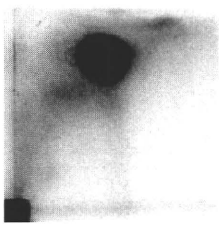
人情報は調査以外の目的には用いないことする。組換えDNA実験を行う場合には、各班員の所属する研究機関の委員会の許可を得たのち規定に従い実施する。また、本研究では、変異原物質や発がん性が予想される化合物を扱うことから、それらによる環境汚染を起こさないよう、取扱いに十分注意して実験を行う。

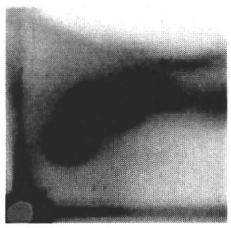
C. 研究結果

①$^{32}$P-ポストラベル法による解析の結果、NIANとdCおよびdGとの反応により、それぞれ、1個および3個のスポットが確認され、付加体が生成されていることが示唆された(図1)。次に、NIANとdCの反応により生成する付加体の化学構造を解析するため、NIANとdCの反応混液中に観察された新規物質に相当するピークをHPLCで分離・精製し、NMR等の機器分析を行なった。その結果、主な反応精製物として、dCの脱アミノ化物質であるdUが形成していることがわかった。尚、現在その他の付加体に関して、引き続き構造解析を行なう予定である。

図1



3'-dCp+ NIAN



3'-dGp+ NIAN

②日本国内における粉塵の濃度と変異原性についても測定した結果、平均値で見た場合、全国的に春期に粉塵濃度が最も高く、変異原性は冬期に最も高く次いで春期が高かった。また、粉塵濃度および変異原性が高い日にちは、後方流跡線解析により中国大陸からの気塊が日本国内に流入している傾向があることがわかった。現在、更にサンプル数を増やして解析を行なっている。また、粉塵中の芳香族炭化水素化合物等の定量についても試みる予定である。

D. 考察

胃がんは、中国、日本等のアジア地域に共通して高い罹患率を示す。白菜等のアブラナ科の野菜にはIAN等のインドール化合物を多く含み、日本のみならず中国においても頻繁に摂取されていると思われ、これらのインドール化合物がアジア地域における胃発がんに関わっている可能性が示唆された。また、1-NP等の芳香族炭化水素化合物は、両国民が共通して曝露している環境発がん物質である。これら化合物はヒトの肺がんを始めとする様々なヒトのがんへの関与が示唆されているものであり、今後は、これら化合物の曝露レベルの評価およびヒト発がんへの関与に関して日中間で研究の連携を進めることが必要だと思われる。

E. 結論

日本と中国に共通した環境発がん物質のヒト発がんへの関与に関して研究連携を進めることが必要である。

F. 健康危険情報

なし

G. 研究発表

論文発表

1) Murakami, Y., Imai, N., Miura, T., Sugimura, T., Wakabayashi, K., Totsuka, Y., Hada, N., Yokoyama, Y., Suzuki, H., Mitsunaga K., Chemical confirmation of the structure of a mutagenic aminophenylnorharman,9-(4'-aminophenyl)-9H-pyrido[3,4-b]indole: an authentic synthesis of 9-(4'-nitrophenyl)-9H-pyrido[3,4-b]indole as its relay

compound. Heterocycles, 80; 455-462, 2010.

2) Wei M, Totsuka Y, et al., Low-dose carcinogenicity of 2-amino-3-methylimidazo[4,5-f]quinoline in rats: Evidence for the existence of no-effect levels and a mechanism involving p21(Cip□/□WAF1). Cancer Sci. 102: 88-94, 2011.

3) Matsubara S, Takasu S, Tsukamoto T, Mutoh M, Masuda S, Sugimura T, Wakabayashi K, Totsuka Y., Induction of Glandular Stomach Cancers in Helicobacter pylori-infected Mongolian Gerbils by 1-Nitrosoindole-3-acetonitrile., Int J Cancer, 2011 in press.

4) Totsuka Y, Kato T, Masuda S, Ishino K, Matsumoto Y, Goto S, Kawanishi M, Yagi T, Wakabayashi K., In vitro and in vivo genotoxicity induced by fullerene (C60) and kaolin. Genes Environ., 33: 14-20, 2011.

H. 知的財産権の出願・登録状況

なし

# 研究成果の刊行に関する一覧表

雑誌

| 発表者氏名 | 論文タイトル名 | 発表誌名 | 巻号 | ページ | 出版年 |
|---|---|---|---|---|---|
| Sasako M, Inoue M, et al. | Gastric Cancer Working Group report. | Jpn J Clin Oncol | 40 Suppl 1 | i28-37 | 2010 |
| Sobue T, Inoue M, et al. | Cancer Registry and Epidemiological Study Working Group report. | Jpn J Clin Oncol | 40 Suppl 1 | 76-81 | 2010 |
| Matsuda T, Sobue T, et al. | Cancer incidence and incidence rates in Japan in 2005: based on data from 12 population-based cancer registries in the Monitoring of Cancer Incidence in Japan (MCIJ) project. | Jpn J Clin Oncol | 41(1) | 139-47 | 2011 |
| Matsuda T, Sobue T, et al. | Population-based survival of cancer patients diagnosed between 1993 and 1999 in Japan: a chronological and international comparative study | Jpn J Clin Oncol | 41(1) | 40-51 | 2011 |
| Matsuda T, Sobue T, et al. | Cancer incidence and incidence rates in Japan in 2004: based on data from 14 population-based cancer registries in the Monitoring of Cancer Incidence in Japan (MCIJ) Project. | Jpn J Clin Oncol | 40(12) | 1192-200 | 2010 |
| Matsuda T, Sobue T, et al. | Do the Japanese feel more suspicious about cancer registration than the British? | Cancer Epidemiol | 34(2) | 122-30 | 2010 |
| Shin HR, Sobue T, et al. | Recent trends and patterns in breast cancer incidence among Eastern and Southeastern Asian women. | Cancer Causes Control | 21(11) | 1777-85 | 2010 |
| Shin HR, Sobue T, et al. | Secular trends in breast cancer mortality in five East Asian populations: Hong Kong, Japan, Korea, Singapore and Taiwan. | Cancer Sci | 101(5) | 1241-6 | 2010 |
| Ito H, Sobue T, et al. | Nonfilter and filter cigarette consumption and the incidence of lung cancer by histological type in Japan and the United States: Analysis of 30-year data from population-based cancer registries. | Int J Cancer | 128(8) | 1918-28 | 2010 |
| Moore MA, Sobue T. | Strategies for cancer control on an organ-site basis. Asian Pac J Cancer Prev | Asian Pac J Cancer Prev | Suppl 2 | 149-64 | 2010 |
| Long N, Sobue T, et al. | Cancer epidemiology and control in north-East Asia - past, present and future. | Asian Pac J Cancer Prev | Suppl 2 | 107-48 | 2010 |
| 祖父江友孝 | がん登録の進歩 | 腫瘍内科 | 7(1) | 56-61 | 2011 |
| 祖父江友孝 | 臨床家にとっての地域がん登録の意義、今後の展望 | 外科治療 | 102 | 346-352 | 2010 |

| 発表者氏名 | 論文タイトル名 | 発表誌名 | 巻号 | ページ | 出版年 |
|---|---|---|---|---|---|
| Tamakoshi A, Lin Y, et al. | Impact of smoking and other lifestyle factors on life expectancy among Japanese: findings from the Japan Collaborative Cohort (JACC) Study. | J Epidemiol | 20 | 370-376 | 2010 |
| Lin Y, et al. | An overview of genetic polymorphisms and pancreatic cancer risk in molecular epidemiologic studies. | J Epidemiol | 21 | 2-12 | 2011 |
| Tamakoshi A, Lin Y, et al. | Relationship of sFas with metabolic risk factors and their clusters. | Eur J Clin Invest | 40 | 527-533 | 2010 |
| Yorozuya K, Lin Y, et al. | Evaluation of Oncotype DX Recurrence Score as a prognostic factor in Japanese women with estrogen receptor-positive, node-negative primary Stage I or IIA breast cancer. | J Cancer Res Clin Oncol | 136 | 939-944 | 2010 |
| Tamakoshi A, Lin Y, et al. | BMI and all-cause mortality among Japanese older adults: findings from the Japan collaborative cohort study. | Obesity | 18 | 362-369 | 2010 |
| 田中政宏、他 | 世界の大腸癌の罹患・死亡の動向 | 大腸癌 FRONTIER | 3 | 26-34 | 2010 |
| Tanaka M, Inoue M, et al. | Hepatitis B and C virus infection and hepatocellular carcinoma in China: Review on the epidemiology and control measures. | J Epidemiol | | In press | 2011 |
| Tanaka M, et al. | Trends of stomach cancer mortality in Eastern Asia in 1950-2004 : Comparative study of Japan, Hong Kong and Singapore using age, period and cohort analysis. | Int J Cancer | | In press | 2011 |
| Murakami Y, Totsuka Y, et al. | Chemical confirmation of the structure of a mutagenic aminophenylnorharman,9-(4'-aminophenyl)-9H-pyrido[3,4-b]indole: an authentic synthesis of 9-(4'-nitrophenyl)-9H-pyrido[3,4-b]indole as its relay compound. | Heterocycles | 80 | 455-462 | 2010 |
| Wei M, Totsuka Y, et al. | Low-dose carcinogenicity of 2-amino-3-methylimidazo[4,5-f]quinoline in rats: Evidence for the existence of no-effect levels and a mechanism involving $p21^{Cip/WAF1}$. | Cancer Sci | 102 | 88-94 | 2011 |
| Matsubara S, Totsuka Y, et al. | Induction of Glandular Stomach Cancers in Helicobacter pylori-infected Mongolian Gerbils by 1-Nitrosoindole-3-acetonitrile. | Int J Cancer | | In press | 2011 |
| Totsuka Y, et al. | In vitro and in vivo genotoxicity induced by fullerene (C60) and kaolin. | Genes Environ | 33 | 14-20 | 2011 |

JJCO Japanese Journal of Clinical Oncology

*Jpn J Clin Oncol 2010;40(Supplement 1)i28–i37*
*doi:10.1093/jjco/hyq124*

# Gastric Cancer Working Group Report

**Mitsuru Sasako[1,*], Manami Inoue[2], Jaw-Town Lin[3], Christopher Khor[4], Han-Kwang Yang[5] and Atsushi Ohtsu[6]**

[1]Upper GI Surgery Division, Department of Surgery, Hyogo College of Medicine, Hyogo, [2]Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan, [3]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan, [4]Gastroenterology and Hepatology, Singapore National University Hospital, Pulau Bukom, Singapore, [5]Department of Surgery, Seoul National University Hospital, Seoul, Republic of Korea and [6]Research Center for Innovative Oncology, National Cancer Center, Chiba, Japan

*For reprints and all correspondence: Mitsuru Sasako, Upper GI Surgery Division, Department of Surgery, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo 663-8501, Japan. E-mail: msasako@hyo-med.ac.jp

**Epidemiology:** Gastric cancer is the second most common cancer in Asia, more than half of the world's gastric cancer cases arise in Eastern Asia, and the majority of Asia's cases still occur in the distal part of the stomach.
**Etiology and Prevention:** The etiology of gastric cancer consists of genetic susceptibility, *Helicobacter pylori* infection and environmental risk factors. *Helicobacter pylori* eradication treatment, consumption of fresh vegetables and fruits and use of aspirin and non-steroidal anti-inflammatory drugs seem to reduce the risk of gastric cancer.
**Endoscopy and Diagnosis:** Screening for gastric cancer is cost-effective in countries with high incidence. Risk stratification may increase the cost-effectiveness of screening in populations at moderate risk. Endoscopic resection is curative in a subset of patients with early cancer.
**Surgery and Adjuvant Treatment:** R0 resection with D2 lymph node dissection has produced the best survival data. Some kind of post-operative adjuvant chemotherapy including S-1 is recommended after D2 surgery.
**Chemotherapy for Advanced Gastric Cancer:** As chemotherapy for gastric cancer, fluoropyrimidines plus platinum are the most widely accepted first-line regimens, whereas taxanes or irinotecan are mostly used in second- and third-line settings. Differences in the approval and medical insurance systems may influence the status of these regimens. Trastuzumab in combination with fluoropyrimidines/platinum will be a standard regimen for HER2-positive gastric cancer. Many new targeting agents are currently under investigation, and Asian countries are playing important roles in investigation and development of new and better treatments for this malignancy.

*Key words: gastric cancer – Helicobacter pylori – D2 lymphadenectomy – adjuvant chemotherapy – endoscopic treatment – chemotherapy*



The Gastric Cancer Working Group report was divided into five chapters: epidemiology, etiology and prevention, endoscopy and diagnosis, surgery and adjuvant treatment and chemotherapy for advanced gastric cancer.

## EPIDEMIOLOGY

In spite of the remarkable spontaneous decline in the incidence of stomach cancer in most Western countries, in Asia it is still one of the two most common cancers, following only lung cancer and accounting for 13% of all cancers in Asia (Fig. 1) (1). Estimation of the distribution of gastric cancer in the world in 2002 showed that 56%, more than half of all new cases in the world, occurred in Eastern Asia, with 41% from China and 11% from Japan (Fig. 2) (1). The highest incidences occurred in Korea and Japan. Gastric cancer is relatively common in Asia, Eastern Asia, other Asia, South America and Central and Eastern Europe, whereas it is rare in other European areas and Northern America (Fig. 3) (1). In the common areas, including Eastern Asia, cancer of the distal part of the organ is still the

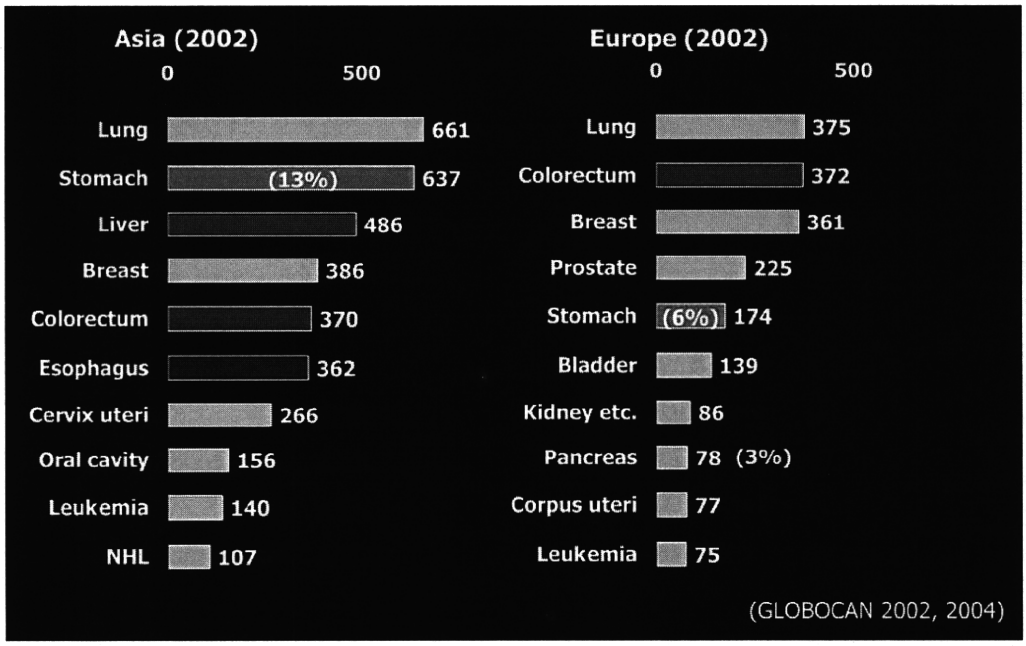



**Figure 1.** Number of new cases for 10 common cancers (both sexes).

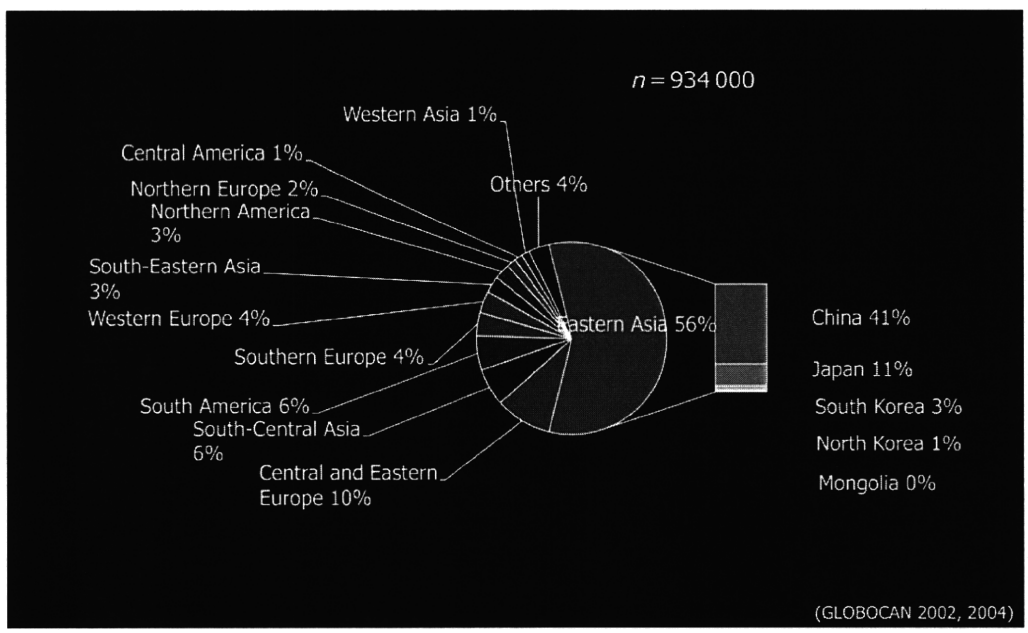



**Figure 2.** Estimated distribution of gastric cancer in the world in 2002.

most frequent, whereas the proximal gastric cancer is more common in Western countries (Fig. 4) (2).

In conclusion, gastric cancer is the second most common cancer in Asia, more than half of the world's gastric cancer cases still arise in Eastern Asia, and the majority of those cases still occur in the distal part of the stomach. An increased trend for EC-junction adenocarcinoma is suggested in Western countries, but there is no evidence of such a trend in Asia.

## ETIOLOGY AND PREVENTION

Three major factors are involved in the development of gastric cancer: *Helicobacter pylori* infection, genetic

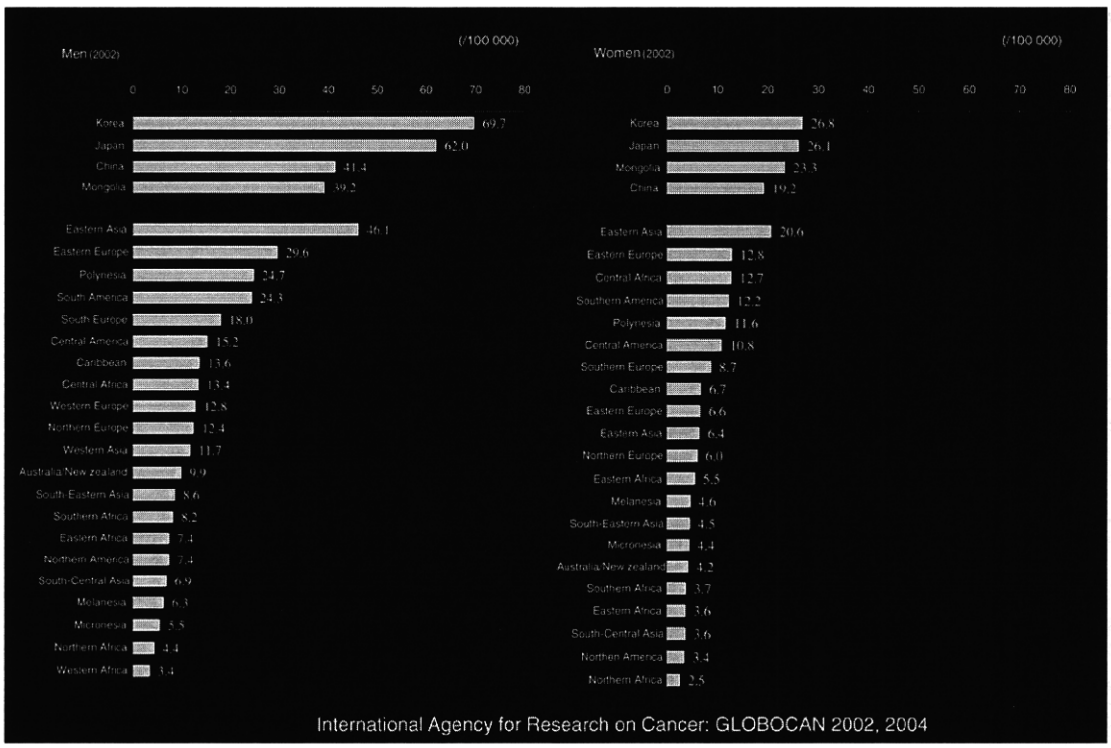



**Figure 3.** Age-standardized incidence rate of gastric cancer in various area of the world (2002 estimate).

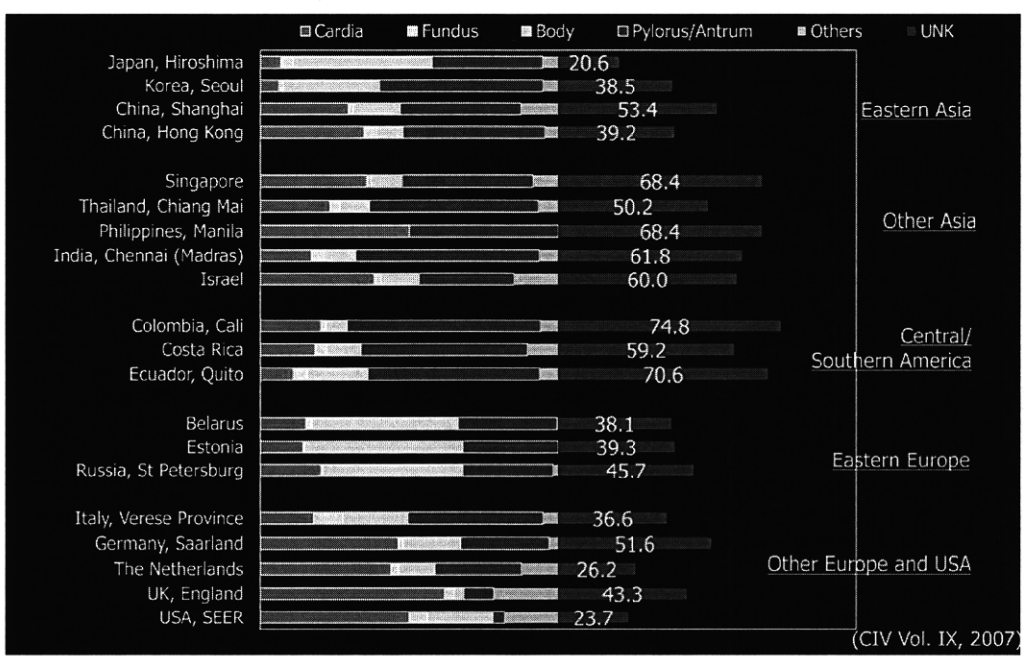



**Figure 4.** Subsite distribution of gastric cancer, 2000.

susceptibility (CDH1 etc.) and environmental factors (such as smoking, a high-salt diet and low vegetable consumption) (3). *Helicobacter pylori* infection is the most important. A study by Dr Uemura et al. (4), published in the *New England Journal of Medicine*, found no development of gastric cancer in cases without *H. pylori* infection, whereas

2.9% of 1246 cases with *H. pylori* infection developed gastric cancer over a period of 7.8 years. A randomized controlled study in China also showed that *H. pylori* eradication was more effective in patients without atrophic gastritis than those with it (5). Dr Fukase in Japan reported that in a randomized controlled study comparing eradication of *H. pylori* with no eradication after endoscopic mucosal resection (EMR) of early gastric cancer at the 3-year follow-up point significantly reduced the number ( 9 versus 24) of metachronous gastric cancer developed in the eradication group compared with the control group. It was concluded that prophylactic eradication of *H. pylori* after EMR for early gastric cancer should be performed to prevent the development of metachronous gastric cancers (Fig. 5) (6). These results suggested that it was never too late to eradicate *H. pylori* for prevention of gastric cancer. An Italian group performed a meta-analysis of the published data regarding whether *H. pylori* eradication treatment can reduce the risk of gastric cancer. It was concluded that 1.1% of treated patients would develop gastric cancer, in contrast to 1.7% of untreated patients. In six studies with about 6700 participants followed for 4–10 years, the relative risk was 0.65, and it was concluded that *H. pylori* eradication treatment seemed to reduce gastric cancer (7). In Taiwan, a nationwide cohort study followed 80 000 patients with *H. pylori*-infected peptic ulcers for 10 years. These patients were divided into early- and late-eradication cohorts. It was concluded that early *H. pylori* eradication showed no significant difference in the gastric cancer risk compared with the general population, but late eradication was associated with an increased risk of gastric cancer. Older age, male gender, gastric ulcer, no regular NSAIDs use and late *H. pylori* eradication represented independent risk factors for gastric cancer development (Fig. 6) (8).

Fock et al. concluded that fruits and vegetables are associated with a reduced risk of gastric cancer in his paper in the *Journal of Gastroenterology and Hepatology*. Supplementation of vitamins and minerals may be unnecessary, at least in healthy subjects with no nutritional deficiencies (9). In a meta-analysis study, all studies proved that both aspirin and NSAIDs are useful for preventing cardia and non-cardia gastric cancer (10). There is insufficient evidence for any benefit from green tea, vitamins and antioxidants. The biological behaviors of distal and proximal gastric cancers are quite different, but the prevention regimens have been the same, centered on eradication of *H. pylori* infection.

The Working Group concluded that the etiology of gastric cancer consists of genetic susceptibility, *H. pylori* infection and environmental risk factors. *Helicobacter pylori* eradication treatment, consumption of fresh vegetables and fruits and use of aspirin and NSAIDs (11) seem to reduce the risk of gastric cancer.

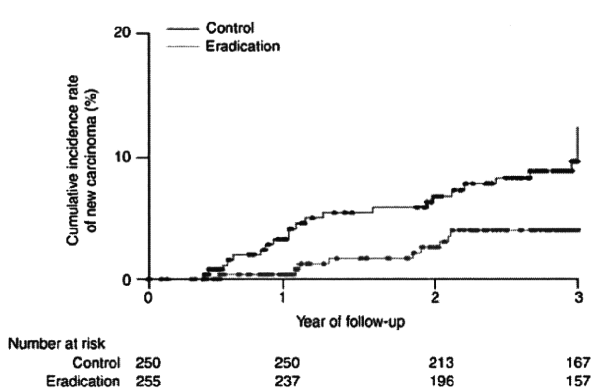



**Figure 5.** Kaplan–Meier analysis of the cumulative incidence rate of new carcinoma. Source: Fukase et al. (6).

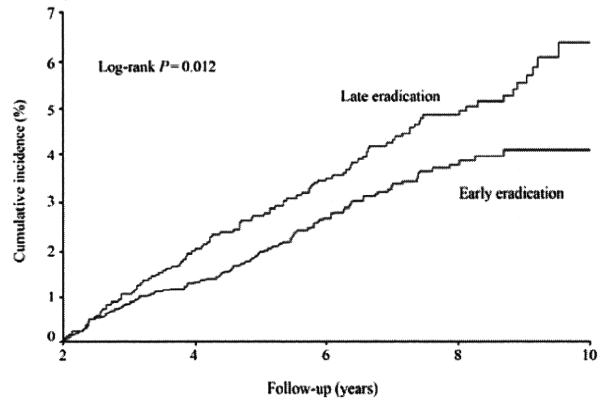



**Figure 6.** Cumulative incidence of gastric cancer in two groups, early eradication and late eradication groups. Source: Wu et al. (8).

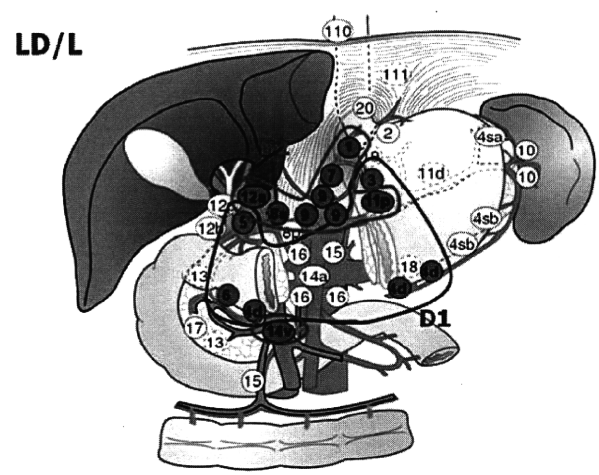



**Figure 7.** Regional lymph node group according to the location of tumor. Source: Sasako et al. (21) and Yoon and Yang (22).

## ENDOSCOPY AND DIAGNOSIS

Experience in Japan has shown that access to screening and early endoscopy increased the proportion of early-stage

gastric cancers, leading to improved survival (12). Cost is a major barrier to screening. Screening is considered to be cost-effective in high-incidence countries, but perhaps not where the incidence of gastric cancer is moderate or low. Risk stratification may help to focus limited resources on patients at greatest risk, and thereby increase the cost-effectiveness of screening (13). Serum pepsinogen-based tests may help to identify a subset of patients with atrophic gastritis, who are especially at a high risk. In a country with high incidence of gastric cancer, such as Japan, it is still very cost-effective to screen even if the cost of endoscopy is high. Singapore and some other countries in East Asia have a moderate incidence of gastric cancer, and screening these populations could be cost-effective if the cost were moderate (13). In Japan, the government-supported screening program has been based on barium, and although very successful, it accounts for less than 10% of all cancers that are diagnosed by screening. Most are detected due to early or easy access to endoscopy, either through outpatient clinics or through health screening outside of the government's screening program (14).

High-quality endoscopy is important and may be facilitated by endoscope preparation, such as lens cleaning, and by patient preparation ahead of endoscopy by the use of defoaming agents, mucolytics and antispasmodics, which make the field of interest much clearer. Techniques such as adequate air insufflation, systematic examination of the entire stomach, use of contrast agents, image enhancement and cognitive training may also help improve yield rates.

Accurate specimen collection and recording of endoscopic findings are important. There is some discordance between Western- and Japanese-trained pathologists in the biopsy definition of early gastric cancer. In the West, the gold standard for diagnosing cancer is to detect invasion of tumor cells into the lamina propria, muscularis mucosae or submucosal layer, whereas in Japan, it is more important to detect cellular atypia or structural atypia, regardless of invasion, when making a diagnosis of cancer. The revised Vienna classification has helped resolve some of these differences and may be a good starting point for consensus between Western and Japanese pathologists (15).

Gotoda et al. (16) reported that there is a clearly defined subgroup of patients with early gastric cancer that has a virtually negligible risk of nodal metastasis. Such patients could be treated definitively by local resection, with the expected long-term outcome equivalent to radical surgery. Further development led to the expanded criteria for endoscopic therapy of early gastric cancer, with *en bloc* resection being the primary goal (17). Endoscopic resection can be considered curative if the lesion shows differentiated histopathology, is limited to the mucosal layer or $<500$ μm submucosal invasion, with clear vertical and lateral margins, and no lymphovascular involvement. EMR has the advantages of short procedure time and low risk of perforation, which make it an attractive option for small lesions. EMR for differentiated, non-ulcerated early cancer $<20$ mm in diameter is associated with an excellent 10-year survival rate of 99% (18). Endoscopic submucosal dissection (ESD) is associated with a lower local recurrence rate than EMR because the technique permits *en bloc* resection without size limitation. Procedure times for ESD are longer, however, with higher delayed bleeding and perforation risk (19). A recent long-term follow-up study showed that ESD for early gastric cancer, which met the expanded criteria, resulted in 5-year overall and disease-specific survival rates of 97% and 100%, respectively (20). Training opportunities in ESD for endoscopists from outside Japan and Korea, however, remain limited.

In conclusion, screening for gastric cancer is cost-effective in countries with high incidence. Risk stratification may increase the cost-effectiveness of screening in populations at moderate risk. Barium meal-based screening is government-funded in Japan, but is less accurate than gastroscopy. Gastroscopic screening is desirable in high-risk populations. High-quality endoscopy may increase diagnostic yield in early cancer. Endoscopic resection is curative in a subset of patients with early cancer as defined by the expanded criteria. EMR has shown long-term outcomes comparable with surgery in patients with small lesions, and similar outcomes with ESD for larger lesions in experienced hands. Standardization between Western- and Japanese-trained pathologists in diagnosing gastric cancer is urgently needed. Structured training programs for ESD should be set up in high-volume centers and made accessible to suitable regional candidates.

## SURGERY AND ADJUVANT TREATMENT

For gastric cancer, so-called D1, or perigastric lymph node, dissection is common in Western countries, whereas in high-incidence countries like Japan and Korea, so-called D2 dissection is considered to be the standard (Fig. 7) (21,22).

An RCT from UK comparing D1 versus D2 found very high mortality but failed to show a difference (23,24). The trial was flawed due to the very high mortality, inclusion of a large proportion of stage I and absence of any description regarding the quality of lymph node dissection. A Dutch trial started 20 years ago also showed much higher mortality for D2 compared with D1 dissection and demonstrated no survival benefit (25,26). These two trials were closed before reaching the plateau of the learning curve, and the high postoperative mortality offset the effect of the D2. D2 dissections should be carried out in specialized centers.

An RCT in Taiwan compared D1 and D2 showed survival benefit of D2 dissection with reasonable morbidity and mortality (Fig. 8) (27).

To investigate even more extensive dissection of gastric cancer, a Japanese group compared D2 with D2 plus paraaortic nodal dissection (28,29). The results showed slightly higher morbidity, but without increase in mortality. These morbidity and mortality results were acceptable. However,

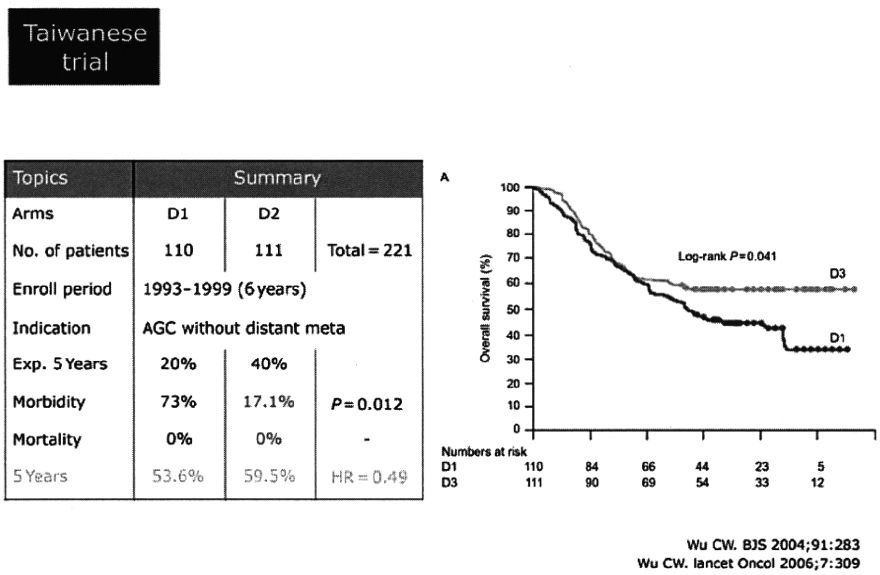



**Figure 8.** Nodal dissection for patients with gastric cancer: a randomized controlled trial. Source: Wu et al. (27).

no survival difference was observed, and D2 was thus the optimal surgery in that RCT. Comparison of reports from various countries reveals that the mortality is higher when the volume is lower, again demonstrating that D2 dissection should be performed in high-volume and/or specialized centers.

Regarding the role of adjuvant treatment, a major trial in Europe showed survival benefit from perioperative chemotherapy, but less than half of the patients underwent D2 dissection and the study also included esophageal cancer cases (30).

An RCT performed in the USA investigated the role of post-operative chemoradiotherapy and also showed significant survival benefit (31,32). However, only 10% of the patients underwent D2 dissection, there was a very high rate of local recurrence, and the surgery was not standardized among the participating hospitals. Subgroup analysis found survival benefit only in D0 or D1, but not in the D2-dissected group. The study thus showed that D0/D1 dissection was insufficient treatment.

In a Japanese randomized trial, curative D2 dissection alone was compared with D2 followed by post-operative chemotherapy by oral S-1 (33). In contrast to the Western studies, almost all of the cases in this study underwent D2 dissection, and the 3-year survival rate showed a 10% improvement (Fig. 9). A clinical trial of adjuvant treatment is being conducted in Korea, China and Taiwan, and 1024 cases have been enrolled. The results will be available within a few years. A Japanese group and a Korean group are working together to assess, for the first time, the role of reductive gastrectomy in Stage IV gastric cancer treatment (34). The chemotherapy applied in both arms is S-1 plus cisplatin. Although a very difficult project, it is very important, and it is hoped that other Asian countries will join this collaboration in the future.

In conclusion, with regard to the extent of surgery, R0 resection with D2 lymph node dissection has produced the best survival data. Some kind of post-operative adjuvant chemotherapy including S-1 is recommended after D2 surgery. In areas with a high incidence of gastric cancer, the quality of treatment can be kept very high, with both endoscopic treatment and surgery. At the moment, at least in Asia, D2 dissection should be considered as the standard.

## CHEMOTHERAPY FOR ADVANCED GASTRIC CANCER

There are now four active cytotoxic agents for advanced gastric cancer, consisting of fluorouracils, platinum, taxanes and irinotecan. The fluorouracils include 5-FU, S-1 and capecitabine, and the platinum include cisplatin and oxaliplatin. During the last decade, various randomized trials investigated the optimal combination of these four chemotherapy drug groups in Japan, Korea and China (Table 1). Capecitabine plus platinum was at least non-inferior to 5-FU plus cisplatin in terms of survival (35,36). S-1 plus cisplatin showed a comparable median time to progression to those in capecitabine or 5-FU plus cisplatin in Western studies (37,38), whereas the Japanese studies yielded relatively longer survival than the Western studies. These favorable survival in Japanese studies compared with the Westerns might be caused by longer survival after failure of the first-line therapy associated with higher rates of subsequent therapy than in the Western studies (Fig. 10).

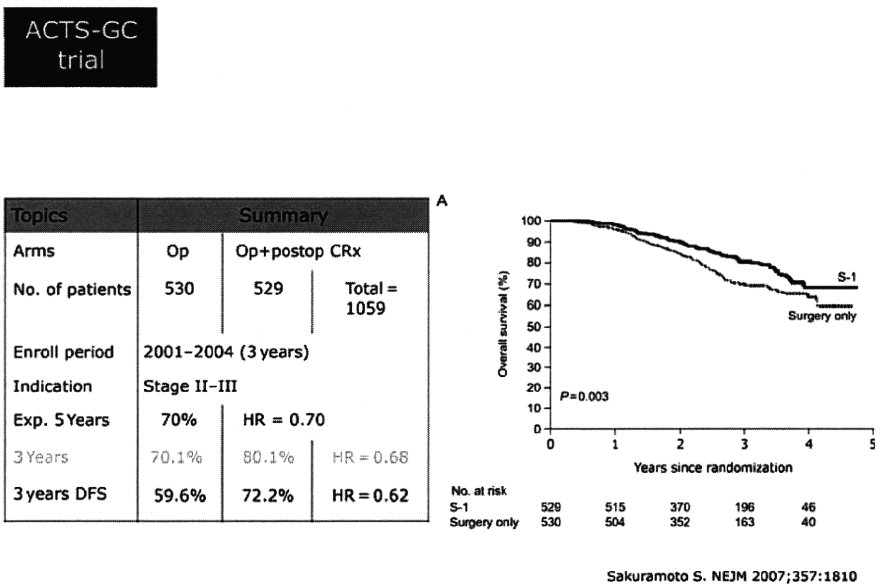



**Figure 9.** Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. Source: Sakuramoto et al. (33).

**Table 1.** Results of randomized trials using newer regimens: advanced gastric cancer

| Study | Treatment | *n* | RR (%) | MTTP (months) | MST (months) | *P* value[a] |
|---|---|---|---|---|---|---|
| V325 (JCO2006) | CDDP + FU (CF) | 230 | 25 | 3.7 | 8.6 | |
| | Docetaxel + CDDP + FU (DCF) | 227 | 37 | 5.6 | 9.2 | 0.02 |
| V306 (ASCO2005) | CDDP + FU (CF) | 163 | 26 | 4.2 | 8.7 | |
| | CPT-11 + FU (IF) | 170 | 32 | 5.0 | 9.0 | NS |
| ML07132 (ASCO2006) | FU + CDDP (FP) | 156 | 29 | 5.0 | 9.3 | |
| | Capecitabine + CDDP (XP) | 160 | 41 | 5.6 | 10.5 | NS |
| JCOG9912 (ASCO2007) | FU | 234 | 9 | 2.9[b] | 10.8 | |
| | S-1 | 234 | 28 | 4.2[b] | 11.4 | NS |
| | CPT-11 + CDDP | 236 | 38 | 4.8[b] | 12.3 | NS |
| SPIRITS (ASCO2007) | S-1 | 150 | 31 | 4.0[b] | 11.0 | |
| | S-1 + CDDP | 148 | 54 | 6.0[b] | 13.0 | 0.037 |
| TOP002 (ASCO-GI2008) | S-1 | 162 | 27 | | 10.5 | |
| | S-1 + CPT-11 | 164 | 42 | | 12.8 | NS |

[a]Test for superiority in OS.
[b]PFS.

The approval status of active agents for gastric cancer differs among four East Asian countries. Capecitabine and oxaliplatin are not yet available in Japan, and S-1 and oxaliplatin are not available in Taiwan (Table 2). In Japan, approval is always associated with medical reimbursement, but that is not always the case in other countries. The differences caused by the medical insurance systems may affect the survival results larger than by ethnic differences in biology or pharmacokinetics. In countries with limitations on medical reimbursement for second- or further line chemotherapy, such as Western countries and Asian countries other than Japan, triplet regimen such as docetaxel + cisplatin + 5-FU is becoming more popular. However, in Japan, all agents that have been approved are covered by medical reimbursement at any line of chemotherapy, which cause that FUs plus platinum are the most popular first-line

**Table 2.** Approval status of active agents in gastric cancer

| Agents | Japan | Korea | China | Taiwan |
|---|---|---|---|---|
| 5-FU | ○ | ○ | ○ | ○ |
| S-1 | ○ | ○ | ○ | × |
| Capecitabine | × | ○ | ○ | ○ |
| Cisplatin | ○ | ○ | ○ | ○ |
| Oxaliplatin | × | ○ | ○ | × |
| Paclitaxel | ○ | ○ | ○ | ○ |
| Docetaxel | ○ | ○ | ○ | ○ |
| Irinotecan | ○ | ○ | ○ | ○ |

○, medical reimbursement in Japan; ×, medical reimbursement in ex-Japan.

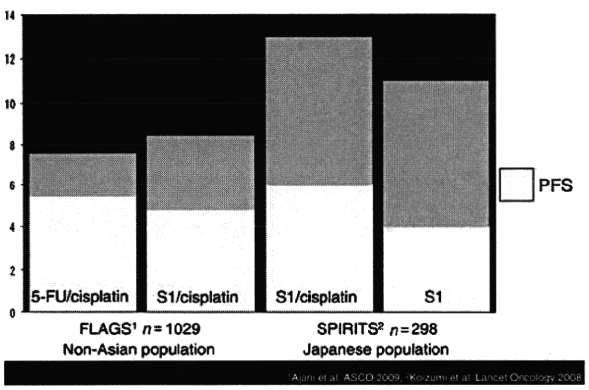



**Figure 10.** Survival in advanced gastric cancer: Japanese versus Western population.

regimens followed by taxane or irinotecan. In conclusion, no global standard regimen has been established yet as the first-line standard chemotherapy for metastatic cancer. In Asian countries, FU and platinum combinations are the most widely used regimens, with median progression-free survivals of 5–6 months. Differences in the approval and medical insurance systems may influence the status of these regimens.

The ToGA study compared the cytotoxic combination (5-FU or capecitabine + cisplatin) with and without trastuzumab in patients with HER2-positive gastric cancer (Fig. 11) (39). This is a global randomized trial, but more than half of the patients have been recruited from East Asian countries, including Korea, Japan and China. Trastuzumab showed a significant survival advantage compared with the cytotoxic agent combinations, with a hazard ratio of 0.74. From the Asian point of view, the ToGA trial indicates that trastuzumab in combination with FU/platinum will be a new option for HER2-positive gastric cancer. Moreover, the HER2-positive population will become an independent entity, as in breast cancer, although further studies are needed. Regional

**Table 3.** International investigational new drug registration randomized controlled trials for metachronous gastric cancer: leading countries

| Agents | Study name | Leading country | Region | Enrollment status |
|---|---|---|---|---|
| Trastuzumab | ToGA | Korea | Asia, EU, SA | Published |
| Bevacizumab | AVAGAST | Japan | Asia, EU, N/S A | Completed |
| Cetuximab | EXPAND | Germany | EU, Asia | Recruiting |
| Lapatinib (first line) | LOGiC | Korea | Asia, EU, N/S A | Recruiting |
| Lapatinib (second line) | TYTAN | Japan | Asia | Recruiting |
| Panitumumab | REAL3 | UK | EU | Recruiting |
| Everolimus | GRANITE-1 | Japan | Asia, EU, N/S A | Recruiting |

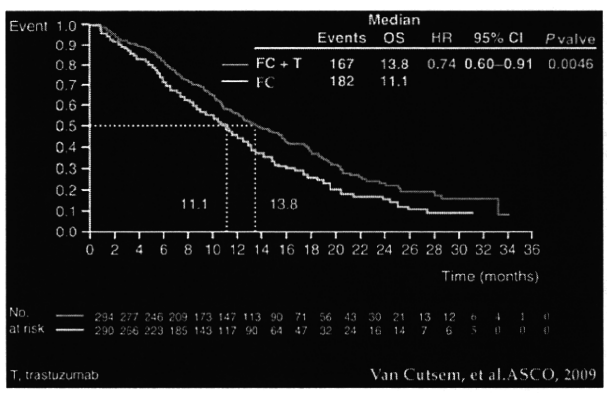



**Figure 11.** Overall survival results in ToGA trial.

differences, such as the HER2-positive rate, may be clarified by further analyses. Five of seven ongoing global RCTs for metastatic gastric cancer are led mainly by Japan and Korea. Asian countries are playing a major role in the development of new agents for gastric cancer (Table 3) (40).

In conclusion, FUs plus platinum are the most widely accepted first-line regimens for gastric cancer, whereas taxanes or irinotecan are mostly used in second- and third-line settings. Differences in the approval and medical insurance systems may influence the status of these regimens, and the improvement in these status is hopefully done in many countries. Trastuzumab in combination with FUs/platinum will be a standard regimen for HER2-positive gastric cancer, and the recent phase II/III trials showed favorable median survival times exceeding 1 year. Many new targeting agents are currently under investigation and the roles of Asian countries in the development of new agents will become important.

## Conflict of interest statement

None declared.

## References


1. Ferlay J, Bray F, Pisani P, Parkin DM. *GLOBOCAN 2002:* Cancer Incidence, Mortality and Prevalence Worldwide IARC CancerBase No. 5. version 2.0. Lyon: IARC Press 2004. Available from: http://globocan.iarc.fr
2. Curado MP, Edwards B, Shin HR, Storm H, Ferlay J, Heanue M, et al., editors. Cancer Incidence in Five Continents, Vol. IX, IARC Scientific Publications No. 160. Lyon: IARC 2007.
3. Wu MS, Chen CJ, Lin JT. Host-environment interactions: their impact on progression from gastric inflammation to carcinogenesis and on development of new approaches to prevent and treat gastric cancer (Review). *Cancer Epidemiol Biomarkers Prev* 2005;14:1878–82.
4. Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, et al. *Helicobacter pylori* infection and the development of gastric cancer. *N Engl J Med* 2001;345:784–9.
5. Wong BC, Lam SK, Wong WM, Chen JS, Zheng TT, Feng RE, et al., China Gastric Cancer Study Group. *Helicobacter pylori* eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. *JAMA* 2004;291:187–94.
6. Fukase K, Kato M, Kikuchi S, Inoue K, Uemura N, Okamoto S, et al., Japan Gast Study Group. Effect of eradication of *Helicobacter pylori* on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. *Lancet* 2008;372:392–7.
7. Fuccio L, Zagari RM, Eusebi LH, Laterza L, Cennamo V, Ceroni L, et al. Meta-analysis: can *Helicobacter pylori* eradication treatment reduce the risk for gastric cancer? *Ann Intern Med* 2009;151:121–8.
8. Wu CY, Kuo KN, Wu MS, Chen YJ, Wang CB, Lin JT. Early *Helicobacter pylori* eradication decreases risk of gastric cancer in patients with peptic ulcer disease. *Gastroenterology* 2009;137:1641–8.
9. Fock KM, Talley N, Moayyedi P, Hunt R, Azuma T, Sugano K, et al. Asia-Pacific consensus guidelines on gastric cancer prevention. *J Gastroenterol Hepatol* 2008;23:351–65.
10. Wang WH, Huang JQ, Zheng GF, Lam SK, Karlberg J, Wong BC. Non-steroidal anti-inflammatory drug use and the risk of gastric cancer: a systematic review and meta-analysis. *J Natl Cancer Inst* 2003;95:1784–91.
11. Wu CY, Wu MS, Kuo KN, Wang CB, Chen YJ, Lin JT. Effective reduction of gastric cancer risk with regular use of nonsteroidal anti-inflammatory drugs in *Helicobacter pylori*-infected patients. *J Clin Oncol* 2010;28:2952–7.
12. Yamazaki H, Oshima A, Murakami R, Endoh S, Ubukata T. A long-term follow-up study of patients with gastric cancer detected by mass screening. *Cancer* 1989;63:613–7.
13. Dan YY, So JB, Yeoh KG. Endoscopic screening for gastric cancer. *Clin Gastroenterol Hepatol* 2006;4:709–16.
14. Suzuki H, Gotoda T, Sasako M, Saito D. Detection of early gastric cancer: misunderstanding the role of mass screening. *Gastric Cancer* 2006;9:315–9.
15. Schlemper RJ, Kato Y, Stolte M. Review of histological classifications of gastrointestinal epithelial neoplasia: differences in diagnosis of early carcinomas between Japanese and Western pathologists. *J Gastroenterol* 2001;36:445–56.
16. Gotoda T, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T, et al. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. *Gastric Cancer* 2000;3:219–25.
17. Gotoda T. Endoscopic resection of early gastric cancer. *Gastric Cancer* 2007;10:1–11.
18. Uedo N, Iishi H, Tatsuta M, Ishihara R, Higashino K, Takeuchi Y, et al. Longterm outcomes after endoscopic mucosal resection for early gastric cancer. *Gastric Cancer* 2006;9:88–92.
19. Cao Y, Liao C, Tan A, Gao Y, Mo Z, Gao F. Meta-analysis of endoscopic submucosal dissection versus endoscopic mucosal resection for tumors of the gastrointestinal tract. *Endoscopy* 2009;41:751–7.
20. Isomoto H, Shikuwa S, Yamaguchi N, Fukuda E, Ikeda K, Nishiyama H, et al. ESD for early gastric cancer: a large-scale feasibility study. *Gut* 2009;58:331–6.
21. Sasako M, Saka M, Fukagawa T, Katai H, Sano T. Surgical treatment of advanced gastric cancer: Japanese perspective. *Dig Surg* 2007;24:101–7.
22. Yoon SS, Yang HK. Lymphadenectomy for gastric adenocarcinoma: should west meet east? *Oncologist* 2009;14:871–82.
23. Cuschieri A, Fayers P, Fielding J, Craven J, Bancewicz J, Joypaul V, et al. Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial. The Surgical Cooperative Group. *Lancet* 1996;347:995–9.
24. Cuschieri A, Weeden S, Fielding J, Bancewicz J, Craven J, Joypaul V, et al. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. *Br J Cancer* 1999;79:1522–30.
25. Bonenkamp JJ, Songun I, Hermans J, Sasako M, Welvaart K, Plukker JT, et al. Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. *Lancet* 1995;345:745–8.
26. Bonenkamp JJ, Hermans J, Sasako M, van de Velde CJ, Welvaart K, Songun I, et al. Dutch Gastric Cancer Group. Extended lymph-node dissection for gastric cancer. *N Engl J Med* 1999;340:908–14.
27. Wu CW, Hsiung CA, Lo SS, Hsieh MC, Chen JH, Li AF, et al. Nodal dissection for patients with gastric cancer: a randomised controlled trial. *Lancet Oncol* 2006;7:309–15.
28. Sano T, Sasako M, Yamamoto S, Nashimoto A, Kurita A, Hiratsuka M, et al. Gastric cancer surgery: morbidity and mortality results from a prospective randomized controlled trial comparing D2 and extended para-aortic lymphadenectomy—Japan Clinical Oncology Group study 9501. *J Clin Oncol* 2004;22:2767–73.
29. Sasako M, Sano T, Yamamoto S, Kurokawa Y, Nashimoto A, Kurita A, et al. Japan Clinical Oncology Group. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. *N Engl J Med* 2008;359:453–62.
30. Cunningham D, Allum WH, Stenning SP, Thompson JN, van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;355:11–20.
31. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001;345:725–30.
32. Enzinger PC, Benedetti JK, Meyerhardt JA, McCoy S, Hundahl SA, Macdonald JS, et al. Impact of hospital volume on recurrence and survival after surgery for gastric cancer. *Ann Surg* 2007;245:426–34.
33. Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med* 2007;357:1810–20.
34. Fujitani K, Yang HK, Kurokawa Y, Park do J, Tsujinaka T, Park BJ, et al., Gastric Cancer Surgical Study Group of Japan Clinical Oncology Group; Korea Gastric Cancer Association. Randomized controlled trial comparing gastrectomy plus chemotherapy with chemotherapy alone in advanced gastric cancer with a single non-curable factor: Japan Clinical Oncology Group Study JCOG 0705 and Korea Gastric Cancer Association Study KGCA01. *Jpn J Clin Oncol* 2008;38:504–6.
35. Kang Y, Kang WK, Shin DB, Chen J, Xiong J, Wang J, et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomized phase III non-inferior trial. *Ann Oncol* 2009;20:666–73.
36. Cunningham D, Starling N, Rao S, Ivelson T, Nicolson M, Coxon F, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Eng J Med* 2008;358:36–46.
37. Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol* 2008;9:215–21.
38. Ajani JA, Rodriguez W, Bodoky G, Moiseyenko V, Lichinitser M, Gorbunova V, et al. Multicenter phase III comparison of cisplatin/S-1

with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS Trial. *J Clin Oncol* 2009;27:1547–53.
39. Van Cutsem E, Kang YK, Chung H, Shen L, Sawaki A, Lordick F, et al. Efficacy results from ToGA trial: a phase III study of trastuzumab added to standard chemotherapy (CT) in first-line human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer. *J Clin Oncol* 2009;27:18S (Abstract LBA 4509).
40. Ohtsu A. Chemotherapy for metastatic gastric cancer: past present and future. *J Gastroenterol* 2008;43:256–64.

JJCO Japanese Journal of Clinical Oncology

*Jpn J Clin Oncol 2010;40(Supplement 1)i76–i81*
*doi:10.1093/jjco/hyq131*

# Cancer Registry and Epidemiological Study Working Group Report

**Tomotaka Sobue[1,*], Manami Inoue[2], Hideo Tanaka[3] and 46 Members**

[1]Division of Cancer Information and Surveillance Division, National Cancer Center, [2]Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo and [3]Division of Epidemiology and Prevention, Aichi Cancer Center Hospital and Research Institute, Aichi, Japan

*For reprints and all correspondence: Tomotaka Sobue, Division of Cancer Information and Surveillance Division, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. E-mail: tsobue@ncc.go.jp

**International Agency for Research on Cancer:** The International Agency for Research on Cancer serves as a global reference for cancer information. The Cancer Information Section of the International Agency for Research on Cancer publishes the world's largest information database on cancer incidence and supports cancer registries by providing administrative facilities and training, etc. Many Asian countries have published cancer registries, but Indonesia and Bangladesh have yet to do so.
**International Association of Cancer Registries:** The International Association of Cancer Registries is a non-governmental organization that promotes information exchange between cancer registries internationally. It supports cancer registries by means of fellowship funds and computer programs.
**Cooperative Studies:** Asian cooperative studies using cancer registration data are essential for combating cancer in the region. For a cooperative study, countries first need to exchange cancer data and then conduct a comparative study using non-individualized data. The third step is collection of individualized, anonymous data, which would improve comparability.
**Collaborative Epidemiological Studies:** The Asia Cohort Consortium, which includes investigators from various countries, is a complicated collaboration. Good epidemiological research collaboration requires researchers' comprehension of the significance of multinational collaborative studies, good coordination, adequate funding and balanced collaboration.
**Conclusions:** Asia faces various problems in relation to cancer registry, including inadequate quality, weak infrastructure, insufficient coverage, etc. Epidemiological studies are hampered by differences in expertise and resources, limited understanding of epidemiology, etc. To alleviate those problems, an organization for Asian cooperation on cancer registration should be established. Adequate funding of registries and activities is essential. Collaborative and comparative epidemiological studies based on data from cancer registries are needed.

*Key words: cancer registries – epidemiological studies – collaboration – network*



The Cancer Registry and Epidemiological Study Working Group comprised almost 50 members from 19 countries. Its discussions focused on the registry systems and collaborative work necessary for attacking the problem of cancer in the Asia-Pacific region.

## INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

The International Agency for Research on Cancer (IARC)'s mission is cancer research for cancer prevention. It also serves as a global reference for cancer information, including geographical variations, incidence and trends over time. The IARC also provides education and training for low-resource countries. The Cancer Information Section (CIS) includes three groups: biostatistics, data analysis and descriptive epidemiological production. One of the core activities of the CIS is to issue the cancer incidence in five continents series, which is the world's largest database of information on cancer incidence and has been invaluable for conducting cancer research, establishing cancer control programs and determining healthcare policies around the world. The CIS also supports cancer registries by providing administrative

facilities, conducting site visits, providing individual and group training, etc. In 2009, Asian Workshops were held in Vietnam and Bhutan.

Various Asian countries have published cancer registries over recent years. Data from 77 registries in 18 countries were submitted for inclusion in the IARC's *Cancer Incidence in Five Continents Vol. IX*, and 44 (55%) of those registries in 15 countries were accepted. (1) Sixty per cent of the world's population lives in Asia, and 6 of the 10 most-populated countries are in Asia, consisting of China, India, Indonesia, Pakistan, Bangladesh and Japan. Unfortunately, there has still been no cancer registry data from two of those Asian countries, Indonesia and Bangladesh (Table 1).

GLOBOCAN 2002 estimated 4.8 million cases of cancer and 3.4 million deaths in Asia, representing almost 45 and 50%, respectively, of the world's cases. (2) GLOBOCAN data are being updated, and the objective is to provide estimates of cancer incidence, mortality and prevalence for 28 major cancers. Estimated data for 2008 showed that the number of cancer cases in Asia had increased by ~10% since 2002, but deaths increased only slightly.

## INTERNATIONAL ASSOCIATION OF CANCER REGISTRIES

The International Association of Cancer Registries (IACR) is a non-governmental organization that was founded in 1966 to foster the exchange of information between cancer registries internationally, aimed at improving the quality of data and comparability between registries. The number of member countries has been increasing, especially Asian nations. In 2009, members from 26 countries covered ~20% of the world's population. The IACR is affiliated with two scientific journals, the European Journal of Cancer Prevention and the Asian Pacific Journal of Cancer Prevention. The IACR standards have been presented in a number of publications, aimed at improving the quality of data and comparability between registries. The IACR provides support to cancer registries by means of fellowship funds (the Calum Muir Memorial Fellowship and the Constance Percy Memorial Fund) and also computer programs. Many Asian countries have cancer registries, but some do not, including North Korea, Cambodia and Laos. Meetings to set up an Asian Network of Cancer Registries were held in Korea in 2008 and Thailand in 2009. Then a survey was conducted regarding the establishment of an Asian Network of Cancer Registries, and 22 responses were obtained from 109 Asian registries (Fig. 1). Seven main objectives of networking were favored for the organization, including training for standardization of networking, planning and execution of collaborative research, evaluation of cancer control and treatment outcomes, meetings and discussions, etc. Regarding the name, half of the respondents preferred 'Asian Association of Cancer Registries', whereas the other half preferred 'Asian Network of Cancer Registries'.

**Table 1.** Cancer Registries in Asia

| Eastern (6) | South-Eastern (11) | South-Central (14) | Western (18) |
|---|---|---|---|
| **China**: 43 + (A) | **Brunei**: N | Afghanistan | Armenia |
| **Japan**: 35 + (A) | Cambodia | **Bangladesh** | **Bahrain**: N |
| **South Korea**: 8 + N | **Indonesia** (H) | **Bhutan**: N | **Cyprus**: N |
| North Korea: | Lao | **India**: 10 (A) | **Israel**: N |
| **Mongolia**: N | **Malaysia**: 2 + N | **Iran**: 2 | **Jordan**: N |
| **Taiwan**: N | Myanmar | Kazakhstan | **Kuwait**: N |
| | **Philippines**: 4 | Kyrgyzstan | **Oman**: N |
| | **Singapore**: N | Nepal: 2 | **Turkey**: 2 |
| | Timore | **Pakistan**: 2 | Others: |
| | **Thailand**: 19 + (A) | **Sri Lanka** | |
| | **Vietnam**: 6 | Others | |

Bold: Countries where registries are in operation.

## DESIGNING COOPERATIVE STUDIES

A major element in the overall strategy for combating cancer in Asia-Pacific countries in the future is the effective design and execution of cooperative studies using cancer registration data and international comparisons with Asian countries. The rationale is that society, the mass media and health authorities pay more attention to cancer incidence and trend data when they are compared with other countries, rather than only within their own country. Moreover, the results contribute to improved cancer control planning in the participating countries.

Prior to a cooperative study, countries need to exchange data regarding cancer in each of their countries. In Japan, the incidence of hepatocellular carcinoma (HCC) has been decreasing because of reduced hepatitis C virus (HCV) infection rates due to improved hygiene and prevention of

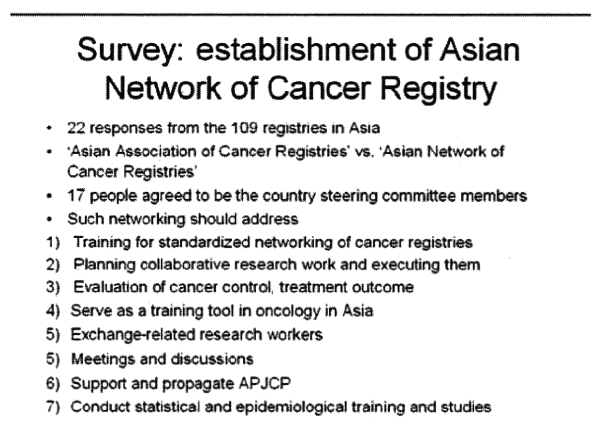



**Figure 1.** Survey: Establishment of Asian Network of Cancer Registry.

blood-borne infection (3). Information in this regard may be helpful to countries where HCV-related HCC is endemic, such as Mongolia, Myanmar and Taiwan.

Another example is lung cancer. Many Asian countries have high smoking rates in males. Male smoking rates in Japan have been decreasing, and the incidence of lung cancer has been decreasing since 1993, and also reduced incidence of squamous cell carcinoma because of a change from non-filter to filter cigarettes. The incidence rate of squamous cell carcinoma has been decreasing since 1994, whereas the incidence rate of adenocarcinoma increased until 1998, after which it plateaued. It took nearly 30 years for the decrease in non-filtered cigarettes to translate into a decrease in squamous cell carcinoma. Although it takes a long time, anti-smoking policies reduce the incidence of lung cancer. Evidence of this has been presented in Western countries, and it is important to advance such policies in Asia, as well, in order to reduce lung cancer.

A study group financially supported by a Grant-in-Aid for Comprehensive Cancer Control from Japanese Ministry of Health, Labor and Welfare conducted a collaborative study using a population-based cancer registry in East Asia (4). They have reported a 5-year relative survival rate of stomach cancer patients diagnosed between 1997 and 1999. The survival rates were higher in Japan, and even in Korea and Taiwan, than in Europe and the USA. The breast cancer 5-year survival rate was very high in Japan, Korea and Taiwan, and almost the same as in the EU and USA, whereas the survival rate of breast cancer was low in the Philippines, and hence improvement is needed there. The highest cervical cancer 5-year survival rate was seen in Korea, whereas several regions in Japan were not so high. Elucidation of the reasons for the lower rates in Japan is needed. Again, the Philippines had the lowest 5-year survival rate for cervical cancer, as well.

The next stage for cooperative studies is to collect individualized, anonymous data, which would make it possible to elucidate the factors that cause differences between populations, such as age, clinical stage at diagnosis, treatment procedures, etc. Individualized, anonymous data would also improve the comparability of survival data among the participating regions.

In conclusion, designing cooperative studies using cancer registry data involves a first stage in which information is exchanged among the participating countries to facilitate cancer control planning, a second stage consisting of a comparative study using non-individualized data and a third stage using individualized data (Fig. 2). Good human relationships among researchers are also very important, and the APCC represents a good platform for nurturing such good relationships.

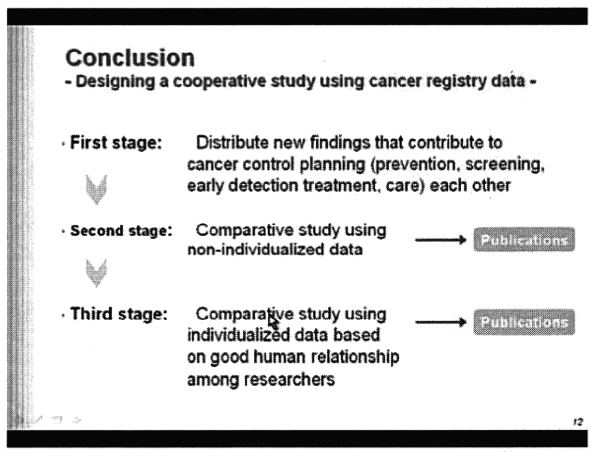



**Figure 2.** Designing a cooperative study using cancer registry data.

## COLLABORATIVE EPIDEMIOLOGICAL STUDIES FOR CANCER PREVENTION

With regard to collaborative epidemiological studies to collect evidence concerning cancer risk and protective factors in the Asian region, recent trends show that the number of studies has been increasing, meta-analysis/pooled analysis of multiple studies has become very popular, and the importance of estimating the population-attributable fraction in each country/region/world has been recognized.

Collaboration between two countries is fairly simple, consisting of securing a research grant/funding, data collection by investigators and co-investigators in each country, and data analysis and manuscript preparation. The data center, data analysis and manuscript preparation are usually in the country of the principal investigator, while the grant is usually executed in the currency of the funding host.

In the case of collaboration between multiple countries, things get more complicated. The principal investigator is in one country, with a network including co-investigators collecting data in each of the participating countries, and the data analysis and manuscript preparation are performed at a data center, usually in the country of the principal investigator. However, the location of the data center and the manuscript writer are flexible.

An even more complicated example of collaboration is the Asia Cohort Consortium, which includes investigators from various countries and who change in accordance with the topic (Fig. 3). Interesting features are that the data center is outside Asia, in the USA, and the researchers include not only Asians but also Europeans and Americans, because they get funding, by topic, from their countries. Also, there is no firm funding base for network maintenance.

The funding agency in support of epidemiological research can be a domestic organization or an international organization. In the case of a domestic organization, the study is based in that country and is usually research topic-oriented. In the case of an international organization, the study base can be anywhere, and it is a potential research platform.

For good epidemiological research collaboration in Asian countries, the following points are important: each researcher must have an understanding of the significance of

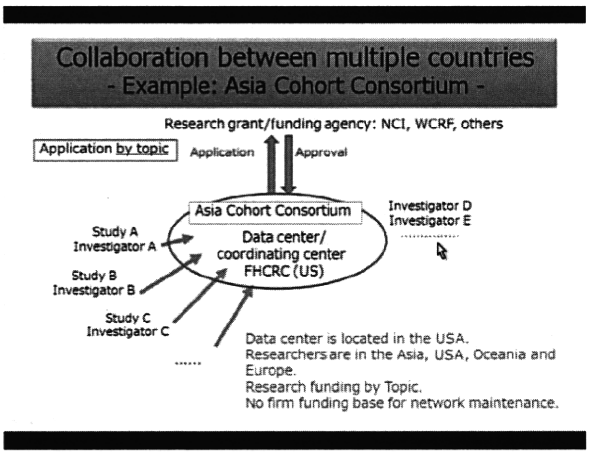



**Figure 3.** Collaboration between multiple countries: Example: Asia Cohort Consortium.

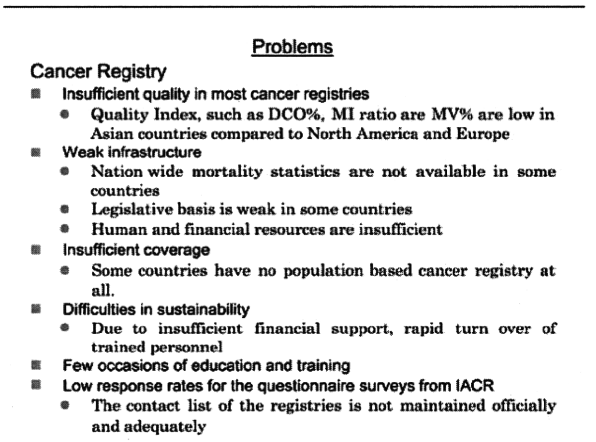



**Figure 4.** Problems: Cancer Registry.

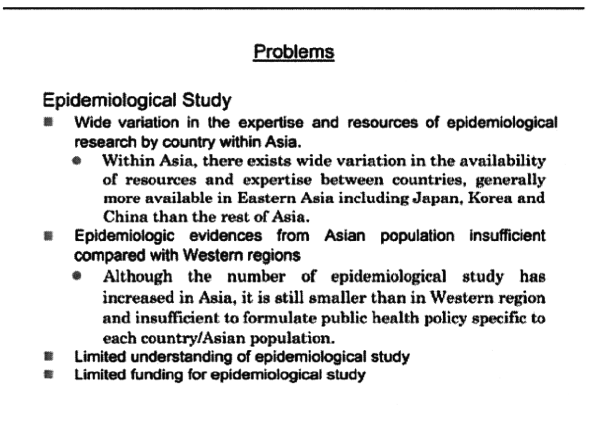



**Figure 5.** Problems: Epidemiological Study.

multinational collaborative studies; the leader must be a good coordinator; funding must be available for network maintenance and a multinational consortium; and the collaboration must be balanced and provide equal opportunity.

## CONCLUSIONS

The problems that are faced in relation to cancer registry in Asia are various (Fig. 4). They include insufficient quality of most registries, weak infrastructure, inadequate coverage in some countries, difficulty in sustainability due to insufficient financial support and turnover of trained personnel, few opportunities for education and training, and low response rates to IACR questionnaire surveys. Similarly, problems in relation to epidemiological studies include wide variation in expertise and resources among Asian countries, and limited understanding of epidemiology in some nations, which constrains funding for epidemiological studies (Fig. 5). Other key problems are the lack of opportunity for contact between experts in Asia via collaborative activities and language barriers among Asian countries.

As solutions, from the perspective of researchers, the highest priority should be placed on information-sharing among researchers within the Asia-Pacific region. Newly developed and widely used techniques, such as those for record linkage, should be shared. In addition, there is a need to promote coordination meetings/workshops/symposia, provide training courses, establish international standards and promote collaborative studies, publication and a common database for pooled analysis, both for cancer registries and epidemiological studies. In order to do this, an organization for Asian cooperation on cancer registration should be established in the field of cancer registries. In addition, a common hub for collaborative research will be needed for epidemiological studies. More opportunities for collaborative research projects, activities and publications would improve the research skills and expertise in the region.

From the perspective of international organizations, such as the IARC and IACR, in a 2009 meeting the governing council of the IARC discussed how to provide greater support to cancer registries in developing countries. The IARC/IACR is planning to create a password-protected online system, so that questionnaires can be completed online and updated every year. The website would also allow registries to update their contact information. In October 2010, an Asian session will be held as a post-conference of the IACR annual meeting in Yokohama, Japan and Asian cooperation in cancer registration will be one of the main themes. To maintain a network of cancer registries, or an Asia Cohort Consortium, it will be necessary to maintain funding not only for topic-specific research proposals, but also for the research platform itself. To that end, funding should also be requested of other organizations.

In the future, the Asia-Pacific region must make full use of the platforms afforded by the WHO, IARC/IACR, UICC Headquarters, APFOCC and liaison societies in order to promote and achieve its goals of establishing cancer registries, accumulating cancer statistics, promoting and performing epidemiological studies and formulating regional and national cancer control programs.

With regard to concrete actions, from the perspective of researchers, there must be continued development of collaborative research projects and activities in subregions such as West Asia, Central Asia, Southeast Asia, East Asia and the Pacific. Publication of these activities should be encouraged to improve research skills and expertise in the study of Asia-Pacific populations. In that context, a steering committee for Asian cooperation for cancer registration will be assembled for the kick-off meeting in Yokohama 2010. At the same time, it will be proposed that the IARC supports the administrative work needed to maintain the network. Finally, collaborative and comparative epidemiological studies based on data from cancer registries should be promoted.

## Funding

This working group meeting was financially supported by The Health and Labor Sciences Research Grant for Third Term Comprehensive Control Research for Cancer from Ministry of Health, Labor and Welfare, Japan, Grant-in-Aid for Cancer Research on Priority Areas from the Ministry of Education, Science, Sports Culture and Technology, Japan, 20th Asia Pacific Cancer Conference (President: Dr Hideyuki Akaza) and International Union Against Cancer (UICC) Asia Regional Office.

## Conflict of interest statement

None declared.

### Appendix

Abdulbari Bener, Epidemiology and Medical Statistics, Weil Cornell Medical College in Qatar, Hamad Medical Corporation, Qatar; Adriano V. Laudico, Department of Surgery, University of the Philippines Manila, Philippine General Hospital, Philippines; Aleyamma Mathew, Cancer Registry and Epidemiology, Regional Cancer Centre, India; Alireza Mosavi-Jarrahi, Deparment of Social Medicine, Medical School Shahid, Beheshti University of Medical Sciences, Iran; Cahyono Kaelan, Department of Pathology, Hasanuddin University, Indonesia; Chisato Nagata, Department of Epidemiologyand Prevention Medicine, Gifu University Graduate School of Medicine, Japan; Chun-Xiao Wu, Department of Cancer Control and Prevention, Shanghai Municipal Center for Disease Control and Prevention, China; Daehee Kang, Department of Molecular Medicine and Biopharmaceutical Sciences, Seoul National University College of Medicine, Korea; David Roder, Cancer Council South Australia, Australia; Dong-Hyun Kim, Department of Social and Preventive Medicine, Hallym University College of Medicine, Korea; Ediati Triningsih, Department of Pathology, Gadja Mada University Faculty of Medicine, Indonesia; Evlina Suzanna Sinuraya, Department of Pathology, Dharmais National Cancer Center, Indonesia; Francine Baumann, Cancer Registry of New Caledonia, New Caledonia; Hai-Rim Shin, Western Pacific Regional Office, World Health Organization, Philippines; Hideaki Tsukuma, Cancer Control & Statistics, Osaka Medical Center for Cancer and Cardiovascular Diseases, Japan; Javad Shokrishirvany, Department of Gastroenterology, Babol University of Medical Sciences, Iran; Jun Miyake, Department of Mechanical Science and Bioengineering, Graduate School of Engineering Science, Osaka University, Japan; Kazuo Tajima, Aichi Cancer Center Hospital and Research Institute, Japan; Keitaro Matsuo, Division of Epidemiology and Prevention, Aichi Cancer Center Hospital and Research Institute, Japan; Keun-Young Yoo, Department of Preventive Medicine, Seoul National University College of Medicine, Korea; Malcolm Moore, UICC Asian Regional Office, Asian Pacific Journal of Cancer Prevention / Asian Pacific Organization for Cancer Prevention, Japan; Marc Goodman, Cancer Research Center, University of Hawaii, U.S.; Maria Rica Mirasol Lumague, Department of Health - Rizal Cancer Registry, Rizal Medical Center, Philippines; Mashhura Soipova, Uzbek Ministry of Health, Uzbekistan; Mei-Shu Lai, Institute of Preventive Medicine, College of Public Health, National Taiwan University, Taiwan; Mohammad Ali Mohagheghi, Department Surgery, The Cancer Institute, Imam Khomeini Medical Complex, Iran; Ngoan Tran Le, Occupational Health, Hanoi Medical University, Viet Nam; Noorwati Sutandyo, Dharmais Cancer Hospital, Indonesia; Nor Hayati Othman, Pathology, Universiti Sains Malaysia, Malaysia; Norie Kawahara, Research Center for Advanced Science & Technology, The University of Tokyo, Japan; Nurbek S. Igisinov, Department of Scientific Programs Management, Astana Medical University, Kazakhstan; Reza Ghadimi, Department of Social Medicine and Health, Babol University of Medical Sciences, Iran; Shinkan Tokudome, National Institute of Health and Nutrition, Japan; Shiro Hinotsu, Department of Pharmacoepidemiology, Kyoto University; Sohee Park, Cancer Registration and Biostatistics Branch, National Cancer Center Research Institute, Korea; Sultan Eser, Izmir Cancer Registry, Turkey; Suminori Kono, Department of Preventive Medicine, Kyushu University Faculty of Medical Sciences, Japan; Sunia Foliaki, Centre for Public Health Research, Massey University, New Zealand; Supannee Promthet, Department of Epidemiology, Faculty of Public Health, Khon Kaen University, Thailand; Surapon Wiangnon, Department of Pedriatrics, Faculty of Medicine, Khon Kaen University, Thailand; Tetsuya Mizoue,

Department of Epidemiology and International Health, Research Institution International Medical Center of Japan; Tohru Masui, National Institute of Biomedical Innovation, Japan; Wanqing Chen, Chun-Xiao Wu, National Office for Cancer Prevention and Control, China; Yasmin Bhurgri, Karachi Cancer Registry, Pakistan; Yoon-OK Ahn, Department of Preventive Medicine, Seoul National University College of Medicine, Korea; You-Lin Qiao, Department of Cancer Epidemiology, Cancer Institute, Chinese Academy of Medical Sciences and Peking Union Medical College, China.

## References

1. Curado MP, Edwards B, Shin HR, Storm H, Ferlay J, Heanue M, et al. editors. *Cancer Incidence in Five Continents*, Vol. IX. IARC Scientific Publications No. 160. Lyon: IARC 2008.
2. Ferlay J, Bray F, Piani P, Parkin DM. *GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide IARC CancerBase No. 5. version 2.0.* Lyon: IARC Press 2004.
3. Tanaka H, Imai Y, Hiramatsu N, Ito Y, Imanaka K, Oshita M, et al. Declining incidence of hepatocellular carcinoma in Osaka, Japan, from 1990 to 2003. *Ann Intern Med* 2008;148:820–6.
4. Tanaka H, Tanaka M, Chen W, Park S, Jung KW, Chiang CJ, et al. Proposal for a Cooperative Study on Population-based Cancer Survival in Selected Registries in East Asia. *Asian Pac J Cancer Prev* 2009;10(6):1191–8.