

Research Center for Cancer Prevention and Screening

Preface

The Japanese Government initiated the Third-Term Comprehensive 10-Year Strategy for Cancer Control in 2004, aimed at a dramatic decrease in the incidence and mortality rates of cancer in Japan. In order to achieve these aims, development of efficacious methods for cancer screening and cancer prevention and dissemination of information about cancer at the national level are particularly important. Consequently, the Research Center for Cancer Prevention and Screening (RCCPS) was established in the campus of the National Cancer Center, Tokyo, in February 2004. Research on cancer prevention and screening is directly in line with the aim of the Third-Term Comprehensive Cancer Control Project. Initially, this center was composed of four divisions, the cancer screening division, cancer screening technology division, epidemiology and prevention division, and statistics and cancer control division. After the establishment of the Center for Cancer Control and Information Service in October 2006, the last of the above mentioned divisions was transferred from the RCCPS to this new center.

In April 2008, a change in the organization was made to clarify the function of each division in the RCCPS. As a result, in two out of three divisions, names were changed: the cancer screening division became the Screening and Development division, and the cancer screening technology division became the Screening Assessment and Management Division. All clinicians moved to the former division.

The Screening and Development Division is responsible for multiphasic cancer screening using a variety of imaging modalities, such as helical-CT, positron emission tomography (PET) and total colonoscopy, to identify cancer patients among the participants in the study at the RCCPS. The performance characteristics of the screening modalities are measured in collaboration with other Divisions. In addition, clinical evaluation aimed at the application to cancer screening of not only new imaging modalities such as CT-colonography, MRI (3.0 Tesla), and mammography with a tomosynthesis system, but also of PET-pharmaceuticals (except FDG), is under way in collaboration with several divisions of the National Cancer Center Hospital. Among the 9,485 subjects who underwent the general courses for first time, 495 some type of cancers have been detected (5.2%). The Center is planning to provide general screening courses, including vision examinations, fundus examination, tonometry, ECG, and optimal brain checkups in addition to cancer screening.

The Screening Assessment and Management Division is responsible for data collection, integrated management, analysis and dissemination of information on cancer screening at the national level. Studies to evaluate the efficacy of cancer screening programs and development and updating of screening guidelines are undertaken at this division. Guidelines for colorectal, stomach and lung cancer screening have already been published. In addition, construction of a quality assurance system is under way. Studies on developing new technologies for early detection of cancer are performed, as well as measurements of the sensitivities and specificities of such modalities. These studies are intensively promoted to establish screening systems that would allow a reduction in the mortality and incidence rates of cancer in the country.

The Epidemiology and Prevention Division plans and conducts independent and collaborative studies on cancer etiology and prevention, with special focus on dietary factors, gene-environmental interactions and effective measures for cancer prevention. In this respect, several epidemiological projects are currently in progress, including ecological, case-control, cohort and intervention studies, while the methodological backgrounds of dietary assessment (nutritional epidemiology) and molecular biomarkers (molecular epidemiology) are intensively investigated.

I would like to express my sincere appreciation for the support that we have received from the Ministry of Health, Labour and Welfare, other governmental organizations, private organizations, individuals, and also the Foundation for the Promotion of Cancer Research. Moreover, I am grateful for the diligent efforts of my colleagues who have devoted their time and talent to developing the RCCPS.

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Organization

Chief Director:

Takamasa Kayama

Director:

Noriyuki Moriyama

Screening Technology and Development Division

Chief: Yukio Muramatsu

Screening Assessment and Management Division

Chief: Hiroshi Saito

Epidemiology and Prevention Division

Chief: Shoichiro Tsugane

Activities of the Divisions

SCREENING TECHNOLOGY AND DEVELOPMENT DIVISION

Yukio Muramatsu, Ryutaro Kakinuma, Takashi Terauchi, Nachiko Uchiyama, Yasuo Kakugawa, Minoru Machida, Seiko Kuroki, Minoru Matsumoto, Chihiro Tsunoda, Gen Iinuma* Yosuke Otake*, Takahiro Kasamatsu*, Tomoyasu Kato*, Mitsuya Ishikawa*, Syunichi Ikeda*, Takashi Onda*, Shiho Gomi*, Masahiro Suzuki*, Hiromitsu Daisaki*, Takeshi Murano*, Chieko Nagashima*, Naoki Shimada*, Eiko Taguchi*, Hiromi Kimura*, Midori Hashimoto*, Akiko Sakurai*, Emi Masuda*, Daisuke Kano, Yoshie Nagumo*, Yoshi Kosai, Miyuki Mandai, Akiko Kutsuzawa, Michiko Kawakami, Yukiko Okamura, Mari Kanega, Mizuho Nomoto, Miho Ishikawa, Noriko Sasaki, Teiko Oki, Yoshie Iga (*NCCH)

Introduction

In April 2008, a change in the RCCPS organization was made to clarify the function of each of its divisions. As a result, what was originally the Cancer Screening Division became the Screening and Development Division. Cancer screening is performed by medical staff from the new division. There are 7 radiologists, 3 gastroenterologists, 1 pharmacist, 7 radiologic technologists, 2 ultrasonographic technologists, 2 medical laboratory technologists, and 6 nurses. A gynecologist at the NCCH supports gynecological examinations. 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 (1.5T and 3.0T), 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 CRT monitors.

Routine Activities

1. Course of cancer screening

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 is prepared for the lung and female genital cancer, 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. Applicants with a cancer diagnosis and/or history of cancer treatment, such as surgery or endoscopic mucosal resection or chemotherapy within the previous one year, are excluded.

3. Cancer screening methods

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, 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

Cancer screening examinations were carried out in 3942 (new, 1575; repeater, 2367) participants from Jan. to Dec. in 2011. Two thousand seven hundred and sixty four participants underwent multi-phasic

programs (new, 1210; repeater, 1554). Cancer screening for the lung, female organs, breast and alimentary tract were independently performed in 565 (new, 15; repeater, 550), 58 (new, 14; repeater, 44), 80 (new, 12; repeater, 68), and 135 (new, 19; repeater, 116) participants, respectively. Moreover, CTC was carried out in 340 (new, 305;repeater,3 5) participants. Recent accurate data on cancers have not been obtained due to lack of adequately long follow-up data from our 2011 patients. We have therefore presented confirmed data from the previous year. Malignant tumors were detected in 76 out of 1260 new participants and in 40 out of 1766 repeaters who underwent multi-phasic clinical programs in 2010.

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 Activity

- (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 of breast

surgeons at the NCC hospital. 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 have been in the process of evaluation.

- (2) CT-colonography with the new method of fecal preparation was provided in November 2011.
- (3) In order to establish guidelines for the management of pulmonary nodules detected by 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 a super high-resolution CT scanner is also being developed.
- (5) The clinical usefulness of C11-methionine-PET in several kinds of brain tumors detected at the NCCH has been assessed.
- (6) The clinical usefulness of MRI (3.0T) in cancer screening 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 follow-up data has been started.

Published Papers

1. Goshima S, Kanematsu M, Watanabe H, Kondo H, Mizuno N, Kawada H, Shiratori Y, Onozuka M, Moriyama N, Bae KT. Gadoteric acid disodium-enhanced MR imaging: differentiation between early-enhancing non-tumorous lesions and hypervascular hepatocellular carcinomas. *Eur J Radiol*, 79:e108-112, 2011
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SCREENING ASSESSMENT AND MANAGEMENT DIVISION

Hiroshi Saito, Chisato Hamashima, Toshiaki Kobayashi, Kumiko Saika, Yuri Mizota, Ryoko Machii, Ayako Aoki, Yoshiki Ishikawa, Koichi Nagata, Noriaki Takahashi, Sayuri Amanuma, Junko Asai, Kanoko Matsushima, Kazuko Matsuda, Hiromi Sugiyama, Keiko Kawarabata, Akiko Totake, Aoi Sato, Sayaka Kamo

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. 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).

Studies Evaluating Cancer Screening

A randomized controlled trial evaluating one-time colonoscopic screening (CS) for colorectal cancer was started in 2009. We have been responsible for designing and managing the study as the head office of the study. The study fields were extended to a part of the neighboring Daisen city as of this year. The cumulative number of subjects who were recruited and gave informed consent, and who were thus enrolled in the study, was 3712 during the 29 months after starting recruitment, corresponding to 37% of the planned number. The fields will further be extended to whole areas of Daisen city which has a population 5 times as large as this year's target population, aiming at a marked increase in recruiting study participants.

The results of a case-control study, conducted in four cities in Tottori prefecture, suggested a 33% reduction in the mortality rate of gastric cancer among the population who had undergone endoscopic screening within 12 months. Another case-control study to evaluate gastric cancer screening using endoscopy is ongoing in Niigata city.

Studies on Quality Assurance (QA) in Cancer Screening

Checklists (CLs) as a structure indicator in quality assurance at screening facilities, municipalities, and prefectures have been evaluated regarding their appropriateness by an expert panel. During this year, the appropriateness of cervical and breast cancer screening programs were evaluated. Good consensus on the appropriateness of those CLs was obtained. In addition to the three CLs, which were previously evaluated, panels of the five CLs have been completed this year.

An intervention study to evaluate the efficacy of the feedback on QA results of the data was started in 2009 with the endpoints of improvement of the CL scores and process indicators in subsequent years. The study was conducted by randomly allocating 1270 municipalities, corresponding to 71% of the municipalities in the country, into study and control groups in which data feedback was collected differently. The third feedback was performed this year. The results will be obtained through a planned review in 2014, at the completion of this trial.

Studies on Raising Participation Rates in Screening Programs

We have been conducting several intervention studies to evaluate the call-recall system and various invitation tools for screening participation which were developed by a health-communication technique. We demonstrated that, for breast cancer screening, messages to individual subjects, tailored according to the characteristics of those persons, could raise screening uptake more efficiently than the usual invitation letter.

Assessment and Management of Cancer Screening Programs at the National Level

With regard to assessment of cancer screening, an evidence report on screening for hepatitis-related diseases has been developed. To prepare revision of

the guidelines for breast cancer screening, new evidence has been collected. In addition, we developed the guidelines for the lay population on lung and gastric cancer screening using an original method involving the public, which was developed in 2009.

For Cancer Screening Management, we calculated cancer screening uptake rates in each of the 1800 municipalities in the country in 2009 by the standardized method using the formula which was authorized by the Ministry of Health, Labour and Welfare (MHLW). The data are being published on the website of the Center for Cancer Control and

Information Services at the NCC. To disseminate knowledge and skills for quality assurance activity in prefectures to be performed toward municipalities within each prefecture, we are organizing workshops targeting the chief members of the quality assurance committee of each prefecture. The contents of the workshop are also developed using the above mentioned CLs.

The above two activities are performed in part as the project of the Center for Cancer Control and Information Services. The former activity will be continued on an annual basis.

EPIDEMIOLOGY AND PREVENTION DIVISION

Shoichiro Tsugane, Manami Inoue, Shizuka Sasazuki, Motoki Iwasaki, Norie Sawada, Taichi Shimazu, Taiki Yamaji, Reiko Suzuki, Azusa Hara, Junko Ishihara, Masayuki Tatemichi, Tsutomu Miura, Yuko Yamano, Sana Yokoi, Minatsu Kobayashi, Ribeka Takachi, Yoshitaka Tsubono, Takehiro Michikawa, Yuri Ishii, Hideyo Ochi, Kayo Ohashi, Michiko Okajima, Yingyan Gong, Yurie Shinozawa, Izumi Suenaga, Ayako Toyama, Tomomi Mukai, Izumi Matsumoto, Ai Noda, Jun Umezawa, Masahiro Matsuyama

The Epidemiology and Prevention Division 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.

Population-based Prospective Study (the JPHC 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 division 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 21,024 deaths, 16,962 cases of cancers, 5,888 cases of strokes and 1,130 cases of myocardial infarctions, had been documented as of October, 2011.

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

Total Cancer: In women, past and recent use of vitamin supplements increased the risk of cancer partly explained by preexisting diseases or unhealthy background, while consistent vitamin supplement use might reduce the risk of cardiovascular disease (CVD) (1). **Colorectal Cancer:** Intake of marine n-3 polyunsaturated fatty acids might be inversely related to the risk of cancer in the proximal site of the large bowel (2). Higher consumption of red meat was significantly associated with a higher risk of colon cancer among women as was higher consumption of total meat among men, although the highest quintile of red meat consumption could be considered moderate

by Western standards (3). **Liver Cancer:** Compared to the hepatitis virus-negative group, the hazard ratio (HR) of developing hepatocellular carcinoma (HCC) was 35.8-fold higher in HCV monoinfection, but a titer-dependent increase in risk was not identified (4). HBV mono-infected subjects with A1762T/G1764A double mutation could be at high risk of HCC development during the natural course of HBV infection (5). **Lung Cancer:** Plasma genistein concentration was inversely associated with lung cancer risk in Japanese women (6). **Breast Cancer:** Low body mass index (BMI) at age 20 years (y) was substantially associated with an increased risk of breast cancer, while high recent BMI and subsequent BMI gain from age 20 y were associated with increased risk of postmenopausal estrogen receptor (ER)+ progesterone receptor (PR)+ tumors (7). Active participation in leisure-time physical activity may contribute to a decrease in breast cancer risk, particularly for ER+PR+ tumors (8). **Thyroid Cancer:** High green tea consumption was positively associated with thyroid cancer risk in premenopausal women, but inversely in postmenopausal women (9). Coffee consumption and thyroid cancer risk was associated in neither men nor women. **Cardiovascular disease:** Being shorter in height was associated with increased risk of total stroke, either hemorrhagic or ischemic stroke but not with risk of coronary heart disease (CHD) (10). Higher total dietary fiber was associated with reduced risk of CVD only in non-smokers (11). Diabetes mellitus (DM) was a significant risk factor for all types of ischemic stroke, but not for intraparenchymal or subarachnoid hemorrhage (12). Diabetes and elevated glucose levels were also associated with incident CHD (13). Pulse pressure was positively associated with risk of stroke among persons with normal systolic blood pressure levels (14). Higher BMI levels and a weight gain of $\geq 10\%$ over 5 years were associated with an increased risk of stroke in women, whereas this association was weak in men (15). **Type II Diabetes:** Fish consumption was associated with a lower risk of type 2 DM in men but not in women (16). Weight gain from age 20 y was associated with

an increased risk of type 2 DM, which was further enhanced by weight gain in later life in women (17). Known risk factors for diabetes like age, smoking, family history and so on established in Western populations also increased the risk of diabetes in a Japanese population defined on the basis of HbA1c values (18). **Suicide:** Higher intakes of fish, EPA, or DHA were not associated with a lower risk of suicide (19). Those with the highest level of social support had a significantly decreased risk of suicide, which suggests that avoiding social isolation may decrease the incidence of suicide (20). Men living without a spouse and women living with a parent(s) only were at increased risk of suicide, while women living together with a spouse and child(ren) were at decreased risk of suicide (21). **Metabolic syndrome:** Social support increased the risk of metabolic syndrome among Japanese men, a finding that was opposite to what has previously been reported in Western studies, while there was no such association in women (22). **Validation study:** Validity of the study for the cases of self-reported cancer (23) and self-reported fracture (24) were investigated as well as effect of cooking loss in the assessment of vitamin intake (25).

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

The ethnic differences in the incidence of cancer suggest an interaction between environmental and genetic factors. Several epidemiologic studies in Brazil, a multi-ethnic nation with 1.2 million people of Japanese ancestry, are in progress. A cross-sectional study was conducted using a control group of case-control studies in Nagano, Japan, and São Paulo, Brazil to clarify the difference in hormone levels (26). In postmenopausal women older than age 55 y, Japanese Brazilians had significantly higher levels of estrogens and androgens than in Japanese and levels similar to or higher than in non-Japanese Brazilians. Hospital-based case-control studies of patients aged 20-74 years with invasive breast cancer and matched controls in Nagano and in São Paulo showed that antibody-dependent cell cytotoxicity (ADCC) might not play a major role in the etiology of breast cancer (27). A colorectal adenoma case-control study in Japanese Brazilians in São Paulo is in progress.

Other Epidemiological Studies

Studies are being conducted to search for the

cause of cancer and develop effective cancer prevention methods, using samples from subjects seen at the Research Center for Cancer Prevention and Screening (RCCPS). A self-administered food frequency questionnaire (FFQ) developed for and validated in rural residents was also validated for middle-aged urban cancer screenees (28).

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 (29-31) and some interventional studies are in progress, as well as some pooled analyses (32). Evidence on smoking, alcohol, anthropometry, fruit and vegetables, 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/). Based on the judgments, current evidence-based cancer prevention recommendations for Japanese provided by the study group were also updated.

International Collaborative Projects

International collaborative projects to contribute on the global scale with a focus on Asian cancer prevention strategies (Japan-China cooperative research work (33, 34), Asia Cohort Consortium (ACC) (35, 36), Asia Breast Cancer Consortium (37, 38), Pooling project of Prospective Studies of Diet and Cancer, WHO Global Burden of Disease Project, etc (39).) are in progress. Most studies that have evaluated the association between BMI and the risks of death from any cause and from specific causes have been conducted in populations of European origin. ACC revealed that being underweight was associated with a substantially increased risk of death in all Asian populations. The excess risk of death associated with a high BMI, however, was seen among East Asians but not among Indians and Bangladeshis.

Other Studies

Analysis of the epidemiological or clinical data was carried out as well as some contribution to The 7th Asia Cancer Forum (40) and The Lancet Special Series on Japan (41), the Hokkaido study (42) and the Nishiaizu Study (43). Risk factors for breast cancer were reviewed with recent evidence in Japan (44).

Published Papers

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