The 11th
Aichi Cancer Center
International Symposium

Forefront of Cancer Prevention Strategy in Asia

President of Aichi Cancer Center: Ryuzo Ohno

Organizing Committee of the 11th Aichi Cancer Center International Symposium
Kazuo Tajima (Chairperson)
Masae Tatematsu
Shigeo Nakamura
Kenji Wakai
Hayao Nakanishi
Hirotaka Osada
Kaoru Hirose
Keitaro Matsuo
Hidemi Ito
Hiroshi Yamaguchi
Takanori Umeda

February 5, 2005
Aichi Cancer Center, Nagoya, Japan
PROGRAM OF SYMPOSIUM

9:30-9:35 Opening Remarks: Ryuzo Ohno

Comprehensive epidemiologic studies in hospital

Chairperson: T. Rajkumar (Cancer institute, Chennai, India),
Shinkan Tokudome (Nagoya City University)

09:35-9:55 Keitaro Matsuo (Aichi Cancer Center)
A challenging strategy for cancer epidemiology in hospital.

09:55-10:35 Carlo La Vecchia (Istituto di Ricerche Farmacologiche, Milan, Italy)
Diet and risk in Mediterranean countries

Cohort study and cancer risk assessment in Asia

Chairperson: Wang Yixun (Liaoning province Tumor Hospital and Institute,
Liaoning, China),
Hiroyuki Shimizu (Gifu University)

10:35-10:55 Kenji Wakai (Aichi Cancer Center)
The Japan Collaborative Cohort (JACC) Study

10:55-11:25 Keun-Young Yoo (Seoul National University, Seoul, Korea)
Korean Multi-center Cancer Cohort Studies for Genomic Epidemiology:
Current Status and Perspectives

11:25-11:50 Suminori Kono (Kyushu University)
The Self Defense Forces Cohort Study

11:50-12:15 Shoichiro Tsugane (National Cancer Center)
A population-based prospective study on cancer and major chronic
diseases: the JPHC Study

12:15-13:15 Lunch

Infection and cancer prevention

Chairperson: Petcharin Srivatanakul (National Cancer Institute, Bangkok, Thailand),
Masae Tatematsu (Aichi Cancer Center)
13:15-13:35  Yuzuru Ikehara (Aichi Cancer Center)
Polymorphisms of two fucosyltransferase genes (Lewis and Secretor genes) involving type I Lewis antigens are associated with the presence of anti-Helicobacter pylori IgG antibodies.

13:35-14:05  Wang Yixun (Liaoning province Tumor Hospital and Institute, Liaoning, China)
Study of the Association of Human Papillomavirus Infection and Cervical Cancer in China

Chairperson:  Robert Burton (Strategic Leader, UICC, Melbourne, Australia),
Masanao Miwa (University of Tsukuba)

14:05-14:30  Hideo Tanaka (Osaka Medical Center for Cancer and Cardiovascular Diseases)
Hepatitis virus and hepatocellular carcinoma

14:30-15:00  Petcharin Srivatanakul (National Cancer Institute, Bangkok, Thailand)
Liver flukes and Cholangiocarcinoma

15:00-15:30  Coffee Break

**Forefront strategy of cancer prevention**

Chairperson:  Malcolm Moore (APOCP Coordination Director, Bangkok, Thailand)
Yasuhito Yuasa (Tokyo Medical and Dental University)

15:30-15:55  Nobuyuki Hamajima (Nagoya University)
New strategies of individualized cancer prevention

15:55-16:25  T.Rajkumar (Cancer Institute, Chennai, India)
Breast cancer susceptibility and chemoprevention

Chairperson:  Keun-Young Yoo (Seoul National University, Seoul, Korea)
Kazuo Tajima (Aichi Cancer Center)

16:25-16:50  Kei Nakachi (Radiation Effects Research Foundation)
Natural immunological host defense and cancer prevention

16:50-17:20  Robert Burton (Strategic Leader, UICC, Melbourne, Australia)
Forefront of cancer prevention in Asia

17:20-17:25  Concluding Remarks: Toshitada Takahashi
Welcome Remarks

Ryuzo Ohno
President, Aichi Cancer Center

On behalf of the organizing committee, I am very pleased to welcome you to the 11th Aichi Cancer Center International Symposium. My special thanks go to the speakers, chairpersons and other participants who have traveled a long distance to join us here in Nagoya.

Our first international symposium was held in 1994 when Aichi Cancer Center celebrated its 30th anniversary, in the newly built International Conference Center. Since then the symposium has been held annually, each organizing committee selecting timely topic on basic or translational research, prevention, diagnosis or treatment of cancer.

The theme of this year’s symposium is the Forefront of Cancer Prevention Strategies in Asia. This topic was selected since prevention offers one of the best modalities to conquer cancer and considerable progress has been made in developing an effective strategy in recent years. The symposium features of 4 sessions; the first focuses on Comprehensive epidemiologic studies in hospital, the second on Cohort studies and cancer risk assessment in Asia, the third Infection and cancer prevention and the fourth the Forefront strategy for cancer prevention.

I sincerely hope that this meeting will provide an excellent opportunity to explore the current status and future perspectives in cancer prevention in Asian countries. I also wish that the symposium can make a major contribution towards victory in the war against cancer in Asia, and the other region of the World.
A challenging strategy for cancer epidemiology in hospital.

Keitaro Matsuo
Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, Nagoya, Japan

Population-based approaches have are the gold standard of analytical epidemiologic study in the field of cancer, however, but are not practical in certain conditions; e.g., where there is a low incidence or a requirement for biomarkers. In such conditions, hospital-based efforts are advantageous.

We have developed a comprehensive cancer epidemiology study system called HERPACC (Hospital-based Epidemiologic Research Program at Aichi Cancer Center), the first version (HERPACC-I) which was started in 1988. Every first visit outpatient was systematically requested to enroll in the program and fill out a common questionnaire covering lifestyle factors. Case status was identified via hospital-based cancer registration. Until 2000, data for 12,500 cancer patients and 83,000 non-cancer outpatients were pooled in HERPACC-I. In a second version of HERPACC, started in 2001, we added a protocol for obtaining blood samples and semi-quantitative food frequency questionnaire, and this is ongoing.

We are now planning to conduct a cohort study using non-cancer subject enrolled in HERPACC. Direct comparison of results of case-control studies and cohort study using same HERPACC population is a unique and challenging approach for cancer epidemiology.

In this presentation, several results of HERPACC-based epidemiological studies will be introduced.
Keitaro Matsuo, M.D., Ph.D., M.Sc.

Researcher
Division of Epidemiology and Prevention
Aichi Cancer Center Research Institute
Nagoya, Japan

1996  M.D., Okayama University Medical School
1999-2002  Graduate School of Medicine, Nagoya University
(Ph.D., Nagoya University 2002)
Research Trainee, Division of Epidemiology and Prevention, Aichi
Cancer Center Research Institute
2002-2003  Department of Epidemiology, Harvard School of Public Health
(M.Sc., Harvard School of Public Health)
Postdoctoral Fellow, International Agency for Research on Cancer
2004  Researcher, Division of Epidemiology and Prevention, Aichi Cancer
       Center Research Institute
Various aspects of the Mediterranean diet are considered favourable non only cardiovascular disease, but also on several common epithelial cancers. These include frequent consumption of vegetables and fruit, which was analyzed using data from a series of case-control studies conducted in Northern Italy on over 12,000 cases of 20 cancer sites and 10,000 controls. For most epithelial cancers, the risk decreased with increasing vegetable and fruit consumption, with relative risks (RR) between 0.3 and 0.7 for the highest versus the lowest tertile. For digestive tract cancers, the population attributable risks for low intake of vegetables and fruit ranged between 15 and 40%. A number of antioxidants (including carotenoids, lycopene and flavonoids) and other micronutrients showed an inverse relation with cancer risk, but the main components responsible for the favourable effect of a diet rich in vegetables and fruit remain undefined. Fish, and consequently a diet rich in n-3 fatty acids, tended to be another favourable diet indicator. In contrast, subjects reporting frequent red meat intake showed RR above unity for several common neoplasms. Whole grain food (and hence possibly fiber) intake was related to reduced risk of several cancers, particularly of the upper digestive tract. In contrast, refined grain intake and, consequently, glycaemic load and glycaemic index were associated to increased risk of different types of cancers.

In conclusion, a low risk diet for cancer in the Mediterranean would imply increasing fruit and vegetables as well as avoiding increasing meat and refined carbohydrate consumption. Olive oil and other unsaturated fats, which are also typical aspects of the Mediterranean diet, should also be preferred to saturated ones.
Carlo La Vecchia, M.D., M.Sc.

**Head**
Laboratory of Epidemiology
Istituto di Ricerche Farmacologiche di Mario Negri, Milan, Italy

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<th>Year</th>
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<tr>
<td>1979</td>
<td>MD, University of Milan, Italy</td>
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<tr>
<td>1983</td>
<td>M.Sc., Clinical Medicine (Epidemiology), University of Oxford, UK</td>
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<td>1979-89</td>
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<td>1989-</td>
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<td>1987-92</td>
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<td>1992-</td>
<td>Associate Professor of Epidemiology, University of Milan, Milan, Italy.</td>
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<td>1996-2000</td>
<td>Adjunct Associate Professor of Epidemiology, Harvard School of Public Health, Boston, MA, USA</td>
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<td>2002-</td>
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<tr>
<td>2002-05</td>
<td>Adjunct Professor of Medicine, Vanderbilt University, Nashville, TN, USA</td>
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The Japan Collaborative Cohort (JACC) Study

Kenji Wakai
Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, Nagoya, Japan

The Japan Collaborative Cohort Study (JACC Study; Chairman of the study group: Akiko Tamakoshi at Nagoya University Graduate School of Medicine) is a nationwide, multicenter cohort study, with 24 participating research institutions. The study started in 1988 to 1990, when 110,792 inhabitants aged 40 to 79 years completed a baseline questionnaire. They were enrolled from 45 study areas throughout Japan.

The baseline questionnaire covered lifestyle factors including smoking and drinking habits, physical activity, and dietary habits, as well as medical history, education, family history of cancer, height and weight, and occupation. In addition to completing the questionnaire survey, 39,242 participants donated peripheral blood samples at health screening check-ups. The serum samples were stored at -80°C until analyzed for nested case-control studies. For 61,557 subjects (55.6% of the total) in selected areas, we ascertained the incidence of cancer by means of linkage with the records of population-based cancer registries, supplemented by a review of medical records. The vital and residential status of subjects was determined using resident registration records, and causes of death were identified from death certificates.

During the follow-up through 1999 for death and through 1997 for cancer incidence, 4,528 cancer deaths (in all study areas) and 3,437 incident cases of cancer (in the selected areas) were documented. Members of the JACC Study Group have extensively examined associations of lifestyle or other factors and serum components with the risk of cancer incidence and death. More than forty original articles have been published from the study including papers from nested case-control studies utilizing the stored sera. The follow-up of subjects and the analysis of data and serum samples are still on going.

The JACC Study has generated a significant body of information for primary cancer prevention in Asia. It also may provide a good model for nationwide or international multicenter cohort studies, in which individual participating institutions are independent and maintain their originality in research but all contribute to one large cohort.
Kenji Wakai, M.D., Ph.D.

Section Head
Division of Epidemiology and Prevention
Aichi Cancer Center Research Institute
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1984-1990  M.D., Nagoya University School of Medicine
1990-1991  Resident, Anjo Kosei Hospital
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1994-1999  Research Associate, Department of Preventive Medicine/Biostatistics and Medical Decision Making, Nagoya University Graduate School of Medicine
2000-2003  Assistant Professor, Department of Preventive Medicine/Biostatistics and Medical Decision Making, Nagoya University Graduate School of Medicine
2003-2004  Senior Researcher, Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute
2004-present  Section Head, Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute
Korean Multi-center Cancer Cohort Studies for Genomic Epidemiology: Current Status and Perspectives

Keun-Young Yoo
Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, Korea

Human genome epidemiology is the systematic application of the epidemiologic method to the genome to assess the impact of genetic variation on health and disease. Cohort studies are the ultimate application of human genome epidemiology. The Korean Multi-center Cancer Cohort (KMCC) is a multi-center prospective cohort to meet the requirement of genome epidemiological studies on cancer etiology, which had been conducted since 1993. Data on general lifestyle, physical activity, diet, reproductive factors, and agricultural exposures were obtained through direct interview using a structured questionnaire. Anthropometric measurements and some clinical laboratory findings have also been collected and stored in the web-based database system. A biological materials bank with blood (serum, plasma, buffy coat, packed erythrocytes) stored at -70°C and urine at -20°C has been established for the genome epidemiological studies on the cancer etiology. DNA yield study revealed the PCR products for \( \beta \)-globin from nearly all of the samples (98%) from the long term-stored buffy coat specimen in the KMCC. Follow-up for the cancer occurrence has been commencing based on an active surveillance system by health personnel in each district, and a passive surveillance system through record linkages between the central cancer registry, the national death certificate, and the national health insurance claim databases in Korea. As of August 2004, total number of observation for the cohort with biologic specimen was 20,342. Until December 2002, total 382 incident cancer cases have been identified by the passive surveillance and total number of follow-up was 64,999 person-years. Five leading sites of cancer incidence were stomach, lung, liver, colorectum, esophagus in men, and uterine cervix and breast in women. A fundamental question about genomic cohort is how large should it be in order to estimate the main effect of a SNP or haplotype and to detect gene-environmental and gene-gene interactions. On this purpose, the Korean Genomic Epidemiology Society has recently been founded, and a few of new genomic cancer cohorts, i.e. KOEX, KCDC, KNCC, etc., have been launched under the supervision of the Society. The recruitment goal and the design of each cohort will briefly be introduced. Along with other cancer cohorts in Japan, the Korean Genomic Cancer Cohort could provide more convincing evidence on new etiologies of cancer and on the cancer prevention strategy in the Asian-Pacific region.
Keun-Young Yoo, M.D., Ph.D.

Professor and Chairman
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1974-1978  M.D., Seoul National University College of Medicine
1979-1981  M.P.H. (Epidemiology),
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1981-1985  Ph.D. (Preventive Medicine),
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1986-1987  Instructor, Department of Preventive Medicine, SNUMC
1988-1993  Assistant Professor, Department of Preventive Medicine, SNUMC
1994-1998  Associate Professor, Department of Preventive Medicine, SNUMC
1999-Present Professor, Department of Preventive Medicine, SNUMC
2000-Present Chairman, Department of Preventive Medicine, SNUMC
The Self Defense Forces Cohort Study

Suminori Kono
Department of Preventive Medicine, Kyushu University Faculty of Medical Sciences, Fukuoka, Japan

Taking into account the advantage of the comprehensive medical examination for retiring self-defense officials at the Self Defense Forces (SDF) hospitals, the author initiated the SDF Health Study at the SDF Fukuoka Hospital in October of the year 1986, when he was a part-time physician there. Sigmoidoscopy, abdominal ultrasonography, and a 75-g oral glucose tolerance test were included as procedures in the preretirement health examination during a 5-day admission. This health examination was not mandatory, but was received by almost all retiring officials. A lifestyle questionnaire was introduced to inquire about smoking, alcohol use, physical activity, and habitual consumption of limited items of foods and beverages. At the time of the inception of the SDF Health Study, much interest had been focused on increased risk of colon or colorectal cancer associated with low blood cholesterol levels observed in prospective studies. Thus the first cancer-related study was to examine the relation between serum lipids and colorectal adenomas, and the outcome was no material relation with serum total cholesterol. The SDF Health Study was once deployed at four SDF hospitals across the nation.

A series of studies have revealed increased risk of colorectal adenomas associated with cigarette smoking, alcohol use, physical inactivity, abdominal obesity, and non-insulin dependent diabetes mellitus. Total colonoscopy was introduced as a routine procedure in the year 1995; at that time the study had retreated to Kyushu. This approach established that cigarette smoking and alcohol use were associated with a greater risk of adenomas in the distal segment of the colorectum while diabetes mellitus was more markedly related to an increased risk of proximal colon adenomas. It was also found that the association between cigarette smoking and colorectal adenomas did not vary with genetic polymorphisms of CYP1A1, GSTM1, and GSTT1, which are key enzymes in the metabolism of tobacco-related carcinogens. The SDF Health Study evolved to a prospective cohort study in April of the year 2004. Informed consent was obtained as regards the follow-up health survey as well as for donation of venous blood for genetic analysis. Details of the design of the cohort study and conduct of the baseline survey will be discussed.
Suminori Kono, M.D., Ph.D.

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<td>1984 - 1986</td>
<td>Associate Professor of Clinical Epidemiology</td>
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<td>Associate Professor of Public Health</td>
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<td>Fukuoka University School of Medicine, Fukuoka</td>
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<td>1990 - 1995</td>
<td>Professor of Public Health</td>
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<td>National Defense Medical College, Tokorozawa</td>
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A population-based prospective study on cancer and major chronic diseases: the JPHC Study

Shoichiro Tsugane
Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan

Lifestyle is closely related to occurrence of cancer and other chronic diseases. Biological specimens such as plasma and white blood cells are expected to provide useful information on exposure-disease relations considering genetic susceptibility using recent biochemical and molecular techniques. To investigate factors associated with cancer and other chronic diseases in Japan where the disease profile (coronary heart disease is a minor cause of death and the stomach continues to be the most frequent cancer site) and diet are substantially different from Western countries, we launched a population-based prospective study in 1990. Approximately 140,000 men and women aged 40-69 years were selected based on resident registration in 29 communities covered by 11 public health center areas nationwide. At the baseline survey, a self-administered questionnaire including items on simple food frequency, blood (3 aliquots of plasma and 1 buffy coat) and health check-up data (anthropometric measures, blood pressure, biochemical measures such as lipids and liver function test) were collected from 110,000 (80%), 49,000 (35%) and 48,000 (34%) persons, respectively. At year six, a follow-up survey (same survey items as those at baseline plus a semi-quantitative food frequency questionnaire with validity information compared with 4 season 7 day diet records) was conducted, and 100,000 questionnaires, 35,000 blood samples and 33,000 health check-up reports were collected. Further at year eleven, the self-administered questionnaire used at year six was repeated and collected from 97,000 persons. Mortality and immigration, as well as disease incidence (cancer, cerebrovascular disease, ischemic heart disease, diabetes, etc.), were treated as endpoints. Among all cohort subjects, 10,500 deaths, 8,900 cancers, 2,900 strokes and 600 myocardial infarctions were documented as of October 2004. Several findings from the JPHC study will be presented.
Shoichiro Tsugane, M.D., D.M.S.

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1988 - 1994 Head, Environmental Epidemiology Section, Epidemiology Division,
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1992 - 1993 Visiting Scholar, Department of Nutrition and Epidemiology, Harvard
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1994 - Chief, Epidemiology & Biostatistics Division, National Cancer
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2003 - Chief, Epidemiology and Prevention Division, Research Center for
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Polymorphisms of two fucosyltransferase genes (Lewis and Secretor genes) involving type I Lewis antigens are associated with the presence of anti-Helicobacter pylori IgG antibodies.

Yuzuru Ikehara
Division of Oncological Pathology, Aichi Cancer Center Research Institute
Nagoya, Japan

Recent progress in the molecular analysis of *H. pylori* infection has revealed that the bacteria attach to the gastric mucosa through the blood group antigen-binding adhesin, BabA and a clinical relevance has been shown for the babA2 gene encoding BabA adhesin with regard to *H. pylori*-related diseases. BabA binds to both Le\(b\) [Gal (\(\beta\) 1.2Fuc) \(\beta\) 1.3GlcNAc(\(\beta\) 1.4Fuc)-R] and H type I blood group carbohydrate structures [H type I structures; Gal (\(\beta\) 1.2Fuc) \(\beta\) 1.3GlcNAc-R] expressed on the foveolar epithelium of the gastric mucosa. (see Figure1 for the type I Le antigen synthetic pathway in secretor tissues)

We have been studying Lewis blood type antigens using biochemical and molecular biological methods and have obtained the following results concerning type I Le antigen synthesis. Individuals homozygous for nonfunctional alleles of *Le* gene (*lele*) fail to express type I Le antigen (so called Le negative). In the human fucosyltransferase family, only the Le enzyme (FUT3, Fuc-T III) exhibits fucose transfer activity toward a type I precursor (Gal \(\beta\) 1.3GlcNAc-R) or H type I structure with \(\beta\) 1.4 linkage. The Se enzyme (FUT2, Fuc-T II) exhibits fucose transfer activity toward the type I precursor with \(\beta\) 1.2 linkage and is responsible for Le\(b\) expression on erythrocytes, solely determining the secretor status, and making a marked contribution to Le\(b\) expression in colorectal tissues. Individuals homozygous for nonfunctional alleles of the Se gene (*sese*) fail to express
ABH blood antigens in secreted fluids (so called for non-secretors), whereas those very rare individuals homozygous for nonfunctional alleles of the $H$ gene ($h/h$) fail to express ABH blood antigens on erythrocytes. Considering the type I Le antigen synthetic pathway, it is possible that the type I precursor structure for acceptor substrate is used by Se and Le enzymes, with some competition between the two.

The present study was performed to investigate the possibility that $Se$ and $Le$ gene polymorphisms alter the risk of $H.\, pylori$ infection. Two hundred and thirty-nine participants were genotyped for $Se$ and $Le$ and tested for the presence of anti-$H.\, pylori$ IgG antibodies. Using the normal gastric mucosa from 60 gastric cancer patients, we further assessed immunohistochemically whether type I Le antigen expression depended on the $Se$ and $Le$ genotypes.

The $H.\, pylori$ infection rate was positively associated with the number of $Se$ alleles ($se/se$ group, 45.1%; $Se/se$ group, 64.6%; and $Se/Se$ group, 73.3%) and negatively associated with the number of $Le$ alleles ($le/le$ group, 76.4%; $Lelle$ group, 68.3%; and $Le/Le$ group, 55.6%). When the subjects were classified into three groups [low risk, ($se/se, Le/Le$) genotype; high risk, ($Se/Se, le/le$), ($Se/Se, Lelle$), and ($Se/se, le/le$) genotypes; moderate risk, other than low- or high-risk group], the odds ratio relative to the low-risk group was 3.30 (95% confidence interval, 1.40-7.78) for the moderate-risk group and 10.33 (95% confidence interval, 3.16-33.8) for the high-risk group (Figure 2). Immunohistochemical analysis supported the finding that $Se$ and $Le$ genotypes affected the expression of $H.\, pylori$ adhesin ligands.

We conclude that $Se$ and $Le$ genotypes impact on susceptibility to $H.\, pylori$ infection.
Yuzuru Ikehara, M.D., Ph.D.

Researcher, 
Division of Oncological Pathology 
Aichi Cancer Center Research Institute 
Nagoya, Japan 

1994 M.D., Shiga University of Medical Science 
1994-1998 Graduate School of Medicine, Shiga University of Medical Science 
(Ph.D., Shiga University of Medical Science1998) 
1998-2001 Researcher, Division of Pathology (Oncological Pathology), Aichi Cancer Center Research Institute 
2001-2003 Research Associate, Department of Molecular Biology (James C. Paulson), The Scripps Research Institute, La Jolla, CA, U.S.A. 
2003- Researcher, Division of Oncological Pathology, Aichi Cancer Center Research Institute
MEMO
Study of the Association of Human Papillomavirus Infection and Cervical Cancer in China

Wang Yixun
GYN Oncology Department, Liaoning province Tumor Hospital and Institute, Liaoning, P. R China

It was in 1980s, the relationship of cervical cancer to HPV started to be elucidated. HPV type 16 and 18 were first isolated directly from cervical cancer in 1983. From that time the strong association between HPV and cervical neoplasms has been reported worldwide. HPV DNA can be detected from 99.7% of cervical cancer specimens. Approximately 90 types of HPV have been identified, some of which are oncogenic or high risk types.

In order to investigate Human Papilloma virus infection prevalence in China, The study of association between HPV infection and cervical cancer was conducted in a high incidence area of cervical cancer - Shanxi province. It was found that for women from 35-50, the high risk HPV infection rate was 24%, which is much higher than 5%-10% reported from the world. For a group of 1997 married women aged 35-45 : exfoliated cells were collected from cervix (by clinician) and from vagina (by subject herself), Hybrid capture 2 assay, which could detect 13 types HPV DNA of high risk, was carried out. HPV DNA detection rate was 20.8%. The infection rate increased with progression of cervical lesions. ($X^2=444.04, P=0.000$). Comparison of 2 groups of aged 35-39 and 40-45, there was no significant difference of infection rate (20.9%; 20.6%, $X^2=0.03, P=0.86$). While compared with normal subjects: the risk odds ratio HPV infection with cervical cancer/high grade CIN and low grade CIN were 254.2 and 26.4 respectively, with attributive risk percentage (ARP) of 98.1% and 83.6%. The sensitivity of the assay for high risk HPV DNA from clinician collected sample was 98%, which was higher than self collected samples of 84%($X^2=5.92, P=0.015$). No significant difference can be seen in specificity. (86%:85%, $X^2=0.00, P=0.997$). We conclude that high risk HPV infection in female genital tract was the major risk factor of cervical cancer and CINs in this area of China.
Wang Yixun, M.D.

Director, Professor, Chief Doctor
GYN Oncology Department,
Liaoning Province Tumor Hospital and Institute
Liaoning, P. R. China

1962 M.D., ShenYang Medical College
1963 - 1978 OB/GYN Doctor in the Second Hospital of Pan Jin, Liaoning
1978 - today Attending Doctor, vice-chief, and Chief GYN Oncologist in Liaoning Tumor Hospital and Institute
1986 - 1987 Post- Doctal Researcher in New Haven Hospital of Yale University in the U.S.
1991 - 1993 Post- Doctal Researcher in New Haven Hospital of Yale University in the U.S.
Hepatitis virus and hepatocellular carcinoma

Hideo Tanaka
Department of Cancer Control and Statistics, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan

Chronic hepatitis B virus (HBV) infection is a major risk factor of hepatocellular carcinoma (HCC) in Asia. Immunization with HBV vaccine is a most effective weapon against HBV infection and its consequences, although the modality differs among Asian countries. A recent cohort study in Japanese blood donors showed coinfection with HBV and hepatitis C virus (HCV) carried a superadditive risk for HCC.

HCV is a blood-borne virus which causes a wide spectrum of liver diseases, ranging from acute hepatitis to HCC. Parenteral infection through blood transfusion, intravenous drug abuse (IVDU) and tattooing, as well as occupational exposure to blood, have been well defined as determinants of HCV transmission. Recently, the incidence of HCV infection among Japanese blood donors was estimated as 2-5 per 10^5 person-years.

Approximately 60% of persons infected with HCV become HCV carriers and about 75% of Japanese with HCC cases are associated with chronic HCV infection. Life time risk of developing HCC among HCV carriers has been estimated as 30% for males and 6% for females, based on data for the age and sex specific incidence rates of HCC among HCV carriers in Osaka. An older age, being male, duration of HCV infection, type Ib infection, co-infection with HBV, having a high serum transaminase level, having a low platelet count, and heavy drinking and smoking are independent factors associated with the development of HCC among HCV carriers. Cohort studies have demonstrated that interferon therapy can significantly lower the incidence of HCC among patients with chronic hepatitis C who showed normalization of the serum transaminase level after completion of the therapy.

In Japan, a nationwide community-based anti-HCV and HBsAg screening system targeting the age group of 40-70 years has been under the process of development by local municipal governments since 2002. The effectiveness of this screening system for preventing HCC will be evaluated in the future.
Hideo Tanaka, M.D., Ph.D.

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1986-1988 Clinical Staff, Department of Internal Medicine, Osaka Prefectural Hospital
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Liver flukes and Cholangiocarcinoma

Petcharin Srivatanakul
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The liver flukes, *Opisthorchis viverrini*, *Opisthorchis felineus* and *Clonorchis sinensis*, are biologically similar, food-borne trematodes which chronically infect the bile ducts and, more rarely, the pancreatic duct and gall-bladder of human beings and other mammals. Infection is acquired by eating raw or undercooked freshwater fish which contain the infective stage (metacercaria) of flukes. Immature flukes migrate up through the ampulla of Vater to the biliary tree, mature in the small intrahepatic ducts and produce eggs, which are passed in the faeces. If the eggs reach a water body and are consumed by an appropriate species of snail, they hatch and undergo asexual multiplication to produce free-swimming larvae, which can penetrate freshwater fish and become encysted metacercariae.

Infection with *Opisthorchis viverrini* is carcinogenic to humans (Group 1). Infection with *O. felineus* is not classifiable as to its carcinogenicity to humans (Group 3). Infection with *C. sinensis* is probably carcinogenic to humans (Group 2A).

Primary cancers of the liver in adults are of two main histological types: hepatocellular carcinoma which is derived from hepatocytes, and cholangiocarcinoma, (CCA) which is derived from the epithelial lining of the intrahepatic bile ducts. About 560,000 new cases of liver cancer, usually hepatocellular carcinoma, occur annually, and contribute significantly to cancer mortality worldwide.

CCA is a relatively rare tumour in most populations but second among primary malignant liver tumours; about 15% of liver cancers are estimated to be CCA. The geographic distribution worldwide coincides with endemic areas of the liver flukes *O. viverrini* and *C. sinensis*. The interaction between genes and the environment and the interplay of environmental factors, which include diet and lifestyle, illustrate the complexity in understanding the susceptibility to environmental exposures.

The highest incidence of CCA is found in areas of Laos and North and Northeast Thailand suffering from endemic infection with the liver fluke, *O. viverrini*. In Khon Kaen (the Northeast Thailand), 86.5% of liver cancer cases are CCA. In both endemic and non-endemic areas, there have been no significant changes in the incidence of CCA in recent years. It is less than 10 years since *O. viverrini* drug therapy was initiated;
since it probably takes 30 years for CCA development after the infection, the trends of CCA are probably not likely to change in the next decade. Patients with CCA are elderly, with no clear sex differences. CCA occurs at rather older ages than hepatocellular carcinoma in most clinical series.

*C. sinensis* parasitizes the bile ducts of millions of individuals in the Far East, particularly China and Korea. In the *C. sinensis* endemic area in Korea, there is also a high incidence of liver cancer. About 20% of liver cancers in Pusan, Korea are CCA.

Chronic infection with the liver fluke, *O. viverrini* is the major risk factor for the development of CCA. Carcinogenesis of CCA is probably related to the length and severity of infection, the host’s immune response, and other variables such as ingestion of dietary carcinogens, for example nitrosamines. In northeast Thailand, several carcinogenic N-nitroso compounds and their precursors exist at low levels in the daily diet. In addition, endogenous nitrosamine formation by liver fluke infection has been reported. Increased levels of urinary nitrates and salivary nitrites are found in *O. viverrini* infected individuals. The subjects living in high-risk areas for fluke infection who had antibodies to *O. viverrini* had a 10-fold greater potential for endogenous nitrosation, measured on the basis of urinary levels of N-nitrosoproline after praline ingestion, than individuals who did not have antibodies. Vitamin C is found to be effective inhibitor for prevention of the formation of endogenous nitrosation. In several studies in hamsters infected with *O. viverrini* and treated with various carcinogenic N-nitrosamines, induction of cholangiocarcinomas and of hepatocellular nodules was enhanced. These results suggest that the interaction between chemical carcinogens, especially nitrosamines, and OV infestation may play role in the development of CCA in Thailand. Both exogeneous and *in situ* nitrosamine formation may lead to DNA alkylation and deamination. It seems that the presence of parasites induces DNA damage and mutations as a consequence of the formation of carcinogens/free radicals and of cellular proliferation of the intrahepatic bile duct epithelium.
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New strategies of individualized cancer prevention

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Generally, health information based on the individuals’ background allows a stronger message to induce behavior changes in lifestyle, supplement intake, health checkup motivation, and medical facility visits. The background for each individual is made up of past exposure experiences, disease history, current biomarker conditions, and genetic traits, as evidenced by a family history. In order to provide attractive cancer prevention methods for individuals, links to such individual background information are becoming important.

To date, several individualized cancer prevention models have been introduced in practice. Preventive measures to block mother-to-child transmission of hepatitis B virus and thus liver cancer is provided for carrier mothers. Preventive mastectomy against breast cancer is conducted for BRCA1 abnormal gene carriers. Intensive checkup and counseling against colorectal cancer are provided for those with FAP and HNPCC related genes. These specific cancer prevention models for carriers are accepted in several societies.

Recent biomarker studies on the most common cancers indicate possible new strategies. Eradication of *Helicobacter pylori* seems effective to prevent gastric cancer for individual with heavy infection. Health services not covered by health insurance started in Japan for those who seek the test and medication for the eradication. Reported gene-environment interactions between genotypes and interventions also provide new models for individualized cancer prevention. For example, the interaction between aspirin use and an A316G polymorphism of the ornithine decarboxylase gene suggests a possibility to recommend aspirin intake more strongly for A-allele-possessing patients at risk of colorectal adenoma/carcinoma.

Genotype announcement may be a new strategy to induce behavior changes to a less risky lifestyle. Awareness of susceptible genotypes or enhanced health consciousness through genotyping could provide opportunities to correct high risk behavior, e.g., smoking and drinking. Concerning smoking, the cessation rate was found to be higher for the announced group in some studies, although not in all cases.

Undoubtedly, the increasing number of available biomarkers will contribute to the establishment of new modes of individualized cancer prevention.
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Breast cancer susceptibility and chemoprevention

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Breast cancer is the second most common cancer among Indian women. The incidence of breast cancer has shown a trend towards gradual increase in the Chennai Metropolitan area over the past two decades, with the current CIR of 19.9 /100,000. While hereditary breast cancers account for 5-10%, the vast majority is sporadic.

BRCA1 and BRCA2 are the major breast cancer susceptibility genes identified to date. However, contrary to the initial predictions, they account for only 15-20% of hereditary cancers. In our series of 61 patients of Hereditary breast &/or ovarian cancers, 8 deleterious mutations were detected. Of the 24 Hereditary breast cancer families tested, four were found to have a deleterious mutation (16%). Only one of the thirteen families with Hereditary breast and ovarian families were detected to have a deleterious mutation in our series. Two out of 20, of the early onset breast cancers (<35 years of age) tested were found to have a disease causing mutation.

Apart from the high-risk genes several low risk genes could also contribute to the development of breast cancer. These low susceptibility genes include those that are involved in carcinogen activation and inactivation, estrogen metabolism, growth factors and their receptors etc. Single nucleotide polymorphisms in these genes could contribute to changes in their functional efficiency. Examples of these include Cyp19 (Trp39Arg), Cyp17 (T-34C) GSTP1 (Ile462Val), GSTM1 (Present/Null), TGF β (Leu10Pro) and c-erbB2 (Ile655Val).

Chemo-prevention is likely to contribute significantly in the prevention of several cancers including that of breast cancer. Tamoxifen for example has been shown to reduce the risk of contralateral breast cancers. The trials evaluating the role of steroidal and non-steroidal aromatase inhibitors are already underway and should provide the critical answers to the efficacy of this approach in the high-risk group.
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The concept of multi-stage carcinogenesis implies that cancer prevention with different strategies is feasible for each stage. Recently emphasis has been placed on defense mechanisms existing in different stages of carcinogenesis, with the immune system as the body’s last line of defense against cancer development. Cancer immunosurveillance—routinely eliminating nascent transformed cells in the body—needs to be proven through investigations of general populations.

We previously reported an elevated incidence of cancer among individuals showing low levels of NK activity in peripheral blood lymphocytes, as compared to medium or high levels, based on a prospective cohort study of a Japanese general population. Large differences were found among individuals in NK activity, and lifestyle factors seemed to explain only a part of these, so we investigated the genetic factors underlying individually variation in NK activity. From the cohort members, we selected two groups with low and high NK activity, each of which consisted of gender- and age-matched individuals who had not experienced any cancer. Next, a phenotype-genotype association analysis was carried out, comparing these two groups in terms of HLA class I genotypes and SNPs in the NKG2D gene.

We found that specific HLA-B and C genotypes were associated with NK activity, implying a role of HLA class I molecules in maintaining a stable repertoire of NK cells; furthermore we succeeded in identifying two haplotype blocks in the NKG2D gene region, each of which generated two major haplotype alleles closely related to low and high NK activity (P<0.0001). In addition, these haplotypes were found to be significantly associated with cancer risk, in terms of a case-control study within this cohort. We previously found that selected lifestyle factors known as good health practices were associated with high NK activity. In our study, we are looking for further evidence of individualized immuno-prevention of cancer: NK activity-enhancing effects of lifestyle may differ among individuals with different NKG2D haplotypes.
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Only primary prevention and early detection and removal of pre-malignant lesions can reduce cancer incidence, although early detection of many cancers and effective treatment can cure the majority of cancer patients. The World Health Organization has estimated that failure to implement effective cancer prevention programs will result in the global burden of cancer increasing from 10 million new cases in the year 2000, to 15 million in 2020 with about 10 million cancer deaths in that year. About 85 percent of cancer is caused by environmental exposure, most of which are due to non-communicable diseases (NCD), and about 20 percent to communicable diseases. About half of the 10 million new cases of cancer in the year 2000 were preventable, using our current knowledge.

In Asia, NCD are now the commonest causes of death and disability, and cancer is either the second or third commonest cause of death in most Asian countries. The major risk factors for NCD in Asia are tobacco use, unhealthy nutrition, physical inactivity and alcohol abuse. In some Asian countries more than half of all adult males use tobacco, and overweight/obesity is a rapidly developing problem in many countries. Therefore integrated NCD prevention programs are being developed and implemented in a number of Asian countries, of which the Philippines is the leading example.

Vaccination (immunisation) is the great hope for prevention of the infectious cancers, and hepatitis B vaccination of newborn children has been progressively introduced in Asia since the early 1980’s. Finally, cervical screening and removal of pre-malignant lesions, using low technology screening tests and simple surgical procedures performed by trained health workers, has great potential to dramatically decrease cervical cancer mortality, which is the second commonest cancer of women in Asia.
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