-82.

Murthy NS, Chaudhry K, Saxena S (2005). Trends in cervical cancer incidence - Indian scenario. *Eur J Cancer Prev*, **14**, 513-8.

Nagata C, Mizoue T, Tanaka K, et al. (2006). Tobacco smoking and breast cancer risk: an evaluation based on a systematic review of epidemiological evidence among the Japanese population. *Jpn J Clin Oncol*, **36**, 387-94.

Ng KP, Saw TL, Baki A, et al (2005). Impact of the expanded program of immunization against hepatitis B infection in school children in Malaysia. *Med Microbiol Immunol*, **194**, 163-8.

Ngoan LT, Yoshimura T (2002). Pattern and Time Trends of Stomach Cancer in Asia from 1950-99. *Asian Pac J Cancer Prev*, **3**, 47-54.

Parkin DM, Bray F, Ferlay J, Pisani P (2005). Global cancer statistics, 2002. *CA Cancer J Clin*, **55**, 74-108.

Phukan RK, Ali MS, Chetia CK, Mahanta J (2001). Betel nut and tobacco chewing; potential risk factors of cancer of oesophagus in Assam, India. *Br J Cancer*, **85**, 661-7.

Pike MC, Kolonel LN, Henderson BE, et al. (2002). Breast cancer in a multiethnic cohort in Hawaii and Los Angeles: risk factor-adjusted incidence in Japanese equals and in Hawaiians exceeds that in whites. *Cancer Epidemiol Biomarkers Prev*, **11**, 795-800.

Prinz C, Schwendy S, Voland P (2006). *H pylori* and gastric cancer: shifting the global burden. *World J Gastroenterol*, **12**, 5458-64.

Sato Y, Tsubono Y, Nakaya N, et al (2005). Fruit and vegetable consumption and risk of colorectal cancer in Japan: The Miyagi Cohort Study. *Public Health Nutr*, **8**, 309-14.

Sauvaget, C., Nagano, J., Hayashi, M., et al (2003). Vegetables and fruit intake and cancer mortality in the Hiroshima/Nagasaki Life Span Study. *Br J Cancer*, **88**, 689-94.

Schapiro L, Susanti I, Hulka J (1996). Cervical cancer screening in Bali: a public health issue. *Southeast Asian J Trop Med Public Health*, **27**, 487-93.

Seow A, Quah SR, Nyam D, et al (2002). Food groups and the risk of colorectal carcinoma in an Asian population. *Cancer*, **95**, 2390-6.

Shin A, Shin HR, Kang D, et al (2005). A nested case-control study of the association of Helicobacter pylori infection with gastric adenocarcinoma in Korea. *Br J Cancer*, **92**, 1273-5.

Sim, H. G.Cheng, C W (2005). Changing demography of prostate cancer in Asia. Eur J Cancer, 41, 834-45.

Sim, X., Ali, R. A., Wedren, S., et al. (2006). Ethnic differences in the time trend of female breast cancer incidence: Singapore, 1968-2002. *BMC Cancer*, **6**, 261.

Srivatanakul P, Sriplung H, Deerasamee S (2004). Epidemiology of liver cancer: an overview. *Asian Pac J Cancer Prev*, **5**, 118-25.

Stanford JL, Herrinton LJ, Schwartz SM, Weiss NS (1995). Breast cancer incidence in Asian migrants to the United States and their descendants. *Epidemiology*, **6**, 181-3.

Su FH, Chen JD, Cheng SH, et al (2007). Seroprevalence of hepatitis-B infection amongst Taiwanese university students 18 years following the commencement of a national hepatitis-B vaccination program. *J Med Virol*, **79**, 138-43.

Sun CL, Yuan JM, Koh WP, Yu MC (2006). Green tea, black tea and colorectal cancer risk: a meta-analysis of epidemiologic studies. *Carcinogenesis*, **27**, 1301-9.

Sunny L (2005). A low fat diet rich in fruits and vegetables may reduce the risk of developing prostate cancer. *Asian Pac J Cancer Prev*, **6**, 490-6.

Suzuki Y, Tsubono Y, Nakaya N, et al (2004). Green tea and the risk of breast cancer: pooled analysis of two prospective studies in Japan. *Br J Cancer*, **90**, 1361-3.

Tamakoshi K, Wakai K, Kojima M, et al (2004). A prospective study of reproductive and menstrual factors and colon cancer risk in Japanese women: findings from the JACC study. *Cancer Sci*, **95**, 602-7.

Tanaka K, Tsuji I, Wakai K, et al (2006). Cigarette smoking and liver cancer risk: an evaluation based on a systematic review of epidemiologic evidence among Japanese. *Jpn J Clin Oncol*, **36**, 445-56.

Thomas DB, Ray RM, Kuypers J, et al (2001). Human papillomaviruses and cervical cancer in Bangkok. III. The role of husbands and commercial sex workers. *Am J Epidemiol*, **153**, 740-8.

Toyomura K, Kono S (2002). Soybeans, soy foods, isoflavones and risk of colorectal cancer: a review of experimental and epidemiological data. *Asian Pac J Cancer Prev*, **3**, 125-32.

Tsai, J. F., Jeng, J. E., Ho, M. S., et al. (1997). Effect of hepatitis C and B virus infection on risk of hepatocellular carcinoma: a prospective study. Br J Cancer, 76, 968-74.

Tsubono Y, Nishino Y, Tsuji I, Hisamichi S (2000). Screening for gastric cancer in Miyagi, Japan: Evaluation with a population-based cancer registry. *Asian Pac J Cancer Prev*, **1**, 57-60.

Tsugane S (2005). Salt, salted food intake, and risk of gastric cancer: epidemiologic evidence. *Cancer Sci*, **96**, 1-6.

Tsugane S, Kabuto M, Imai H, et al (1993). *Helicobacter pylori*, dietary factors, and atrophic gastritis in five Japanese populations with different gastric cancer mortality. *Cancer Causes Control*, **4**, 297-305.

Tsugane S, Sasazuki S, Kobayashi M, Sasaki S (2004). Salt and salted food intake and subsequent risk of gastric cancer among middle-aged Japanese men and women. *Br J Cancer*,

90, 128-34.

Tsukuma H, Tanaka H, Ajiki W, Oshima A (2005). Liver cancer and its prevention. *Asian Pac J Cancer Prev*, **6**, 244-50.

Wakai K, Dillon DS, Ohno Y, et al (2000). Fat intake and breast cancer risk in an area where fat intake is low: a case-control study in Indonesia. *Int J Epidemiol*, **29**, 20-8.

Wakai K, Inoue M, Mizoue T, et al (2006). Tobacco smoking and lung cancer risk: an evaluation based on a systematic review of epidemiological evidence among the Japanese population. *Jpn J Clin Oncol*, **36**, 309-24.

Wang Z, Lubin JH, Wang L, et al (2002). Residential radon and lung cancer risk in a high-exposure area of Gansu Province, China. *Am J Epidemiol*, **155**, 554-64.

Wen W, Shu XO, Gao YT, et al (2006). Environmental tobacco smoke and mortality in Chinese women who have never smoked: prospective cohort study. *BMJ*, **333**, 376.

Wiwanitkit V (2006). Screening for cervical cancer, results from Thailand. *Asian Pac J Cancer Prev*, **7**, 329-30.

Wu-Williams AH, Dai XD, Blot W, et al (1990). Lung cancer among women in north-east China. *Br J Cancer*, **62**, 982-7.

Wu AH, Yang D, Pike MC (2000). A meta-analysis of soyfoods and risk of stomach cancer: the problem of potential confounders. *Cancer Epidemiol Biomarkers Prev*, **9**, 1051-8.

Wu AH, Yu MC, Tseng CC, Hankin J, Pike MC (2003). Green tea and risk of breast cancer in Asian Americans. *Int J Cancer*, **106**, 574-9.

Wu AH, Ziegler RG, Nomura AM, et al (1998). Soy intake and risk of breast cancer in Asians and Asian Americans. *Am J Clin Nutr*, **68**, 1437S-43S.

Wu IC, Lu CY, Kuo FC, et al (2006). Interaction between cigarette, alcohol and betel nut use on esophageal cancer risk in Taiwan. *Eur J Clin Invest*, **36**, 236-41.

Xu ZY, Blot WJ, Xiao HP, et al (1989). Smoking, air pollution, and the high rates of lung cancer in Shenyang, China. *J Natl Cancer Inst*, **81**, 1800-6.

Yamaguchi N, Mochizuki-Kobayashi Y, Utsunomiya O (2000). Quantitative relationship between cumulative cigarette consumption and lung cancer mortality in Japan. *Int J Epidemiol*, **29**, 963-8.

Yamamoto S, Sobue T, Kobayashi M, Sasaki S, Tsugane S (2003). Soy, isoflavones, and breast cancer risk in Japan. *J Natl Cancer Inst*, **95**, 906-13.

Yang BH, Parkin DM, Cai L, Zhang ZF (2004). Cancer burden and trends in the Asian Pacific Rim region. *Asian Pac J Cancer Prev*, **5**, 96-117.

Yiu HY, Whittemore AS, Shibata A (2004). Increasing colorectal cancer incidence rates in Japan. *Int J Cancer*, **109**, 777-81.

Yoo KY, Kang D, Park SK, et al. (2002). Epidemiology of breast cancer in Korea: occurrence, high-risk groups, and prevention. *J Korean Med Sci*, **17**, 1-6.

Yoo KY, Kim Y, Park SK, Kang D (2006). Lifestyle, genetic susceptibility and future trends of breast cancer in Korea. *Asian Pac J Cancer Prev*, **7**, 679-82.

Yoo KY, Tajima K, Inoue M, et al (1999). Reproductive factors related to the risk of colorectal cancer by subsite: a case-control analysis. *Br J Cancer*, **79**, 1901-6.

Yoo KY, Tajima K, Kuroishi T, et al (1992). Independent protective effect of lactation against breast cancer: a case-control study in Japan. *Am J Epidemiol*, **135**, 726-33.

Yu MW, Lien JP, Liaw YF, Chen CJ (1996). Effects of multiple risk factors for hepatocellular carcinoma on formation of aflatoxin B1-DNA adducts. *Cancer Epidemiol Biomarkers Prev*, **5**, 613-9.

Yuan JM, Wang QS, Ross RK, Henderson BE, Yu MC (1995). Diet and breast cancer in Shanghai and Tianjin, China. *Br J Cancer*, **71**, 1353-8.

Zhang M, Holman CD, Huang JP, Xie X (2007). Green tea and the prevention of breast cancer: a case-control study in southeast China. *Carcinogenesis*, **28**, 1074-78.

Zhang X, Reichart PA (2007). A review of betel quid chewing, oral cancer and precancer in Mainland China. *Oral Oncol*, **43**, 424-30.

Zhao FH, Forman MR, Belinson J, et al (2006). Risk factors for HPV infection and cervical cancer among unscreened women in a high-risk rural area of China. *Int J Cancer*, **118**, 442-8.

Zheng T, Duan L, Liu Y, et al (2000). Lactation reduces breast cancer risk in Shandong Province, China. *Am J Epidemiol*, **152**, 1129-35.

Ziegler RG, Hoover RN, Pike MC, et al (1993). Migration patterns and breast cancer risk in Asian-American women. *J Natl Cancer Inst*, **85**, 1819-27.