

Research Center for Cancer Prevention and Screening

Preface

The Research Center for Cancer Prevention and Screening (RCCPS) was established in October, 2003. The organization at the present time consists of three groups and a division: Epidemiology and Prevention Group, Screening Research Group, Research Infrastructure Group, and the Division of Cancer Screening that is responsible for cancer screening services. Our mission is advancing research projects and activities for cancer prevention and screening to provide correct information and the optimal methods in order to keep the largest possible number of people from developing and dying from cancer.

The Epidemiology and Prevention Group worked as one division till May, 2013, and was then reorganized as the Division of Epidemiology and the Division of Prevention. The former conducts research activities to build evidence to understand etiology of cancer while the latter to evaluate evidence and to provide correct information on cancer prevention proposing guidelines. Research activities are reported as one group here. Various scales of epidemiologic studies have been promoted including the Japan Public Health Center-based prospective study (JPHC Study) started in 1990 and the JPHC-NEXT started in 2011. The results contribute to build evidence steadily in Japan and also on a global scale with international collaborative projects. The accumulated experience was used to deal with a project presenting a vision of all molecular epidemiology cohort studies united nationwide. To develop an evidence-based cancer prevention strategy in terms of lifestyle intervention suitable for the Japanese population, some systematic literature reviews and pooled analyses were conducted to update current evidence-based cancer prevention recommendations.

The Screening Research group was organized in June. The Division of Screening Assessment and Management and the Division of Screening Technology and System Development belong to the group. Research activities are reported as the Screening Assessment and Management Division here. The division has conducted studies on the assessment and management of screening programs, particularly nationwide programs, and on other issues relevant to cancer screening. Guidelines on screening for breast cancer and gastric cancer were developed, being revised by comments, and to be open. Quality Assurance (QA) in cancer screening at municipalities was performed using a checklist and was also used to eliminate cancer-screening disparities. A study to calculate a standardized screening rate was undertaken. Furthermore, the survey was conducted in order to grope for the effective countermeasure against low cancer screening rates. A workshop on cancer screening management was held for the members of prefectural committees. A randomized controlled trial (RCT) of colonoscopic screening has been carried out. The Division also participated in other RCTs and conducted a case-control study for gastric cancer screening using endoscopy.

The Research Infrastructure Group to which the Division of Public Health Policy Research belongs was newly installed in June. The division investigates the methods of distribution and dissemination of scientific evidence concerning cancer prevention, screening, and survivorship. To establish a research infrastructure, the Division conducts methodological research and education concerning behavioral science, epidemiology and biostatistics and supports large scale interventional studies. Several leaflets to remind the general population about cancer screening were developed. Workshops were conducted to support local governments. Comics on cancer education for children were produced and distributed.

A large cohort is being established for breast cancer patients. Novel contents were created to enrich the education on the ICR web, an e-learning site for those who are involved in any clinical research.

The Division of Cancer Screening changed its name from the Division of Screening and Development in April and came to be run under the management of vice director of the RCCPS. The Division is in charge of multiphasic cancer screening using several imaging modalities. With informed consent, the data and samples are stored for future research. Malignant tumors were detected in 44 out of 819 new participants and in 43 out of 1745 repeaters who underwent multi-phasic clinical programs in 2012. Detection rates were 5.37% and 2.46%, respectively.

Research results are returned to the public through paper publications, conference presentations, lectures, and information on the *Ganjoho* (Cancer Information) service by the Center for Cancer Control and Information Services and other websites, leaflets and pamphlets, and so on. To achieve our mission, all the members in the RCCPS share a strong will to keep moving forward steadily and diligently.

Shoichiro Tsugane, M.D., D.M.Sc.
Director, Research Center for Cancer Prevention and Screening

Organization

President:

Tomomitsu Hotta

Director:

Shoichiro Tsugane

Epidemiology and Prevention Group

Chief: Shoichiro Tsugane

Epidemiology Division

Chief: Motoki Iwasaki

Prevention Division

Chief: Shizuka Sasazuki

Screening Assessment and Management Group

Chief: Hiroshi Saito

Screening Assessment and Management Division

Chief: Hiroshi Saito

Division of Screening Technology and Development

Chief: Hiroshi Saito

Research Infrastructure Group

Chief: Shoichiro Tsugane

Division of Public Health Policy Research

Chief: Seiichiro Yamamoto

Dupty Director:

Yasuaki Arai

Division of Screening Practice

Chief: Yukio Muramatsu

Activities of the Divisions

Shoichiro Tsugane, Shizuka Sasazuki, Motoki Iwasaki, Norie Sawada, Taichi Shimazu, Taiki Yamaji, Ai Noda, Izumi Suenaga, Hadrien Charvat, Sanjeev Budhathoki, Azusa Hara, Akihisa Hidaka, Manami Inoue, Thomas Svensson, Eiko Saito, Yuri Ishii, Yingyan Gong, Jun Umesawa, Tomomi Mukai, Hiroko Ogata, Kayo Ohashi, Koichi Kawamura, Izumi Matsumoto, Yurie Shinozawa, Noriko Wada, Miho Onishi, Yuko Kato, Yasuko Iba, Michiko Okajima, Ayako Toyama

Introduction

The Epidemiology and Prevention Division has conducted research activities as one division until May, 2013, and was then recognized as two divisions, the Epidemiology and Prevention Divisions. The activities of the divisions are thus described together as The Epidemiology and Prevention Group in this annual report. The group has planned and conducted independent and collaborative studies on cancer etiology and prevention, with a special focus on dietary, environmental and genetic factors. Several epidemiological projects are currently in progress.

Research activities

Population-based Prospective Study (the JPHC Study and the JPHC-NEXT Study)

Diet has been implicated in the etiology of cancer and in the unique patterns of cancer incidence in Japan. However, the epidemiological evidence for this contention has been limited. The group therefore initiated a cohort study, the Japan Public Health Center-based Prospective Study (JPHC Study), in 1990, in collaboration with 11 public health centers and other institutes, in which approximately 140,000 individuals from 11 areas were scheduled to be followed up for at least 30 years. A total of 23,629 deaths, 19,708 cases of cancers, 6,225 cases of strokes and 1,224 cases of myocardial infarctions, had been documented as of December, 2013.

In the cohort, lifestyle factors that were assessed in the baseline and/or 5 and/or 10 year follow up questionnaire, examination data from health checkups or stored blood samples were investigated in relation to the subsequent risk of total death, total or specific cancer and other lifestyle-related diseases.

Death: Although dietary patterns have been linked to depression, no study had yet examined the association between dietary patterns and suicide risk. Among both men and women, a 'prudent' dietary pattern with a high intake of vegetables, fruits, potatoes, soy products, mushrooms, seaweed and

fish was associated with a decreased risk of suicide. Total Cancer: Being a known human carcinogen, total arsenic and inorganic arsenic showed no association with the risk of total cancer in both men and women but their intake tended to be associated with an increased risk of lung cancer especially in currently smoking men (1). The association between social support and risk of cancer incidence and mortality was examined. Low social support was not associated with the risk of total cancer in men and women but was associated with a higher risk of colorectal cancer in men (2). Ten year estimates of the probability of cancer occurrence based on age, sex, and the pattern of adherence to five healthy lifestyle habits (never smoking, moderate or no alcohol consumption, adequate physical activity, moderate salt intake, and appropriate body mass index) was provided. Adherence to all five habits was estimated to reduce the 10-year probability of cancer occurrence by 1/2 in men and 1/3 in women, suggesting the importance of lifestyle improvement (3). Stomach Cancer: No association of plasma isoflavone concentrations with gastric cancer risk was found in a nested case-control study, which supported the previously observed null association between isoflavone intake and gastric cancer risk (4). Liver Cancer: Higher plasma adiponectin levels were associated with an increased risk of primary liver cancer with hepatitis virus infection in a nested case-control study (5). Breast Cancer: For total fruit and vegetable consumption, our results did not provide any substantial association with a decreased risk of breast cancer. Intake of cruciferous vegetable showed a statistically significant association with a decreased risk of breast cancer among premenopausal women (6). The others: Not only cancer but also other non-communicable diseases (NCDs) are designed to be endpoints of the cohort study. Associations between lifestyle factors and suicide (7), stroke (8-11), coronary heart disease (10 and 11), cardiovascular disease (CVD) (12), myocardial infarction (13), dentition status (14) and diabetes (15-19) were investigated.

Recruitment for the JPHC-NEXT study and the collaborative studies set for 100,000 participants started in 2011 and is in progress in several areas

in order to update evidence with the current generation. Men and women of 40-74 years old of age at the baseline survey are to be followed up for 20 years. Overall survival and NCDs such as cancer, CVD, diabetes and mental illness are listed as the main endpoints. The collected data and samples are to be analyzed with up-to-date technology including genomics. A standard protocol for a molecular epidemiology cohort study in Japan is projected to be developed based on the JPHC-NEXT protocol. To conduct verification of a feasibility and validation study to consolidate data together with the other cohort study with its original protocol, a new cohort study by Strategic Funds for the Promotion of Science and Technology was launched and about 7000 men and women were recruited in 2 areas by 2013. The eventual goal of the project is to promote the Japanese Consortium for Cohort Studies of Molecule and Lifestyle presenting a vision of all molecular epidemiology cohort studies united nationwide.

Epidemiological Study of Japanese Brazilians (Sao Paulo-Japan Cancer Study)

Studies on migrants offer some clues as to the relative importance of genetic and environmental factors in the etiology of cancer. Several epidemiologic studies in Brazil, a multi-ethnic nation with 1.2 million people of Japanese ancestry, are in progress. A case-control study was conducted with subjects in Nagano, Japan, and São Paulo, Brazil to clarify whether particular genetic markers of immunoglobulin G (IgG) contributed to the magnitude of natural antibody responsiveness to tumor-associated antigen human epidermal growth factor receptor 2 (HER2) in patients with breast cancer and racially restricted contributions were observed (20). A colorectal adenoma case-control study in Japanese Brazilians in São Paulo is in progress. The validity of the quantitative FFQ used in the study was assessed (21).

Cancer Prevention Study

To develop an evidence-based cancer prevention strategy in terms of lifestyle intervention suitable for the Japanese population, a systematic literature review project (22) and a pooled analysis (23) were conducted. Evidence on smoking, alcohol, anthropometry, fruit and vegetables intake, other foods and lifestyles and infectious diseases as risk

factors of the main cancers in Japan was reviewed to make final or updated judgments, each of which has been made public on the WEB (http://epi.ncc.go.jp/can_prev/) and distribution of booklets. Based on the judgments, current evidence-based cancer prevention recommendations for Japanese provided by the study group were also updated. The evidence-based materials to build up the recommendations were used to develop measures and policies in national health promotions. A population-based double-blind randomised controlled trial in a Japanese population with atrophic gastritis in an area of high stomach cancer incidence was conducted between 1995 and 2000 (Hiraka Study), and suggested that vitamin C supplementation may not have a strong effect on reducing infections in individuals with atrophic gastritis (24). Prediction model applications that calculate changes in risk through lifestyle modification are to put on the internet based on results from JPHC study. Data on the probability of 10-year survival free from cancer and cardiovascular incidence, and, for men, of the 10-year risk of colorectal cancer development are now available (<http://epi.ncc.go.jp/riskcheck/>), and others are under construction.

International Collaborative Projects

International collaborative projects to contribute on to the global scale with a focus on Asian cancer prevention strategies (Japan-China cooperative research work, Asia Cohort Consortium (ACC) (25-27), Asia Breast Cancer Consortium (28 and 29), Pooling project of Prospective Studies of Diet and Cancer, Collaborative Group on Hormonal Factors in Breast Cancer, and a systematic analysis of 24 h urinary sodium excretion and dietary surveys worldwide (30).

Reviews and others

Analysis of the clinical data was carried out (31 and 32) as well as some contribution to a systematic review and meta-analysis on definition of incident type 2 diabetes (33) and a report of the Japan Diabetes Society/Japanese Cancer Association Joint Committee on Diabetes and Cancer (34).

List of papers published in 2013 Journal

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SCREENING ASSESSMENT AND MANAGEMENT DIVISION

Hiroshi Saito, Chisato Hamashima, Kumiko Saika, Ryoko Machii

Introduction

The Screening Assessment and Management Division has conducted studies on the assessment and management of screening programs, particularly nationwide programs, and on other issues relevant to cancer screening.

In addition, the most important mission of the Research Center for Cancer Prevention and Screening in terms of screening is the central activity of assessing and managing cancer screening at the national level, which is closely related to the pillars in the Individual Targets for Cancer Screening in the Basic Cancer Control Plan issued in 2007 and revised in 2012. Thus, the Screening Assessment and Management Division has developed and updated screening guidelines (Cancer Screening Assessment) and constructed quality assurance systems for the screening programs (Cancer Screening Management).

Routine activities

Development of cancer screening guidelines

Guidelines on screening for breast cancer have been developed and will be published in 2014. Gastric cancer screening guidelines have been revised and will also be published in 2014.

Quality Assurance (QA) in cancer screening at municipalities

The division collected the information related to implementation of cancer screening and its management situation using Checklists (CLs) as a structure indicator in quality assurance at municipalities. The division also evaluated process indicators such as rate of work-up, and ranked those indicators in all cities by prefecture in order of excellence so that each city compares its indicator with those of other cities. The overall CL score in 2013 collected this year was improved by 5-9 % for five cancer screening programs as compared to those in 2007. Based on such improvement, we prepared a revised version of the CLs, which was submitted to the Cancer Screening Expert Committee of the Ministry of Health, Labour and Welfare.

The division set up the website which allows mutual communication and support toward

municipalities such as provision of their QA data archives and information relevant to cancer screening. In 2013, CL data were collected from municipalities and evaluation results were fed back to participants on the website. One thousand three hundred and ninety municipalities (82%) utilized the website by registering as members of the site.

Calculation of standardized screening rate

The division calculated the standardized screening rate using an equation to estimate target population size in municipalities. The calculated data were released on the website of the Center for Cancer Control and Information Services. This activity will be continued on an annual basis.

Workshop on cancer screening management

The Division held a one-day educational workshops for the members of prefectural committees of cancer screening management, aiming at activating quality assurance activities in each of the 47 prefectures. The themes this year were breast and cervix. The main contents of the workshops were the methods of quality assurance of the screening programs within each prefecture. Other basic issues required conducting organized cancer screening programs and issues of such as those of screening assessment were also included in the contents.

There were 86 participants in the workshops from 44 prefectures, who consisted of administrative officers (45%) and members of the committee (55%). This activity was performed as a project of the Center for Cancer Control and Information Services and will be continued on an annual basis.

According to the survey on the activity of the prefectural committees, 34 prefectures held meetings to discuss cancer screening management and 22 (8 in the previous year) released the evaluation results of municipalities using CLs for lung cancer. This result suggests the effect of the previously held workshop on the activity of the committees.

Research activities

A randomized controlled trial (RCT) of colonoscopic screening and other RCTs

A randomized controlled trial evaluating one-time colonoscopic screening (CS) for colorectal

cancer was started in 2009. The division has been responsible for designing and managing the study as the head office of the study. The cumulative number of subjects who gave informed consent, and who were thus enrolled in the study, was 6512 at December 2013, corresponding to 65% of the planned number. Data monitoring results showed randomization had been performed successfully. No serious adverse effect was reported associated with screening colonoscopy. Eleven cases of minor complications were reported in the therapeutic procedure. The division have participated also in other RCTs (breast cancer and lung cancer screening) as a member of headquarters of the research and supported those studies.

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DIVISION OF PUBLIC HEALTH POLICY RESEARCH

Seiichiro Yamamoto, Yuri Mizota, Ayumi Nakagawa, Mika Takai

Introduction

The Division of Public Health Policy Research was established in June 2013. The Division investigates the methods of distribution and dissemination of scientific evidence concerning cancer prevention, screening, and survivorship. The aim of our studies is to fill the gap between the scientific evidence and the behavior of the people towards cancer prevention and screening by supporting local government and directly approaching the public. In addition, because of the lack of evidence, we try to establish scientific evidence for cancer survivorship.

As for the activity for establishing a research infrastructure, we conduct methodological research and education concerning behavioral science, epidemiology and biostatistics and support large scale interventional studies.

Research concerning promotion of cancer prevention and screening using social marketing method

The examples of the Division's achievements during 2013 for promoting cancer screening are as follows: development of leaflets for individual reminders regarding for several cancer types such as "5 cancers", "breast cancer", "colorectal cancer", and "cervical cancer" (Figure 1), support of local governments by conducting workshops and developing a website, and intervention for the promotion of cancer screening in several local municipalities as a model. To educate elementary school students about cancer, we developed the comic style book "Gan no Himitsu (Secret

of Cancer)", which is a series of long sellers by Gakken Publishing Co., Ltd (Figure 2). The book was distributed to 23,500 elementary schools and 3,000 public libraries. In addition, 4,005 books were purchased by the local municipalities using their own budgets. We are planning to conduct research for the promotion of HCV testing in collaboration with local municipalities in order to prevent liver cancer.

Research for cancer survivorship

A large cohort is being established for breast cancer patients, to investigate the effect of lifestyle and psychosocial factors on their QOL and prognosis. The cohort consists of several sub-cohorts including collaborative cohorts of clinical trials, a cohort in the National Cancer Center, and a collaborative cohort with Setouchi cancer registry. As of December 2013, we had recruited more than 700 breast cancer patients last year and 3,000 patients in total. The cohort became one of the largest patient cohorts in the world. We are planning to extend the cohorts for other cancers such as colon and rectum.

Education of staffs involved in clinical research

We develop an e-learning site for the education of staff involved in clinical research such as researchers, data managers, clinical research coordinators, and members of institutional review boards. ICRweb (<http://icrweb.jp>) provides more than 120 subject headings. As of December 2013, more than 4,000 users had registered on the site in last year and more than 26,000 users have registered in total.

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Figure 1



Figure 2

DIVISION OF SCREENING PRACTICE

Yukio Muramatsu, Ryutaro Kakinuma, Takashi Terauchi, Gen Iinuma, Nachiko Uchiyama, Yasuo Kakugawa, Minoru Machida, Seiko Kuroki, Minoru Matsumoto, Yosuke Otake, Takehiro Izumo, Chihiro Tsunoda, Takahiro Kasamatsu, Tomoyasu Kato, Mitsuya Ishikawa, Syunichi Ikeda, Satoshi Okada, Yasuaki Arai

Introduction

In April 2013, a change in the Research Center for Cancer Prevention and Screening (RCCPS) organization was made to clarify the function of each of its divisions. As a result, what was originally the Screening and Development Division became the Division of Screening Practice. Cancer screening is performed by medical staff from the new division. There are 8 radiologists, 3 gastroenterologists, 4 gynecologists, 1 pharmacist, 7 radiologic technologists, 2 ultrasonographic technologists, 2 medical laboratory technologists, and 6 nurses. The division is in charge of multiphasic cancer screening using several imaging modalities to develop new cancer screening systems and to evaluate new screening tests. Our Division now has one multi-detector computed tomography (MD-CT) system, two magnetic resonance imaging (MRI) systems (1.5 T and 3.0 T), two positron emission tomography/computed tomography (PET/CT) systems, one cyclotron system, one digital radiography (DR) system with a newly developed flat panel detector, two mammography (MMG) systems, three ultrasonography (US) systems, and three endoscopy systems. All medical images are digitalized and all imaging diagnosis can be made from the cathode ray tube (CRT) monitors.

Routine activities

1. Course of cancer screening

The basic plan for males consists of screening for cancer of the lung, esophagus, stomach, colon, liver, gall bladder, pancreas, kidney, and prostate. In the basic plan for females, the screening for cancer of the breast, uterus, and ovary are added to the plan for males, excluding the prostate. In addition, for both men and women who undergo a complete set of screening, whole body scanning using PET is provided as an option. Other than multi-phasic programs, a screening program has been prepared for lung and female genital cancers, including cancer of the uterus and ovary, breast cancer and gastrointestinal cancer. Blood samples are also

obtained for biochemistry and tumor markers such as CA19-9, CEA, CA125, PSA, and genetic analysis.

2. Eligibility criteria for participants

The cancer screening program at the Research Center for Cancer Prevention and Screening has been planned for applicants 40 years or older who give written informed consent for the screening, including blood samples for genetic analysis, and who take the questionnaire survey concerning lifestyles. These study protocols have been approved by The Institutional Review Board (IRB). Applicants who have been diagnosed as having cancer, and/or have a history of cancer treatment, such as surgery or endoscopic mucosal resection or chemotherapy within the previous one year, are excluded.

3. Cancer screening methods

In the multiphasic cancer screening programs, CT for lung cancer, abdominal US for cancer of the liver, gall bladder, pancreas, and kidney, MRI for cancer of the uterus and ovary, gynecological examinations with Pap-smear, and MMG and US for breast cancer are performed on the first day. On the following day, gastroscopy for cancer of the esophagus and stomach, and total colonoscopy for cancer of the colon and rectum are conducted. If a barium enema is chosen, the examination is carried out on the third day. Moreover, from the beginning of December 2010, CT-colonography (CTC) has been provided as an optional method for cancer screening. FDG-PET is offered on the first day as an option, if the participants wish to undergo the examination.

4. Results of cancer screening

Recent accurate data on cancers have not been obtained due to lack of adequately long follow-up data from our 2013 patients. We have therefore presented confirmed data from the previous year. Two thousand four hundred and sixty six participants underwent multi-phasic programs (new, 753; repeater, 1713). Malignant tumors were detected in 44 out of 753 new participants and in 43 out of 1713 repeaters who underwent multi-phasic clinical programs in 2012 (Tables 1 and 2). Detection rates were 5.84% and 2.51%, respectively.

5. Imaging system

All medical images in our center are digitized. Original or compressed computed radiography (CR), DR, CT, MRI, PET, US, and endoscopy images can be easily and rapidly referenced on the medical information system for research, administration, and clinical expertise (MIRACLE). A reporting system has been established. MIRACLE for cancer screening is used for all routine work.

Research activities

(1) The first breast tomosynthesis system in Japan was installed at RCCPS in September 2009. Since October 2010, a breast tomosynthesis study has started in cooperation with breast surgeons at the National Cancer Center Hospital (NCCH). Regarding the study, NCC IRB approval was granted in December 2008. The sensitivity and specificity of tomosynthesis in comparison with conventional MMG, US, other modalities, and pathological findings are in the process of evaluation. The usefulness of the adjunction of digital breast tomosynthesis to full-field digital mammography in evaluation of the pathological

response after neoadjuvant chemotherapy for breast cancer detected at the NCCH has been assessed.

- (2) The clinical usefulness of CT-colonography has been assessed.
- (3) In order to establish guidelines for the management of pulmonary nodules detected with low-dose chest CT screening, patients with pulmonary nodules between 5 mm and 10 mm in size are being examined in the follow-up clinic.
- (4) A computer-aided system for detection of pulmonary nodules on low-dose CT images is being developed and the clinical usefulness of a super high-resolution CT scanner has been assessed.
- (5) The clinical usefulness of C11-methionine-PET in several kinds of brain tumors detected at the NCCH has been assessed.

Clinical trials

Cancer re-screening for those subjects who have finished a follow-up of five years began in February, 2009 in our center. As a result, a new study based on the follow-up data has been started.

Table 1. Cancerous detection rate in new participants (2012.4.1-2013.3.31)

	No. of cancerous cases	No. of new participants	Detection rate (%)
colo-rectum	16	753	2.12
stomach	8	753	1.06
esophagus	4	753	0.53
prostate	4	494	0.81
lung	4	753	0.53
breast	4	259	1.54
thyroid	2	753	0.27
uterus	2	259	0.77
Total	44	753	5.84

Table 2. Cancerous detection rate in repeat participants (2012.4.1-2013.3.31)

	No. of cancerous cases	No. of repeat participants	Detection rate (%)
colo-rectum	12	1713	0.70
stomach	9	1713	0.53
esophagus	8	1713	0.47
breast	6	571	1.05
prostate	3	1142	0.26
lung	3	1713	0.18
uterus	1	571	0.18
others	1	1713	0.06
Total	43	1713	2.51

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