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Asian studies of cancer chemoprevention: latest clinical results

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Abstract

Chemoprevention trials in Asia, including those already completed and those now ongoing, are reviewed. Information was mainly collected from Japan, Korea and China. Each country features its own characteristics. Cancer chemoprevention trials targeting, from various aspects, hepatocellular carcinoma, gastric cancer and colon cancer have been, and are now being, conducted in Japan. Japan also has a long history of basic carcinogenesis research and carcinogenic research using animal experiments. In Korea, ginseng is the main focus of studies of chemopreventive agents. A large body of information has been collected and prospective studies are also ongoing. In China, the Linxian study, a cooperative study participated in by China and the NCI of the USA, is well known and the results impressive. However, we must exercise caution because, for example, the population of Linxian are chronically deficient in multiple vitamins and trace minerals. This situation may, therefore, differ from that observed in other countries. In any event, chemoprevention studies will be popular from an economical point of view even in Asia because cancer is becoming the number one cause of death in these countries.

Keywords: Cancer; Chemoprevention; Asia; Clinical trials

1. Introduction

Cancer has become the number one cause of death in Japan and some Asian countries since infectious diseases are now more or less under control [1]. Although diagnosis and treatment are the major strategies of controlling cancer, the importance of cancer chemoprevention has gradually emerged in the countries of Asia because (1) advanced cancer is difficult to cure; (2) the basic mechanism of cancer development is now known to result from an accumulation of genetic and epigenetic alterations in cells; (3) the modern concept of multistage carcinogenesis [2] and the classical concept of field cancerisation [3] has promoted the significance of cancer prevention as a new medical science [4]; (4) as in Western countries, the numbers of elderly persons are sharply increasing in Asian countries. This is primarily associated with the fact that cancer incidence increases with age and the life-expectancy of these populations is generally increasing; and (5) traditional Chinese medicine has come to be widely accepted in Asian countries, and as a philosophical concept, food and medicine are recognised as equally important in the prevention and treatment of disease. Few clinical trials are conducted in Asia for cancer chemoprevention, but Japan, China, Korea and other Asian nations have individual characteristics. Clinical trials for cancer chemoprevention previously conducted and those still ongoing will be reviewed.

1.1. Historical background of cancer chemoprevention in Japan

Cancer research in Japan covers all related fields from molecular biology to epidemiology, with a strong tradition in chemical carcinogenesis and carcinogen research ever since the first success by K. Yamagiwa [5] who induced skin cancer by repeated application of tar to the ears of rabbits in 1915. Since then, a large number of animal experiments have been conducted using many carcinogens to induce a whole variety of cancers. Research on primary cancer prevention, however, has been very limited in Japan. This is because secondary cancer prevention, i.e. cancer screening or early detection and early treatment, has been the main strategy against cancer supported by the government since it shifted its focus from one of a nationwide antituberculosis programme during and after World War II to an anticancer programme.

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The importance of primary cancer prevention has gradually come to be recognised amongst scientists; e.g. the necessity of giving up smoking has clearly been demonstrated. Moreover, the number of elderly people is increasing and cancer has been the leading cause of death since 1981 further emphasising the need for primary prevention [6].

The first meeting of the Japan Society for Cancer Chemoprevention (JSCP) was held in Sapporo in 1994 under the presidency of H. Kobayashi, of Hokkaido University. The JSCP membership has gradually expanded from 106 at the first meeting to 324 as of July 1999.

Traditionally, the main activities of JSCP are to inhibit cancer development in animal models whereas the real goal of the group is the prevention of cancer in humans. In fact, the number of epidemiological and intervention studies involving humans in Japan in 1998 was very limited compared with the USA. There are many difficulties involved in conducting large-scale human trials in Japan to prove the efficacy of certain chemopreventive procedures, such as funding, obtaining informed consent, the lack of infrastructures for large-scale trials, and so forth.

1.2. Clinical chemoprevention trials already completed in Japan

One study showed that after complete resection of hepatocellular carcinoma (HCC), the remaining recurrence rate in the liver was approximately 70% at 3 years post-surgery [7]. This is one of the most serious issues in controlling HCC, probably due to such sequential changes as active hepatitis, liver cirrhosis and HCC of the entire liver due to hepatitis C and/or B virus infection. Patients who have surgery and those suffering chronic active hepatitis are regarded as an extremely high-risk population and as ideal targets for chemoprevention trials. Several such studies have been conducted in Japan.

1.2.1. Adoptive immunotherapy for a reduction in post-surgical recurrence of HCC

We conducted a prospective randomised study to determine whether postsurgical adoptive immunotherapy can reduce the high rate of recurrences in the liver. Of 216 patients who underwent hepatectomy between 1992 and 1995, 155 (72%) patients fulfilled the eligibility criteria for histologically proven HCC, Child–Pugh class A or B and curative hepatic resection. These 155 patients were randomised into two groups who received immunotherapy or placebo. As adoptive immunotherapy, five infusions of autolymphocytes activated by anti-CD3 coated beads and IL-2 [8] were conducted over the 6 months postsurgery. The total number of lymphocytes infused per patients were on average 7.1×10^{10} and they were 85% cells CD3 positive; 25% CD4 positive; 89% CD8 positive and 74% HLADR positive. The primary end-point was recurrence-free survival and secondary end-points were incidence of recurrence, recurrence-free interval and overall survival. As of June, 1999, at a median follow-up of 4.5 years, recurrence-free survival in the immunotherapy group was 36%, whereas that in the control group was 22%. This was statistically significant ($P=0.01$) (data not shown).

1.2.2. Prevention of second primary tumours with an acyclic retinoid in patients with HCC

Muto and colleagues [9] proved the efficacy of the acyclic retinoid, polyprenoic acid (Fig. 1), to reduce the rate of recurrent and second primary hepatomas. Polyprenoic acid was known to inhibit hepatocarcinogenesis in the laboratory and induced differentiation and apoptosis in cell lines derived from human HCC. 89 patients who were free of disease after surgical resection or the percutaneous injection of ethanol were randomised to receive either polyprenoic acid 600 mg/day or a placebo for 12 months. Treatment with polyprenoic acid significantly reduced the incidence of recurrent or new HCC. After a median follow-up of 38 months, 27% of the treated group showed recurrence compared with 49% in the placebo group ($P=0.04$).

1.2.3. Randomised trial of effects of interferon-α on the incidence of hepatocellular carcinoma (HCC)

Nishiguchi and colleagues [10] proved the effectiveness of interferon-α (IFN-α) to reduce the incidence of HCC in patients with chronic active hepatitis C infection with cirrhosis. 90 patients were randomly allocated to receive IFN-α (6 MU three times weekly for 12–24 weeks) or symptomatic treatment, and were followed for 2–7 years. HCC was detected in 4% of IFN-α-treated patients and 38% of controls ($P=0.002$).

1.2.4. Interferon therapy reduces the risk of hepatocellular carcinoma: national surveillance programme of cirrhotic and non-cirrhotic patients with chronic hepatitis C in Japan

Yoshida and colleagues [11] proved the effectiveness IFN therapy to reduce the incidence of HCC, adjusting for risk factors such as the degree of liver fibrosis in a

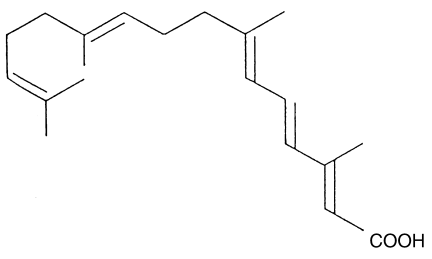

Fig. 1. Chemical structure of acyclic retinoid.

number of patients by retrospective analyses. Of 2890 patients with chronic hepatitis C who had undergone liver biopsies since 1986 and were the subjects of this study, 2400 (83.0%) received IFN and 490 (17.0%) were untreated. HCC developed in 89 IFN-treated patients (3.7%) and in 59 untreated patients (12.0%). The annual incidence of HCC among untreated patients increased with the degree of liver fibrosis, from 0.5% among patients with stage F0 or F1 fibrosis to 7.9% among patients with stage F2 fibrosis ($P=0.0128$) and stage F3 fibrosis ($P=0.0011$). IFN therapy thus, significantly reduced the risk for HCC, especially among virological or biochemical responders.

1.2.5. Prospective cohort study on the effects of drinking green tea on cancer development

Nakachi and Imai [12] conducted a prospective cohort study involving 8552 individuals of Yoshimi town in the Saitama Prefecture commencing in 1986. These persons were all over 40 years of age and answered 90 questions pertaining to their living habits and including their daily consumption of green tea. During the study, 153 men and 109 women died of cancer, and their deaths were analysed by age at death and daily consumption of green tea. Male patients who consumed more than 10 cups per day died 3.6 years later and female patients 7.8 years later than cancer patients drinking fewer than 3 cups per day. Most natives use a cup that holds approximately 180 ml of green tea, and will ingest 0.8–1.3 g green tea extract including 340–540 mg (−)epigallocatechin gallate (EGCG) in 10 cups per day [13] (Fig. 2).

1.2.6. Influence of drinking green tea on breast cancer

Nakachi and colleagues [14], in an analysis of 472 patients, found fewer recurrences of human breast cancer with increased consumption of green tea. Green tea consumption by patients was divided into two groups: fewer than or equal to 4 cups per day and equal to or more than 5 cups. In stage I and II breast cancer patients, a 16.7% recurrence rate was observed in the latter group and a 3.6-year longer disease-free period, than patients in the former group. Stage III cancer patients, however, did not show any significant difference. This suggests that green tea is more effective in the early stages of secondary tumour development.

Fujiki [15] reviewed the basic and clinical research on green tea from the standpoints of cancer chemoprevention.

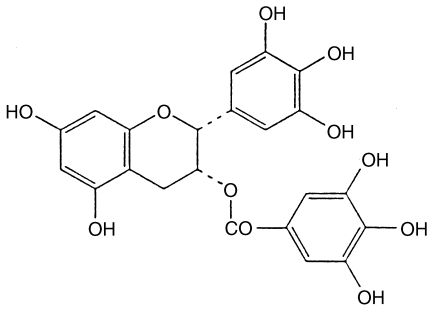

Fig. 2. Chemical structure of (−) epigallocatechin gallate (EGCG).

1.2.7. Prophylactic effect of Lactobacillus casei *on the recurrence of superficial bladder cancer*

A randomised, controlled trial (Study 1) [16] and a double-blind trial (Study 2) [17] were conducted with patients having superficial transitional cell carcinoma of the bladder to assess the prophylactic effect of a *Lactobacillus casei* preparation, Biolactis powder (BLP; 3 g/day p.o.), on tumour recurrence after transurethral resection. Study 1 enrolled 58 patients (eligible patients: BLP group; 23, placebo group; 25), and Study 2 enrolled 138 patients (eligible patients: BLP group; 61, placebo group; 64).

The two groups in Study 1 had comparable clinical characteristics, but their 50% recurrence-free interval after surgery was 1.8-fold longer in the placebo group than in the BLP group (350 versus 195 days, $P=0.03$, logrank test). In Study 2, the patients were stratified into 3 sub-groups by their tumour characteristics (A: multiple primary tumours, B: single recurrent tumours, C: multiple recurrent tumours). BLP treatment significantly prolonged the 50% recurrence-free interval in sub-groups A and B compared with the placebo group (5543 versus 688 days, $P=0.01$, Cox multivariate analysis), but had no significant effect in subgroup C. Also, downgrading of recurrent tumours from Grade 2 to Grade 1 was significantly more common with BLP treatment (Mantel–Haenzel test: $P<0.01$, Wilcoxon test: $P<0.001$). No adverse reactions were noted in Study 1, whilst mild reactions occurred in 3 patients from each of the BLP and placebo groups in Study 2.

These findings indicate that oral BLP is a safe and effective form of prophylaxis against the recurrence of superficial bladder cancer, especially in patients with moderate risk factors (e.g. subgroups A and B in Study 2).

1.3. Clinical chemoprevention trials now ongoing in Japan

1.3.1. Japan Interventional Trial of Helicobacter pylori *(JITHP study)*

Helicobacter pylori was first identified as living in the human stomach in 1983 by Warren and Marshall [18]. Since then, close correlation between *H. pylori* infection and the development of gastric or duodenal ulcers [19] and mucosa-associated lymphoid tissue (MALT) lymphoma [20] has been demonstrated. Naturally, the association of *H. pylori* infection with the progression of atrophic gastritis and the development of gastric cancer has strongly been suspected. Case–control studies [21–23]

indicated a high odds ratio for *H. pylori* infection and gastric cancer. Approximately 70% of Japanese older than 40 years are infected with *H. pylori*. However, the estimated number of gastric cancer patients in Japan in 1993 was 235 000, or only 0.4% of the *H. pylori* infected population. Consequently, to prove a causal relationship between *H. pylori* infection and gastric cancer development, an intervention trial is required. Since 1996, a JITHP study has been initiated involving 377 institutions scattered throughout Japan. In 1999, the number of institutions was selectively reduced to 104.

Eradication of *H. pylori* is conducted with a combination of lansoprazol 30 mg/day, clarithromycin 400 mg/day and amoxycillin 1500 mg/day for 7 days. We need 750 cases to test the effect of eradication on the progression of gastric mucosal atrophy, and 3500 cases to test the effect on the incidence of gastric cancer. We are presently undergoing difficulty in recruiting enough cases for this study.

1.3.2. Interventional trial for colorectal tumours in Osaka

Patients with multiple colorectal tumours were, after complete endoscopic removal of the tumours, randomised into two groups, i.e. a dietary guidance-only group to restrict energy intake from oil and fat to 18–22% of total calories, and a group combining dietary guidance with consumption of wheat bran biscuits. Daily, patients were given 25 g of biscuits in three divided doses, representing 7.5 g/day of wheat bran. This study was aimed at testing the preventive effect of dietary fibre on colorectal tumours. The main endpoints are the recurrence rate of colorectal tumours after 4 years. The recruitment of subjects was begun in 1993 and completed in 1997. A total of 115 patients in Group 1 and 116 patients in Group 2 are being followed up, and the trial will be completed in September 2001. (H. Ishikawa, Osaka Medical Center for Cancer and Cardiovascular Disease.)

1.3.3. Japan Familial Adenomatous Polyposis Prevention Study (J-FAPP Study)

The J-FAPP Study has just been begun for patients with familial adenomatous polyposis to test the effects of wheat bran biscuits and green tea extracts. Regimen 1 is lifestyle modification + non-functional tablets, regimen 2 is lifestyle modification + wheat bran biscuits + non-functional tablets, regimen 3 is lifestyle modification + green tea extract tablets and regimen 4 is life style modification + wheat bran biscuits + green tea extract tablets. The lifestyle modification consists of dietary guidance to restrict energy intake from oil and fat to 18–22% of total energy intake. The biscuits represent 7.5 g/day wheat bran and the green tea tablets consist of 1.0 g of green tea extract. The main endpoints of this study are the number and size of colorectal polyps after 2 years. The targeted total number of patients is 300, i.e. 75 for each regimen. This trial will be completed in March 2003. (H. Ishikawa, Osaka Medical Center for Cancer and Cardiovascular Disease.)

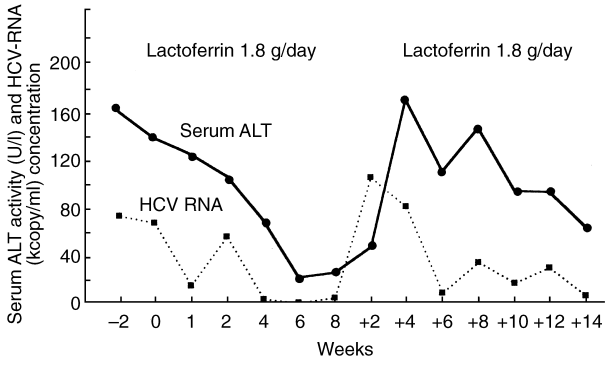

Fig. 3. Oral intake of lactoferrin inhibits hepatitis C virus (HCV) viraemia in chronic hepatitis C [24].

1.3.4. Chemopreventive effect of lactoferrin on Hepatitis C virus (HCV) control in patients with chronic active hepatitis C

Lactoferrin, an 80 KDa siderophilic protein rich in colostrum, is known to have antimicrobial properties [26]. As is shown in Fig. 3, lactoferrin inhibits HCV viraemia in patients with chronic hepatitis C infection [24]. Phase I clinical trials have begun at National Cancer Center Hospital Yokohama City University to determine lactoferrin dosages. (S. Okada, National Cancer Center Hospital, Tokyo.)

1.4. Chemoprevention trials in Korea

As early as 1978, Korean investigators carried out extensive long-term anticarcinogenicity experiments using a mouse lung tumour model and observed an anticarcinogenic effect of Panax ginseng C. A. Meyer extract in 1980 [25]. Ginseng saponin comprises triterpenoidal glycosides of the dammar type with glucose, arabinose, xylose or rhamnose; the ginsenosides-Rx were recognised as the active components in 1965 [26] (Fig. 4). There are several clinical trials already completed or still ongoing in Korea to study the effect of various kinds of ginseng.

1.4.1. Case–control studies on ginseng intake

The effect of ginseng consumption on the risk of cancer was investigated by interviewing 905 pairs of cases and controls matched for age, sex and date of admission to the Korea Cancer Center Hospital in Seoul [27]. Of the 905 cases, 562 (62%) had a history of ginseng intake, compared with 674 of the controls (74%), a statistically significant difference ($P < 0.01$). The odds ratio

(OR) of cancer in terms of ginseng ingestion was 0.56 (95% confidence interval, 0.45–0.69).

Yun and colleagues [28] increased the number of individuals for a case–control study to 1987 pairs to further investigate (1) the types of ginseng products that have the most potent cancer prevention effect; (2) the reproducibility of the dose–response relationship; (3) the duration of ginseng consumption; (4) the types of cancer effectively prevented by ginseng; and (5) the effects of ginseng on cancers associated with smoking. In this study, ginseng users had a lower risk (OR, 0.50) of cancer than non-users. With respect to the type of ginseng, ORs for cancer were 0.37 for fresh ginseng extract users, 0.57 for white ginseng extract users, 0.30 for white ginseng powder users and 0.20 for red ginseng users. The risk decreased with increased frequency and duration of ginseng intake indicating a dose–response relationship. With respect to the type of cancer, ORs were 0.47 for cancers of the lip, oral cavity and pharynx, 0.20 for oesophageal cancer, 0.36 for stomach cancer, 0.42 for colorectal cancer, 0.48 for liver cancer, 0.22 for pancreatic cancer, 0.18 for laryngeal cancer, 0.55 for lung cancer, 0.15 for ovarian cancer and 0.48 for other types of cancers. In cancers of the female breast, uterine cervix, urinary bladder and thyroid gland, no association with ginseng intake was observed.

1.4.2. Cohort study on ginseng intake

Yun and colleagues [29] then performed a cohort study between 1987 and 1992 in a ginseng cultivation area, Kangwha-eup. They studied 4634 adults aged over 40 years who completed a questionnaire on ginseng

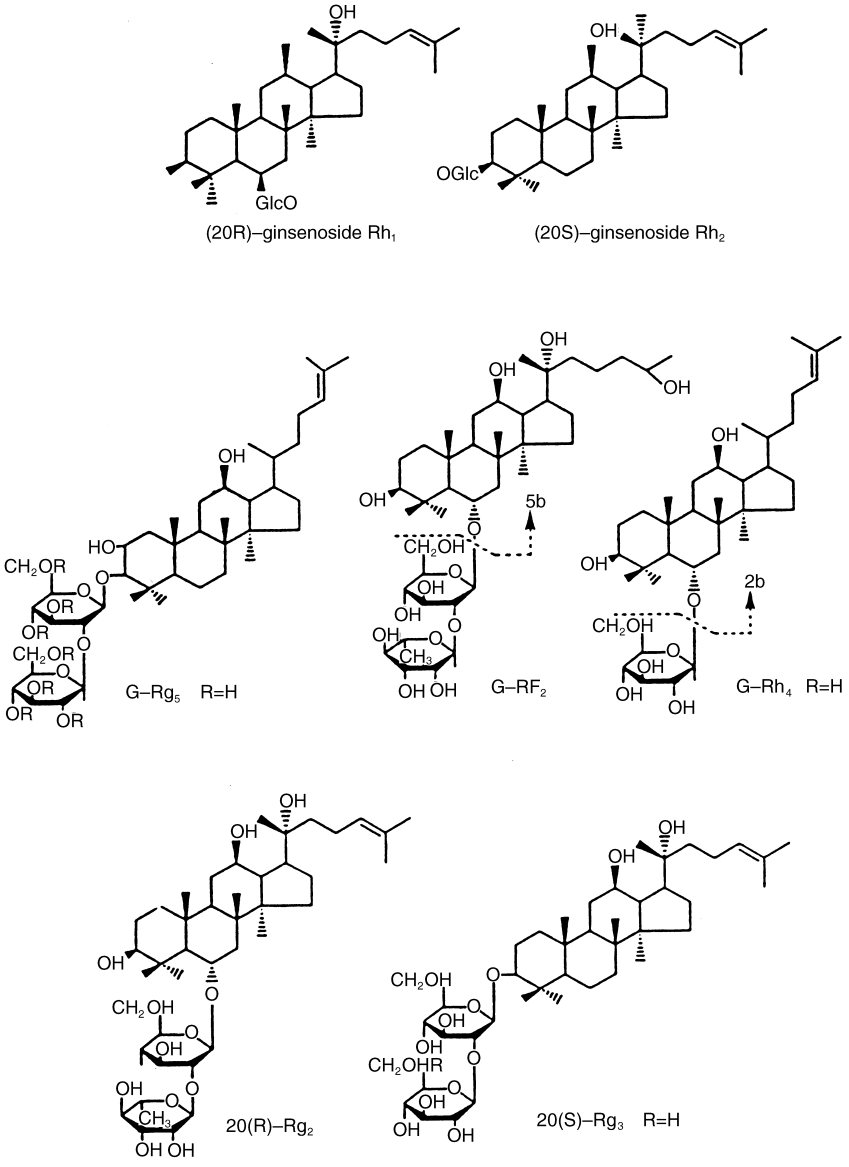

Fig. 4. Chemical structure of the active components of ginseng [30].

intake. Among 355 (7.7%) total deaths during the study, cancer accounted for 79 (22.3%). There were 3267 (70.5%) ginseng users among the 4634 individuals eligible for the analysis. Users had a decreased risk (RR = 0.40) compared with non-users. By type of ginseng, RR was 0.31 for fresh ginseng extract users and 0.34 for users of multiple combinations. No cancer deaths were observed among 24 users of red ginseng. Again, a dose–response relationship was recognised.

1.4.3. Ongoing clinical trials on ginseng

Two trials are being conducted by the Korea Complementary and Alternative Medicine Institute, Seoul, and the Cancer Institute of Zhejiang Medical University, China, to examine the effect of Korean red ginseng extract (once a week for 3 years) administration on cancer incidence. Each research group has been performing a double-blind, placebo-controlled trial including rectal and gastric cancers. To date, 560 patients have been registered [30].

1.5. Chemoprevention trials in China

1.5.1. Linxian study of oesophageal/gastric cardia cancers

A cooperative study by the Cancer Institute of the Chinese Academy of Medical Sciences and the National Cancer Institute, USA was conducted among the high-risk population of Linxian, China to investigate the effect of daily multiple micronutrients on incidence and mortality rates for oesophageal/gastric cardia cancers and on the prevalence of histological dysplasia. The general population trial included more than 30 000 inhabitants of Linxian who received one of four combinations of vitamins/minerals daily for 5 years. Results indicated a 9% reduction in deaths from all causes and a 13% reduction in cancer mortality for people who received a β-carotene/vitamin E/selenium combination, mainly due to a 21% decrease in stomach cancer mortality [31].

1.5.2. Linxian study of oesophageal dysplasia

This trial included 3318 inhabitants with histological evidence of severe oesophageal dysplasia who received either a placebo or a daily supplement containing 14 vitamins and 12 minerals for 6 years. People receiving supplementation with micronutrients showed reduced mortality of 8% in all causes, oesophageal cancer (16%) and stomach cancer (18%) compared with the placebo group. After 30 and 72 months of intervention, endoscopic surveys found a reduced risk of 16 and 14%, respectively, for combined lesions of oesophageal or gastric cancer or dysplasia. People receiving supplementation were 1.2 times as likely to have no dysplasia at 30 and 72 months of intervention compared with subjects receiving the placebo [32].

1.5.3. The third joint trial of the Chinese Academy of Medical Sciences and NCI, USA

This study began in 1995 to treat *H. pylori* in 3411 individuals with gastric dysplasia or precancerous lesions in Linque County, Shanfond Province, by applying amoxicillin and omeprazole or by giving capsules containing vitamins C and E and selenium. A third group was given steam-distilled garlic oil and Kyolic aged garlic extract. Initial data from pill counts, and sampled blood levels of vitamin C, E and S-allylcysteine indicate excellent compliance. This study is still ongoing [33].

1.5.4. The fourth trial on oltipraz

This study began in 1995, recruiting 234 people in Quidong County, to test the effect of oltipraz and placebo [34]. They were selected from 2815 polypectomised patients in Hanghou, Zhejiang Province, and another 560 patients diagnosed with chronic atrophic gastritis in the Second Zhejiang Medical University Hospital to determine whether intervention can reduce the incidence of cancer.

1.6. Chemoprevention trials in other Asian countries

Cancers in the oral cavity in association with betel chewing are well known in Sri Lanka and other southern Asia countries. H. Kobayashi's group is preparing for an intervention trial in Sri Lanka by changing betel chewing to chewing gum. In Thailand, various studies to control the hepatitis B virus by vaccination [35], immunoprophylaxis in neonates at risk [36] and blood donors [37], for example, have been conducted.

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