After World War II, the types of major diseases in Japan underwent dramatic changes. Until 1953, tuberculosis and other communicable diseases had been leading causes of death in Japan, but owing to the improvement of public health conditions and the use of antibiotics, the incidence of classical infectious diseases dropped sharply, while that of non-communicable diseases or lifestyle-related diseases, such as cancer and cerebrovascular diseases, increased markedly. In 1981, cancer became the number one cause of death and the number of cancer deaths continues to increase.

As early as 1965, the Japanese Association of Clinical Cancer Centers was established with the National Cancer Center in Tokyo as the core center. Today, a total of 28 clinical cancer centers throughout Japan belongs to the Association. Some of these cancer centers are supported by the central national Government, while the others are supported by local prefectural governments or private foundations. Although the funding bodies of these centers are different, they share the common features as institutes where all or large portions of their patients have cancers.

These centers are examined for qualification before they become member institutes by executive board members for their suitability as a clinical cancer center. The main purposes of the Association are as follows: first, to ensure a standard state-of-the-art oncology practice and to spread such practice throughout Japan; second, to conduct clinical research through the network of cancer centers; third, to train cancer specialists for dispatch all over Japan; and fourth, to have a common agenda for voicing opinions to be heard by the Government in order to establish or improve health insurance policy. Out of 28 centers, 14 are connected by an information network to allow weekly video-conferences.

In 1990, it was decided to establish a Clinical Cancer Research Forum among these 28 clinical cancer centers with one organizer assigned to each institute every year. The 10th Clinical Cancer Research Forum was held on June 9, 2000, at the International Lecture Hall of the Foundation for Promotion of Cancer Research in Tokyo. Dr Naoki Tsukamoto, Director of the National Kyushu Cancer Center, was the Chairperson of the Organizing Committee for the Forum and the main theme of this meeting was ‘Multiple Primary Cancers’. The purpose of the Forum is to understand the present status of multiple primary cancers and hereditary cancers from the clinical, ethical and social viewpoints.

In the morning, there was a workshop on epidemiology and clinical findings of multiple primary cancers. The goal of this Forum was to understand the current status of multiple primary cancers and hereditary cancers in Japan, especially in cancer centers belonging to the Association. The incidence of multiple primary cancers has apparently increased in Japan, where people enjoy the greatest longevity. Multiple primary cancers are the outcome of heavy exposure to environmental carcinogens and/or the results of strong genetic predisposition to cancer. Multiple primary cancers have important clinical implications in prevention, diagnosis and therapy for cancer in general. It is a model disorder which is effective for the elucidation of cancer-related lifestyle and genetic predisposition. Multiple primary cancer is the target of ethical and social problems, which requires consensus in a society.

It is an issue which should be taken into consideration when establishing cancer control programs: after successful treatment of a patient with cancer, the patient develops a second cancer if he or she lives long enough after the first cancer. It was timely to have this topic as a theme for the 10th Forum now that most of the sequence of the human genome has been elucidated and a large-scale genome analysis for diseases has recently been launched as a millennium project by the Japanese Government, in April, 2000.

The meeting began with opening addresses by Dr Masaaki Terada and Dr Naoki Tsukamoto. The first workshop, entitled ‘Epidemiology and clinical studies on multiple primary cancers’, was chaired by Dr Satoshi Ebihara. Dr Hiroyoshi Koizumi presented the results of analysis on chronological changes of second primary cancer by a hospital-based cancer registry at Kanagawa Cancer Center, showing the increase in second cancers. Dr Hideaki Tsukuma presented the results of data analysis on risk estimates for multiple primary cancers by
record linking between the Hospital Cancer Registry of Osaka Medical Center for Cancer and the Cardiovascular Diseases and Osaka Cancer Registry. It was found that cessation of smoking was effective in the prevention of second cancers following successful treatment of gastric cancer. Dr Ichiro Honda presented the results of a clinicopathological study on 186 cases of multiple cancers associated with gastric cancers.

Dr Toshihiko Sato showed that stomach cancer is the most frequent second cancer following treatment of primary colon cancer. Dr Kohei Yokoi showed that 17.6% of patients with lung cancers resected developed multiple primary cancers and stressed the importance of careful examination for multiple primary cancers at the time of and following surgical treatments. Dr Takashi Hiro showed that the incidence of multiple primary cancers associated with mesopharyngeal cancer patients is the highest among head and neck cancers and that these patients are at high risk for oral, pharyngeal and esophageal cancers.

Endometrial cancer associated with multiple primary cancers was characterized by Dr Toshiaki Saito, who showed that breast, colon and ovarian cancers were the most frequently encountered second cancers. It was also found that a high frequency of negative immunohistochemical staining for MSH-2 and/or MSH-1 was noted for endometrial cancers associated with multiple primary cancers and for those with a positive family history. The first tutorial lecture was provided by Dr Tetsuichiro Muto under the title ‘Diagnosis and treatment of multiple primary cancers in digestive organs’, stressing the importance of the establishment of a surveillance system for second cancers. The lecture was chaired by Dr Kazuhiro Nomura.

Dr Michio Kono chaired a session for oral presentations of case reports on head and neck cancers and lung cancers. Dr Akira Yoshida reported a case with MEN1 gastrinoma which metastasized to the liver after partial pancreatectomy. Dr Kuniaki Anraku reported a double cancer case with parotid gland carcinoma and cutaneous sebaceous cancer. Dr Masahiro Ryucho showed that stomach and lung cancers are the most common second cancers among non-head and neck cancers following the primary head and neck cancers. Dr Chie Ushijima reported that about 9% of lung cancer was associated with multiple primary cancer and that these cancers usually preceded lung cancer. Dr Yoshihiko Kotani showed that about 8.5% of lung cancer cases are accompanied by a metachronous and synchronous multiple primary cancer, including 2.9% cases of multiple primary lung cancers. Dr Yuji Asato reported a heavy smoker patient with triple primary lung cancers with histological diagnosis of squamous cell carcinoma in all three pulmonary lesions. Surveys of eight cases of multiple primary lung cancers in his hospital showed better prognosis than that for monocentric lung cancers.

A session on digestive tract and gastric cancer was chaired by Dr Kou Nagasako. Dr Shiochi Katayama analyzed multiple primary cancers associated with stomach cancer. It was found that synchronous multicentric cancers frequently occur in the stomach and metachronous second cancers in the remaining stomach were observed after 9.7 years on average after the first gastrectomy. Dr Takeo Arakawa reported that 9.5% of patients who underwent endoscopic mucosal resection (EMR) for early gastric cancer had multicentric primary cancers in the stomach and he stressed the importance of detecting multicentric cancers at the initial and follow-up endoscopic examination. It was reported by Dr Masahiko Taniguchi that cancer in the remnant stomach after partial gastrectomy for the primary cancer was mostly in the advanced stage and the importance of a careful follow-up after partial gastrectomy was also stressed here. Dr Hogara Nishisaki reported the usefulness of endoscopy with spraying dye for detection of multicentric primary cancers in the stomach. Dr Takao Inada emphasized the importance of a follow-up study of the residual stomach after an operation for early gastric cancers from the viewpoint of multiple primary early gastric cancer. It was also found that the interval for detection of remnant gastric cancer after EMR was 3 years, whereas that after partial gastrectomy was 5 years and 7 months. Dr Koji Higashino reported a significantly higher incidence of second stomach cancer in patients with hepatocellular carcinoma. It was also found that telomerase could be detected in gastric mucosa from 29% of patients with hepatocellular carcinoma.

Dr Makoto Ogawa chaired a session entitled ‘Genomic instability, gynecological cancer and breast cancer’. Dr Yoji Nishimura showed that multiple primary colon cancers had high microsatellite instability and this could be used to help in the detection of multiple primary cancers. Dr Hideaki Nakashima found that 12% of esophageal cancers, 24% of colon cancers, 20% of monocentric stomach cancers and 70% of multicentric stomach cancers had genomic instability. Dr Toshinobu Nishimura reported that 3.95% of gynecological cancers developed multiple primary cancers. Dr Hisashi Tateiwa reported a case with synchronous cervical cancer and ovarian cancer. He also reported a case with cervical cancer, endometrial cancer and ovarian cancer, found simultaneously. Dr Yoshihito Utada reported the incidence of bilateral breast cancer increased in the past 10 years, ranging from 3.0% in 1967–76 to 6.9% in 1987–96. The relative risk of a patient with unilateral breast cancer developing contralateral breast cancer was ~10-fold.

Dr Ken Yamaguchi gave the second tutorial lecture entitled ‘Familial cancer syndromes and DNA testing’. He provided excellent overviews on the present status of familial cancer syndromes, showing his own data on multiple endocrine neoplasia. He pointed out the important aspects of clinical handling of patients and their families and gave perspectives on understanding of cancer predisposition at genetic levels in relationship to prevention and treatment with special emphasis on the social and ethical aspects of genetic testing. The lecture was timely since the Japanese Government has just increased funding for the human genome project, especially for that related to diseases.

A workshop on therapy-related second cancers was chaired by Dr Shigemitsu Takashima. Dr Naokuni Uike presented their experience of two cases with myelodysplastic syndrome, 27
months and 23 months after treatment with 2-chlorodeoxyadenosine. Both patients were also treated with alkylating agents. Dr Nobuya Monden reported four cases of malignant neoplasms that developed on the reconstructed flap in the oral cavity. Dr Shunichi Shimano reported the results of analysis on multiple primary cancers associated with malignant lymphoma. Dr Tsukasa Yonemoto analyzed 130 cases of osteosarcoma under age 30 years and six cases developed secondary cancer after successful treatment of the first osteosarcoma. Among the 130 cases, three developed osteosarcoma after treatment of childhood cancer. Dr Yoshio Hatae reported a case with secondary acute monocytic leukemia following combination chemotherapy containing adriamycin for osteosarcoma and stressed the possible risk of developing second cancers following treatment with adriamycin.

The third workshop, entitled ‘Multiple primary cancer in familial and hereditary cancer syndromes’, was chaired by Dr Yasuo Koyama. Dr Takashi Tada analyzed 9105 cases of breast cancer patients who underwent surgical treatment. Of these, 811 cases, corresponding to 8.9% of the total, were associated with multiple primary cancers. It was also found that 18.8% of male breast cancer was associated with multiple primary cancers. Out of 811 cases, 533 had breast cancer as second primary cancer. Patients with a family history of breast cancer had an increased risk of multiple primary cancers. Dr Muneaki Sano reported an analysis of 140 cases, corresponding 5.6% of familial aggregates of breast cancer out of 2521 breast cancer cases. Bilateral breast cancer was found in 43.9% in cases of familial aggregates, whereas it was found in only 2.6% of cases without a family history.

Dr Yuji Kumashiro presented data indicating that patients with multiple primary cancers with a family history of gastric cancer had a tendency to have multicentric gastric cancers at an incidence of 38.9%. Dr Hiroko Bando showed that all the cases with a clinical diagnosis of HNPCC by Amsterdam criteria had high microsatellite instability (MSI), while 33–36% of those by Japanese A and B criteria had MSI. The importance of careful follow-ups of patients with positive MSI was emphasized. Dr Nobuhiro Takeshima demonstrated that 18 of 142 cases with ovarian cancer had a family history of ovarian cancer. Between ovarian cancer with a family history and that without a family history, there was no clear difference in the age of onset, histopathological findings and prognosis. Dr Keiko Kazuma was asked to present the present status of genetic counselors in Japan and stressed the importance of genetic counseling in clinical genetic testing.

The topics of the Forum were timely now that the human genome project is near completion and predisposition to cancer becomes an important target of cancer research in the new millennium. We cannot overemphasize the importance of the social and ethical aspects of genetic testing in the new century for cancer prevention and treatment. Despite the tight schedule, there was a lively discussion throughout the meeting and the importance of the cancer network was recognized as a source for good, reliable clinical investigation. The meeting was concluded with closing remarks by Dr Kyosuke Ushio.

Appendix

The meeting was organized by Drs Naoki Tsukamoto and Kyosuke Ushio.

The chairpersons included S. Ebihara (National Cancer Center Hospital East, Kashiiwa), K. Nomura (National Cancer Center Hospital, Tokyo), M. Kono (Hyogo Medical Center for Adults, Akashi), K. Nagasako (Gunma Cancer Center, Gunma), M. Ogawa (Aichi Cancer Center, Nagoya), T. Takashashi (Tokyo Metropolitan Komagome Hospital, Tokyo), S. Takashima (National Shikoku Cancer Center, Matsuyama) and Y. Koyama (Tochigi Cancer Center, Utsunomiya).

The speakers included H. Koizumi (Keangawa Cancer Center, Yokohama), H. Tsukuma (Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka), I. Honda (Chiba Cancer Center, Chiba), T. Sato (Medical Center for Cancer and Cardiovascular Diseases, Yamagata Prefectural Central Hospital, Yamagata), K. Yokoi (Tochigi Cancer Center, Utsunomiya), T. Hirao (Gunma Cancer Center, Gunma), T. Saito (National Kyushu Cancer Center, Fukuoka), T. Muto (Japanese Foundation for Cancer Research, Tokyo), T. Arakawa (Tokyo Metropolitan Komagome Hospital, Tokyo), M. Taniguchi (Kure National Hospital, Kure), T. Ivase (Tsuchi Cancer Center, Utsunomiya), K. Higashino (Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka), Y. Nishimura (Saitama Cancer Center, Saitama), H. Nakashima (National Kyushu Cancer Center, Fukuoka), T. Ibaraki (National Kyushu Cancer Center, Fukuoka), Y. Kotani (Hyogo Medical Center for Adults, Akashi), Y. Asato (Ibaraki Prefectural Central Hospital and Cancer Center, Nishi-Ibaraki), S. Katayama (Kure National Hospital, Kure), T. Arakawa (Tokyo Metropolitan Komagome Hospital, Tokyo), M. Taniguchi (Kure National Hospital, Kure), H. Nishisaki (Hyogo Medical Center for Adults, Akashi), T. Inada (Tsuchi Cancer Center, Utsunomiya), K. Higashino (Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka), Y. Nishimura (Saitama Cancer Center, Saitama), H. Nakashima (National Kyushu Cancer Center, Fukuoka), T. Nishimura (Gunma Cancer Center, Gunma), H. Tateiwa (Hyogo Medical Center for Adults, Akashi), Y. Utada (Japanese Foundation for Cancer Research, Tokyo), K. Yamaguchi (National Cancer Center Research Institute, Tokyo), N. Uike (National Kyushu Cancer Center, Fukuoka), N. Monden (National Shikoku Cancer Center, Matsuyama), S. Shimano (Gunma Cancer Center, Gunma), T. Yonemoto (Chiba Cancer Center, Chiba), Y. Hatae (National Sapporo Hospital, Sapporo), T. Tada (Japanese Foundation for Cancer Research, Tokyo), M. Sano (Niigata Cancer Center, Niigata), Y. Kumashiro (Tokyo Metropolitan Komagome Hospital, Tokyo), H. Bando (Tokyo Metropolitan Komagome Hospital, Tokyo), N. Takeshima (Japanese Foundation for Cancer Research, Tokyo) and K. Kazuma (Faculty Medicine, Graduate School of Medical Sciences, University of Tokyo, Tokyo).