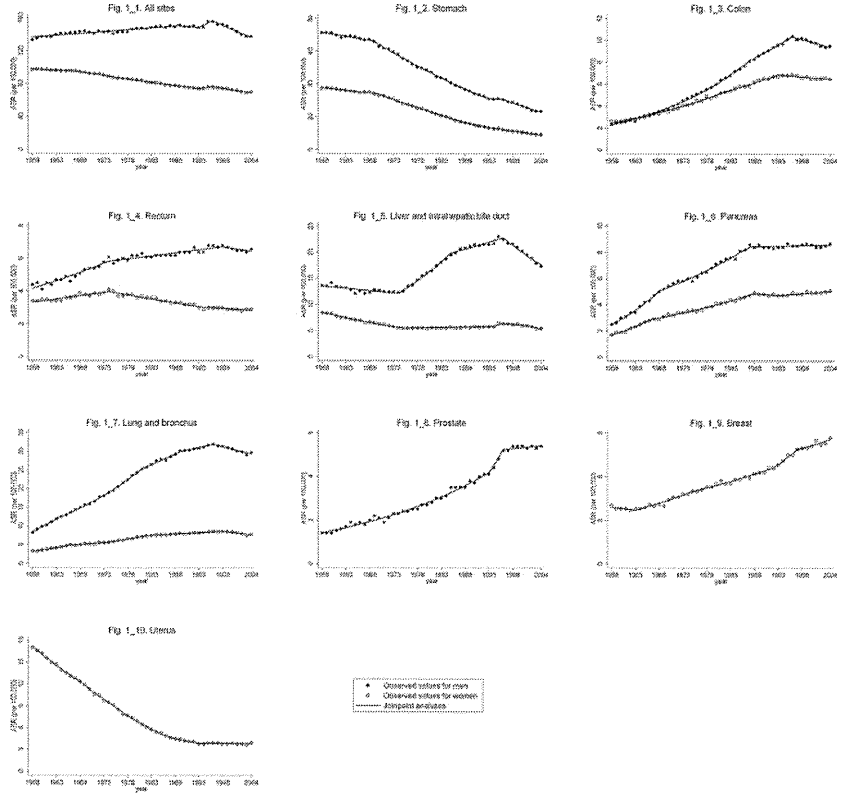

FIGURE 1 – Trends for ASRs (per 100,000) by sex and site during 1958–2004 in Japan, using the World Standard Population.

decreased from 1987 and cancers of the esophagus and urinary bladder decreased from the 1970s. ASRs for stomach cancer showed Pattern 2, with a clear consecutive decreasing trend since 1958 (Table I and Fig. 1).

In women, ASRs for overall cancer showed Pattern 2, leveling off from 1958 to 1967, decreasing by 0.98% per year from 1967 to 1993, leveling off from 1993 to 1996 and decreasing again by 1.22% per year to 2004. ASRs for cancers of the colon, liver, gallbladder, lung and ovary showed Pattern 1, with ASRs decreasing from the 1990s after an increasing trend. ASRs for rectal cancer and leukemia could also be classified into Pattern 1, although ASRs decreased from the 1970s. ASRs for stomach cancer in women resembled that in men, decreasing continuously by Pattern 2. ASRs for cancers of the uterus and urinary bladder could also be categorized into Pattern 2, although the trend for cancer of the uterus leveled off from the 1990s and cancer of the urinary bladder increased slightly after 1993. ASRs for esophageal cancer showed similar changing trends to uterine cancer, although the gradient of declining ASR was more gradual. ASRs for cancers of the pancreas and breast and malignant lymphoma showed Pattern 3, increasing continuously to 2004 (Table II and Fig. 1).

In general, ASRs for cancer in Japan in the most recent line segment (from the last joinpoint until 2004) have been declining for the majority of cancers, including overall cancer. The few exceptions include increases in mortality from cancers of the pancreas, breast and urinary bladder and malignant lymphoma in women. For other cancers such as cancer of the rectum, pancreas, prostate and urinary bladder and malignant lymphoma in men and cancer of the esophagus and uterus in women, the most recent trend has remained relatively stable (Tables I and II).

During the study period, an increasing trend in crude death rate was observed in overall cancer and for all observed cancer sites in both men and women, except for cancers of the stomach in both sexes and cancer of the uterus in women. Crude death rates for

stomach cancer in both sexes showed a decreasing tendency during the observed period, whereas crude death rate for uterine cancer in women decreased until the early 1990s, then increased slightly thereafter.

Compared to those in all ages, truncated (35–64 years) mortality rates were higher in both men and women, with similar patterns in most cancer sites. Different patterns between all ages and truncated age were only observed for overall cancer in men, which decreased continuously during the study period in truncated mortality rates, and uterine cancer in women, for which truncated mortality rates showed an increasing trend in the most recent period (increased slightly from the early 1990s) (data not shown).

Discussion

To the best of our knowledge, this study offers the first nationwide analysis of trends over time using statistical testing for mortalities from cancer in general and the most common cancers in Japan. The use of Joinpoint analysis has allowed statistical testing of directions and sizes of trends in mortality rates for various cancers, detecting some significant changes. Accordingly, Joinpoint analysis provides a much clearer picture of what is happening during a distinct period in specific terms (identifying the years in which significant changes in trends occurred) than a single summary trend statistic.[5,6]

A decline in mortality rates of overall cancer starting in 1996 was identified in both sexes in Japan. The overall decline in recent decades is mostly attributable to reductions in stomach, lung and liver cancers for men and in stomach and gallbladder cancers for women.

The changing trends in cancer mortality rates may be interpreted as resulting from changes in environmental, dietary and socioeconomic factors and potential consequences of early detection, treatment and various public health strategies, which have profoundly changed along with economic growth in Japan in the postwar decades.

The mortality rate from stomach cancer in Japan still ranks as the highest in the world,[1] but has declined markedly in the last few decades, in similar fashion to observations from the United States and some European countries.[3,8] The trend in stomach cancer mortality rate has been attributed to the effects of substantial improvements in food storage and preservation through refrigeration,[9–11] a more affluent diet with increased consumption of fresh vegetables and fruit[9–11] and reductions in the prevalence of *Helicobacter pylori* infection.[9,12] The recent decline trend in mortality rate could also be explained in part by efforts made in early detection[13,14] and improved treatment, as mortality rates declined almost in parallel with incidence in the 1970s and the gap between these rates widened from the early 1980s to the early 1990s.[15]

Prostate cancer remains lower in Japan than in Western populations,[16,17] although the mortality rate has increased more rapidly than in those countries.[16] The traditional Japanese diet is high in isoflavones which are chiefly derived from soybean products and might be protective against this kind of tumor.[18,19] The leveling off of the mortality rate might have been partly caused by improvements in treatment, as incidence has continued to increase since 1996.[15]

Consumption of meat increased sharply from the 1940s to the mid-1970s in Japan[20] and this could be argued to represent the major cause of the increasing trend in colon cancer until the 1990s.[21,22] Meanwhile, increases in alcohol consumption[22] and obesity rate[20] along with declines in physical activity[22] may also account for some of the increase in colon cancer in men.

The mortality rate of breast cancer is high in developed Western industrialized countries and relatively low in Japan and developing countries.[23] Continuous increases in breast cancer mortality rate could be interpreted as indicating increasing lifetime exposure to estrogen, related to early menarche, late menopause, late pregnancies and low parity caused by increases in the ranks of working women.[21,23,24]

The influence of smoking on mortality rate for smoking-related cancers other than lung cancer is less visible, because of the influence of other factors. Declines in mortality rates from lung cancer were not a simple reflection of the decreasing prevalence of smoking over the last few decades in men. According to data from Japan Tobacco Industry, trends in smoking prevalence in Japan over the past 40 years have shown a decline in smoking habits among men, but a leveling off in women. Life-time smoking prevalence among men showed a temporary decrease in the late 1930s birth cohort and increased until the 1950s birth cohort.[25,26] These trends corresponded with changing patterns in lung cancer mortality rates in men, which was lower in the late 1930s birth cohort and increased successively after the 1940s birth cohort.[26–28] As for women, we have no clear explanation for the observed declines in mortality rate, as smoking prevalence was not sufficiently high to impact lung cancer mortality trends. Nevertheless, mortality rates among women aged 65–74 years decreased in 2003 and 2004, at least reflecting the lowest life-smoking prevalence observed in the 1930s birth cohort.[25] Careful monitoring is needed for recent birth cohorts in women, as life-smoking prevalence increased after the 1940s birth cohort.[25] This analysis suggests that aggressive promotion of antismoking measures targeting the birth cohort born after the 1940s is necessary for further reductions in lung cancer mortality in Japan.

The epidemiology of liver cancer is distinctive in Japan, where chronic infection from hepatitis C virus (HCV) rather than hepatitis B virus (HBV) plays the major role in the etiology.[29] Prevalence of antibodies against HCV was highest (3.4%) in the 1930s birth cohort, whereas prevalence of hepatitis B surface antigen (HBsAg) was highest (1.5%) in the 1940s birth cohort among the first blood donor candidates in Japan.[30] These two generations with high prevalence of HCV antibodies and HBsAg corresponded with those observed in liver cancer mortality rates, which peaked in the 1930s and 1940s birth cohorts for men, and in the 1930s birth cohort for women.[31] The social problem of HCV and HBV infection may have contributed to increasing mortality rates for liver cancer from the 1970s. National projects have been implemented with the aim of reducing the threat of infection by HCV and HBV since 1970s,[32] because of the serious social problems associated with these infections. The declining mortality rate of liver cancer since 1996 was largely interpreted as due to declines among men of 45–64 years and women of 50–69 years, which in turn were mainly ascribed to the decreasing prevalence of HCV infections after the 1930s birth cohort.

The drastic decline in the mortality rates for uterine cancer has been ascribed to improvements in sanitation, early detection and therapy. However, this decreasing trend appears to have been stabilizing since 1993. Notably, truncated mortality rates increased from 1993. Analysis of mortality rates by age suggests that younger women (≤59 years old) have shown consecutive increases since the 1940s–1950s birth cohorts, whereas older women (≥60 years old) have shown a consecutive decreasing after the 1905s birth cohort (data not shown). This change may be partly due to the greater prevalence of infection from oncogenic human papilloma virus caused by changes in sexual behavior among younger women.[33] The increase in mortality rate among younger women is offset by declines in older women, leading to the stabilization observed in mortality rate for uterine cancer since the early 1990s. This trend must be monitored among younger women in future.

Cancer screening has been started nationwide for cancers of the stomach and cervix since 1983, for cancers of the breast and lung since 1987 and for colorectal cancer since 1992 under the Health Services Law for the Aged in Japan. Although Pap smears and mammography have been recommended for screening of cervical and breast cancers, respectively, and no methods were recommended for other cancer site screenings in the UICC report of

1990,[34] unique cancer screening policies were conducted in Japan except for cervical cancer at that time. Barium X-ray was adopted for stomach cancer screening, and was accepted only for Japan by the UICC report,[34] physical examination was adopted for breast cancer screening at first, before being changed to mammography with physical examination from 2000, X-ray and sputum cytology were adopted for lung cancer screening and fecal occult blood tests were adopted for colorectal cancer screening. However, these screening seems unlikely to have made any major contribution to reductions in cancer mortality rates by the year 2004, with the exception of cancers of the stomach and uterus (mainly for the cervix), as participation rates in screenings of eligible populations are still relatively low for cancers of the lung, breast and colorectum in Japan.[35]

Potential problems exist in the reliability and validity of death certification for cancers, which may vary across calendar years, when interpreting mortality trends. Deaths certificates are usually considered complete in Japan and cause of death is also considered to have been identified with reasonable accuracy. Mortality rates for cancers in both sexes were unchanged during the coding process related to revisions of the ICD classification system, though the classification and coding on death certificates tended to influence secular trends of mortality rates. We did not distinguish between cancers of the cervix uteri, corpus uteri and unspecified uteri, given acknowledged problems in accurate classification from death certificates.[36] Colon cancer and rectal cancer mortality rates were analyzed separately, because those changes in diagnosis and certification are unlikely to explain the recent fall and stability in these two sites and differences in risk factors associated with cancer at each site.[21,22,32,37–39]

Joinpoint analysis in this study demonstrated favorable declines in overall cancer and the majority of observed cancers in Japan in recent years. However, the aging population and overall increases in risk of cancer have still increased the crude death rate and absolute total number of cancer deaths in Japan. An effective cancer control program including primary prevention (such as antismoking), early detection and treatment should thus be implemented to further reduce cancer mortality, with special emphasis on those anatomical sites of cancer showing higher mortality rates and increasing trends.

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HISTORICAL REVIEW

Cancer Research and Control Activities in Japan - Contributions to International Efforts

Malcolm A Moore[1], Tomotaka Sobue[2]

Abstract

Since the establishment of the Japanese Foundation for Cancer Research in 1908, Japan has experienced a long history of physicians and researchers playing very active roles in both national and international efforts for cancer control. With the opening of the Japanese Foundation for Cancer Research Cancer Institute and Hospital in 1934 and the National Cancer Center in 1962, followed by Aichi Cancer Center in 1964 and then gradually Prefectural Centers across the country, the populace is well endowed with specialist research and clinical facilities. Under the Cancer Control Act, implemented in 2007, these are now being complemented by a network of specialist hospitals also involved in efforts to improve training and cancer registration as well as standardization of cancer treatment. Regional cancer registries have been active since the 1960's and national programs for cervical and stomach cancer screening were introduced in 1984. Subsequently, such early detection efforts have been added for the lung, colorectal, endometrial and breast cancers. There are a large number of academic scientific societies holding regular research meetings and focusing on all the different aspects of cancer control. In addition, there are non-government organizations like the Foundation for Promotion of Cancer Research, the Princess Takamatsu Cancer Research Foundation, the Sapporo Cancer Seminar Foundation and the Hiroshima Cancer Seminar Foundation, all sponsoring international research meetings and other efforts. Other foundations have been established, for example by patient support groups, and policy research and strategic planning are now high priorities of the Government. Japan also continues to contribute to international efforts though its membership in the WHO and the International Agency for Research on Cancer (IARC), as well as through individual memberships in the Intrnational Union Against Cancer (UICC).

Key Words: Japan - cancer control - registration - screening - national activity - international activity

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Early Cancer Research Efforts in Japan

a) Dawn of the Japanese Foundation for Cancer Research

At the turn of the century, in 1900, little attention was being paid to cancer prevention, partly because the majority of causes of death were infectious/parasitic diseases and illnesses related to under-nutrition. However, some Japanese physicians with responsibilities for cancer patient care had become interested in cancer mortality statistics, and it was reported that more than 20,000 cancer deaths were occurring nationwide annually, with a tendency for increase year by year (Abe, 1907; Sato, 1907; Bureau of the Statistics of the Imperial Cabinet, 1943). In 1908, the Japanese Foundation for Cancer Research (JFCR) was launched in Tokyo, albeit more as a response to outside pressures than due to any drive within the country. The society initially consisted of 161 physician members throughout Japan, and was primarily organized as a result of a request from Professor E.von Leiden who had founded the Cancer Research Institute, Berlin, in 1901. He recognized that cancer was a formidable enemy, at that time largely of unknown etiology and very difficult to detect before obvious symptoms, with no effective treatment except for surgical resection for those fortunate individuals diagnosed at an early stage. However, the fact that different cancers showed geographically uneven distributions did suggest roles for environmental causative factors, some of which might be avoidable. Therefore he emphasized that international collaboration for studying studying human cancer was essential.

Since such collaboration would have to be promoted at the national level Dr Leiden asked colleagues in Japan to join in this scheme, after organizing a cancer society. The resultant provisionary committee set up regulations and asked for the understanding and collaboration of physicians interested in oncology throughout Japan. The objectives of the society were, as follows:1) to hold a scientific meeting annually, and to promote information exchange on cancer; 2) to collect cancer statistics; to make

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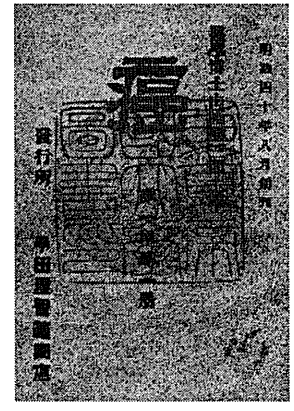
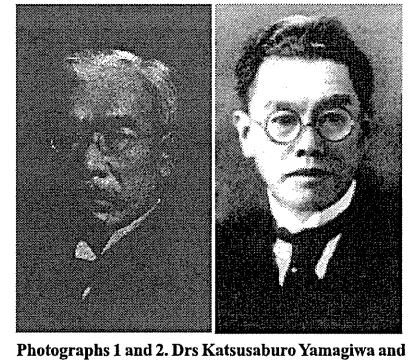


Figure 1. First Issue of the Cancer Journal 'Gann'

policy decisions regarding the direction of cancer research; 3) to educate the public and professionals about new developments and information relevant to the disease; 4) to raise funds from charitable individuals and bodies to promote research; and 5) to establish a cancer hospital and research institute. Most of these objectives were similar to those already established in European countries.

Professor Yamagiwa considered that publishing a cancer journal was central to this effort and in fact had already issued the Japanese Journal of Cancer Research, then entitled Gann (stone or cancer in Japanese) in 1907 (Figure 1), providing a grant for this purpose (Yamagiwa, 1908). The oldest continuing cancer publication, Revue des Maladiees Cancereuse, Paris had only been started in 1896,followed by the Bulletin du Cancer and Zeitschrift for Krebsforschung in 1904. The British Journal of Cancer was only founded as a quarterly in 1947 and the first edition of Cancer Research was published in 1941. He stated that while many respectable papers on cancer were appearing in the different Japanese medical journals, a focus was needed to facilitate their being read by those who wished to study cancer. This journal, Gann, later became the official journal of the Japanese Foundation for Cancer Research (JFCR) and is now continuing to receive international acclaim as 'Cancer Science'.



Photographs 1 and 2. Drs Katsusaburo Yamagiwa and Akira Fujinami

At the opening ceremony of the meeting in 1908, Professor Tanemichi Aoyama of Tokyo University, the first President of the JFCR, expressed reservations about being able to participate in very active international associations, because Japan was small and poor, not only in terms of the industrial economy but also in scientific achievements on cancer. However, the decision was finally made to join in the international scientific network. One strong reason for the positive response to the request of Professor Leyden was the fact that he and his colleagues had been very supportive of Japanese students living in Germany, and there was a wish to return this goodwill. Another factor was the change in the international situation of Japan after the victory in the Japan-Russia war, and there was a feeling that the country should do something to make an international contribution. At the time, many people realized that international respect and sympathy could better be obtained by achievement and involvement in cultural progress, rather than victory of war with its consumption of financial resources and human sacrifice.

At the first scientific meeting of the JFCR in 1908 at Tokyo University, Dr Katsusaburo Yamagiwa (Photograph 1) delivered a special lecture, emphasizing that the best means for cancer prevention was to remove or avoid long standing inflammatory processes and to enhance immunological responses, after reviewing his established studies on cancer from the pathological point of view. He had already written in his book entitled Stomach Cancer (Yamagiwa, 1905) that a close relationship was evident between cancer and chronic inflammation, which might be derived from inadequacies in the diet and other factors in daily life, some of which might be avoidable. It was a lecture with really keen insight at that time, because only now have laboratory and epidemiologic studies comprehensively endorsed the role of(Lifestyle in carcinogenesis. Other presentations, were "Cancer Statistics of Gynaecological Cancer" by Dr. Masanaka Kinoshita and "Comparative Pathology in Relation to Cancer" by Professor Akira Fujinami, a pathologist studying host factors in carcinogenesis and the first man to promote epidemiological studies on cancer based on the population in Japan (Photograph 2).

b) Participation in the International Society for the Study of Cancer (ISSC)

The JSCR decided to become a member of the International Society for the Study of Cancer (ISSC) to be organized in Europe and sent three delegates to the opening of this Association in Berlin, Germany, in 1908. The policy of the ISSC was wholly reflected in the regulations of the JSCR. On their return the Japanese delegates provided the summary of special lectures and the JSCR continuously contributed to the policy of the ISSC by providing Executive Committee members and participating in meetings. Prof. Yamagiwa joined in the Committee for Nomenculature of Tumors and made many proposals of terms that were adopted at that time. In 1922,

at the first scientific meeting of the ISSC after World War I, the main theme was Experimental Tar Cancer, commemorating Yamagiwa and Ichikawa's achievements and a great honor for Japan.

c) Early Experimental Research on Causes of Cancer

The JSCR early set up a Grant-in-Aid system for cancer research and gave prizes for the most distinguished achievements in cancer studies. Most physicians thought it was essential to clarify the cause and pathogenesis of cancer, because otherwise no effective treatment and preventive measures could be developed. Many experimental investigations were conducted and the first JSCR Prize was given to A Fujimami and K Inamoto for their study on 'Transplantable Fowl Tumors' in 1913. The second Prize, in 1914, was shared by H Tsutui for work on 'Experimental Tumors in Mice' and by S Mogi for findings on 'Penile Cancer'. The third was awarded to K Yamagiwa and K Ichikawa for research into 'Experimental Tar Cancer'(1915). Their first success in producing cancer artificially in rabbits by repeated exposure to an external agent was an epoch-making step. The method was simple and reproducible, allowing any scientist to examine the processes involved in the shift from normal to abnormal cells, and finally to cancers. Furthermore, the irritation theory was experimentally verified and the work pioneered experimental studies on carcinogenesis and lead directly to isolation of carcinogenic substances, with major implications for prevention of cancer. Their lead was energetically followed by other researchers in Japan, and for example,in 1935, Sasaki and Yoshida (1935) (see Photograph 3) succeeded in producing liver cancer in rabbits treated with O-amidoazotoluol orally. This proof of systemic carcinogenesis was another monumental achievement in experimental cancer studies. About 40 years had passed since Rehn pointed out a close relationship between aniline dyes and bladder cancer and now Japanese workers were at the forefront in experimental demonstration of the importance of individual chemicals in generation of neoplasia. This emphasis is still continuing, for example with insights into the improtance of heterocyclic amines

Photograph 3. Drs Sasaki and Tomizo Yoshida

generated during cooking processes (Sugimura et al., 2004). One anecdotal study deserves description here, given the prominence now given to tobacco as a medical disaster. In the early 1900s, Chikamatsu (1918) produced stomach cancer in rabbits by treating them with tobacco tar for 400 days perorally. He also succeeded in producing skin cancer by painting tobacco tar using Yamagiwa's method. The paper was written in Japanese and therefore unfortunately remained buried, since it was a very early pointer which clearly warranted more attention.

d) Cancer Statistics and Epidemiological Studies

It is now well established that the basis of a comprehensive national cancer control program is a system of surveillance, with attention to determinants, and outcomes. To collect and analyze exact cancer data is essential for research and prevention. However, at the beginning of the last century it was not easy to routinely document cancer cases and also to achieve an international standard of diagnosis. The latter relies on both macroscopic and microscopic evidence, but this is difficult to regulate, so the data obtained are often non-uniform. The International Classification of Deaths (ICD) was adopted in 1899 by many countries of the world, including Japan, but the classification of cancer was only into five large categories, which were not useful for research and clinical reference. Many physicians tried to analyze cancer data in hospitals in groups and in more detail, for example by organ. However, the data generated were not directly comparable.

The Japanese Government has in fact issued annual mortality statistics by major disease since 1882. From 1899, mortality statistics were published with cause of death, age-sex, present and permanent residence, occupation and other characteristics. Regarding cancer, the ICD classification was changed to 9 categories in 1909 (see Table 1). However, these major sites of cancer were still not sufficient for physicians and researchers to actually do their work, so that data were published for frequency distributions of cancer patients by more sites, after examining clinical and autopsy records in hospitals around 1900 (Abe, 1907; Sato,1907).

There were clearly problems with accuracy and homogeneity in cancer diagnosis between the statistics reported. Low autopsy rates even in the top ranking hospitals at that time hindered promotion of cancer studies. A total of 932,800 deaths by all causes were registered in 1899, and about 20,000 (2.08% of all cases) were due to

Table 1. ICD 2nd Revision Classification, 1909-1922

40 Cancer of the Buccal Cavity
41 Cancer of the Stomach & Liver
42 Cancer of the Peritoneum, Intestines and Rectum
43 Cancer of the Female Genital Organs
44 Cancer of the Breast
45 Cancer of the Skin
46 Cancer of the Other Organs
47 Cancer of Organs Not Specified
48 Other Malignant Tumors

Photographs 4 and 5. Drs Mataro Nagayo and Mitsuo Segi

cancer. Since many deaths were of patients still active in their communities, correct figures for cancer were strongly requested by researchers and officials responsible for disease control. From 1907, a start was made in this area (Nakari and Fujinami, 1908; Fujinami, 1913; Nakari,1913), with examination of all death certificates of the inhabitants from 1901 to 1904 by organ in the Kyoto region. These were the first relatively reliable population-based cancer mortality statistics in Japan, although they included some erroneous classifications on death certificates. Suzuki (1918;1921) succeeded in conducting an epidemiological study of cancer by visiting local villages and towns with populations more than 2000 from 1905 to 1914, over 10 years, and revealed that cancer mortality rates ranged from 6.1 to 14.0 per 10,000 in the Kyoto area. He concluded that cancer mortality varied greatly with the prevailing economic conditions and the predominant lifestyle. The areas where people liked rich foods including meat and alcohol drinking showed higher cancer mortality, while areas where people consumed rice, vegetables and small amounts of fish, with less meat, showed lower cancer mortality. Again these findings resonate with the most recent research into nutritional influence on neoplasia.

Similar epidemiological studies were then conducted in Aichi (Nomura, 1924), Gifu (Nomura and Yoshida, 1924), Shizuoka (Yoshida, 1926) and Yamanashi (Katada, 1926) prefectures by Fujinami's students, working at the Aichi Medical College, Nagoya, and voluminous reports ensued, containing very interesting results. For example, the findings suggested a statistical association between the living environment and/or lifestyle habits and frequency of cancer deaths, and in Yamanashi prefecture, a close relationship between *Schistosomiasis Japonica* infestation and liver cancer was shown already in 1926. Fujinami expected to present the overall analyses of the data of the series of studies in 1934, but unfortunately he suddenly died and none of his colleagues were able to adequately continue his work. Of course the idea of epidemiology was derived from Europe but these early studies were equal in quality and quantity to those conducted anywhere else in the world at that time. They remained buried in the world, as only written in Japanese.

Regarding cancer statistics, Mataro Nagayo (see Photograph 4), a pathologist and the first chairman of the Cancer Institute in 1934, had developed a great interest since 1920s and therefore conducted a nation-wide patient survey sending questionnaires to the major hospitals throughout Japan repeatedly in the 1929-32. It was not an easy task at that period, but finally he published a monograph entitled "Statistical Study on Cancer in Japan" collecting more than 20,000 cases of cancer patients, as a supplement to the journal Gann (Nagayo, 1935).The distribution of cancer by site suggested marked differences in relative frequency compared with those of other countries. and he added cancer mortality statistics for 1915 to 1930 in all Japan, with a total of 1,579 cancer cases autopsied at the Department of Pathology, Tokyo University in 1889-1914. These figures opened the eyes of many physicians and researchers to the necessity for future study. Nagayo deserves particular respect for his emphasis of the importance of cancer statistics and his conclusion that cancer occurrence was largely dependent on environmental factors, with genetic traits seeming to play minor roles. Unfortunately, for the next 20 years there was no one able to maintain the same calibre of activity.

e) Cancer Research Institute and Hospital in Tokyo

It had long been argued that there was an urgent need for a specific institute for cancer and the JFCR, a Corporate Juridical Person in 1915 reestablished in 1933 as the Japanese Foundation for Cancer Research, took on this task. Economic recession in 1920s hindered creation of a cancer hospital and research institute, except a small scale of dispensary in the campus of Tokyo University. However, the Cancer Research Institute and Hospital was finally established in 1934, in Nishi-Sugamo, Tokyo, due to the great efforts of various leading scientists and donations from the Imperial fund. This sealed the success of the early era in cancer control in Japan. The UICC also commenced its activities in the same year in France. Radium was donated to this hospital for therapeutic purposes from a volunteer enterprise which accelerated increase. There were also developments in the provinces, with founding of the Hokkaido Cancer Research Association in 1930 and the Osaka Research Association for Cancer Treatment in 1935, both aiming to achieve modern cancer clinics and cancer prevention activities like the Cancer Institute in Tokyo.

Post-WWII Developments

a) Establishment of Population-based Cancer Registries in Japan

The first survey of cancer morbidity in Japan was conducted from 1951 to 1953, when Dr. Mitsuo Segi (Photograph 5) studied a residential population living within a defined area in Miyagi Prefecture. Segi collected data on all of the cancer patients in all of the hospitals of the prefecture, as well as the death certificates for all of the persons who died from cancer (kept in fifteen prefectural public heath centers). This was only the third cancer registry in the world. Dr Segi furthermore worked out a new standardization of cancer statistics using the 1950 World population, the answer to another task of the

UICC since its inauguration in 1934. This standardization made international comparison of cancer statistics more scientific. He issued a monograph "Cancer Mortality for Selected Sites in 24 Countries (1950-57)" in 1960, which was distributed throughout the world without fee and went on then to issue an additional 5 volumes (the last one contained the statistics for 1966-67 in 1972). These publications were of great help to oncologists and public health workers, and his work has been continued by Japanese epidemiologists up to the present.

He then compiled lists from these two sources of data, checking the names and addresses of all of the cases by hand to eliminate duplications. In 1954, the results of the first year's survey were published in the Tohoku Journal of Experimental Medicine (Segi et al., 1954) in English (the first such report from Japan ever to be published). Next, a report on the 3-year survey from 1951 to 1953 was published in the Journal of the National Cancer Institute (Segi et al., 1957). Segi adopted the new system for reporting and analyzing cancer incidence in the US population, the so-called age-adjusted incidence, in Japan, and compared the cancer incidences between the two populations. Later he adopted the world population in 1950 as a base population for an international comparison of incidence and mortality rates (Segi et al., 1960). After an actual 3-year survey, the first population-based cancer registry for epidemiological purposes was established to collect data on cancer patients (Aoki and Kurihara,1994).

In 1957 and 1958, the cities of Hiroshima and Nagasaki established population-based cancer registries to follow-up the survivors of the atomic bombings of the two cities, in cooperation with local medical associations. These special-purpose registries have been operated by the Atomic Bomb Casualty Commission (ABCC) - Radiation Effects Research Foundation (RERF) to investigate the long-term effects of atomic bomb radiation on human health (Monzen and Wakabayashi, 1986).

In 1962, the prefectural governments of Aichi and Osaka established population-based cancer registries in cooperation with prefectural medical associations (Hanai et al., 1999). In ensuing years, this type of population-based cancer registry spread to Kanagawa (1970), Tottori (1971), Kochi (1973), and Chiba (1975). Around the time when the Health and Medical Services Law for the Aged was enacted in 1983, population-based cancer registries were operating in 14 prefectures and two cities throughout Japan. The new law recommended that all prefectural governors establish cancer registries as a support for the planning of cancer control programs and the assessment of cancer screening. Registries were established in 19 prefectures promptly after the law was enacted. As of 2008, population-based registries are being run in 35 prefectures and 1 city in Japan.

b) Japan's Contributions to the Establishment of the International Association of Cancer Registries (IACR) and the Asian Federation of Organizations for Cancer Control (APFOCC) as well as Ongoing Activities of the International Union Against Cancer (UICC)

In the 6th International Congress of the International Union against Cancer (UICC) held in Tokyo in October 1966, with Tomizo Yoshida of experimental cancer fame as its President, Dr. Segi and Dr. T Soda invited 47 people from 26 countries to take part in a satellite meeting on cancer registries, including 17 physicians then involved in the registries in Japan. During the meeting Drs. William Haenszel and Sidney J Cutler proposed the foundation of an international association for the exchange of information and the promotion of cancer registries worldwide. After clearing many roadblocks and difficulties entailed in the forming of an international association, a subcommittee set up by Segi and others concluded that an international association would encourage the development of cancer registries. The objective of the association would not be to compete with or oppose the World Health Organization (WHO), the International Agency for Research on Cancer (IARC), or UICC, but to support their activities. Shortly afterwards, the International Association of Cancer Registries (IACR) was established. The physicians involved credited the establishment of the association in large measure to the foresight and industry of Dr. Segi. The first annual meeting of the IACR was held at Houston, in the US, by Dr. Cutler in 1970. The sixth annual meeting was held in 1984 at Fukuoka, Japan, hosted by Dr. Takao Shigematsu, and the 2010 meeting will be held in Yokohama with Dr Setsuo Hirohashi in the chair.

Another satellite meeting for Asian oncologists attending the UICC Tokyo Congress was sponsored by Kunio Ota, Tokyo University, Secretary-General of the Tokyo Congress. At this meeting, Asian scientists expressed strong wishes to have opportunities to regularly exchange information within Asia. Dr Ota, who had raised funding, held a cancer meeting in Japan inviting 76 oncologists from Asian countries in 1973, along with members of the WHO, UICC and IARC. This was the first meeting of the Asian Federation of Organizations for Cancer Control (AFOCC). Dr Takeshi Hirayama, Chief of the Epidemiology Division of the national cancer Center Research Insitute, and a very extrovert internationally minded individual, took on the task of Secretary-General of the new federation and then continued in this role until his death. Since 1973, congresses have been held every two years. The name was changed to the Asia-Pacific Federation of Organizations for Cancer Control (APFOCC) in 1979, because members were from then also accepted from the Oceania region. The APFOCC has been closely linked to UICC activities, as a branch organization, playing a special role in holding meetings in different sites within Asia. The next Asian Pacific Cancer Congress is scheduled to be held in 2009 in Tsukuba, Japan, with Dr Hideyuki Akaza as the host.

Within the UICC, it has been a long tradition that a Japanese epidemiologist should play a leading role in its activities and the first UICC Conference on Cancer Prevention in Developing Countries were held at Nagoya, Japan, in 1981 with Dr Kunio Aoki in the chair (see Photograph 6). He was followed by Drs Suketami Tominaga (Photograph 7) and now Kazuo Tajima of Aichi Cancer Center as 'Strategic Leaders' for epidemiology and cancer prevention within the UICC. The Japanese members of the organization, most of which are included

Photographs 6-9. Major Japanese Contributors to UICC Activities: Drs Kunio Aoki, Suketami Tominaga Haruo Sugano, and Tomoyuki Kitagawa

in the Japanese UICC National Committee, have long provided generous financial support to the Geneva office under the leadership of Dr Haruo Sugano (Photograph 8). The same role is now being continued by Dr Tomoyuki Kitagawa (Photograph 9), who has been instrumental in setting up the UICC Asian Regional Office for Cancer Control, with funding primarily from the Japanese members. Japanese pathologists have also made partcularly strong contributions to the UICC TNM (tumour size, lymph nodal involvement, metastasis) classification.

c) Establishment of the National Cancer Center

Following World War II and with increasing awareness of the shift away from infectious diseases to cancer, it became clear that the nation should have a comprehensive 'cancer center' to serve as the nucleus of cancer control measures. Therefore a Preparation Committee for the Establishment of the National cancer Center was formed in 1960, led by Takeo Tamiya, then President of the Japanese Association of Medical Science, with eight other members. Acting on its recommendations the then Ministry of Health and Welfare established the National Cancer Center (NCC) on February 1st, 1962. The hospital was opened in the same year and a new Research Institute in 1981. This is reflected in the NCC symbol (see Figure 2), formed using the inner part of the Japanese character for cancer (癌) by removing the outer section 疒), which denotes sickness in general. The interlocking of the three circles represents the harmony of the three parts:

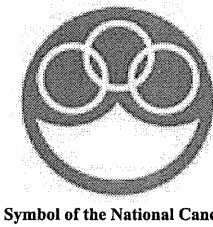


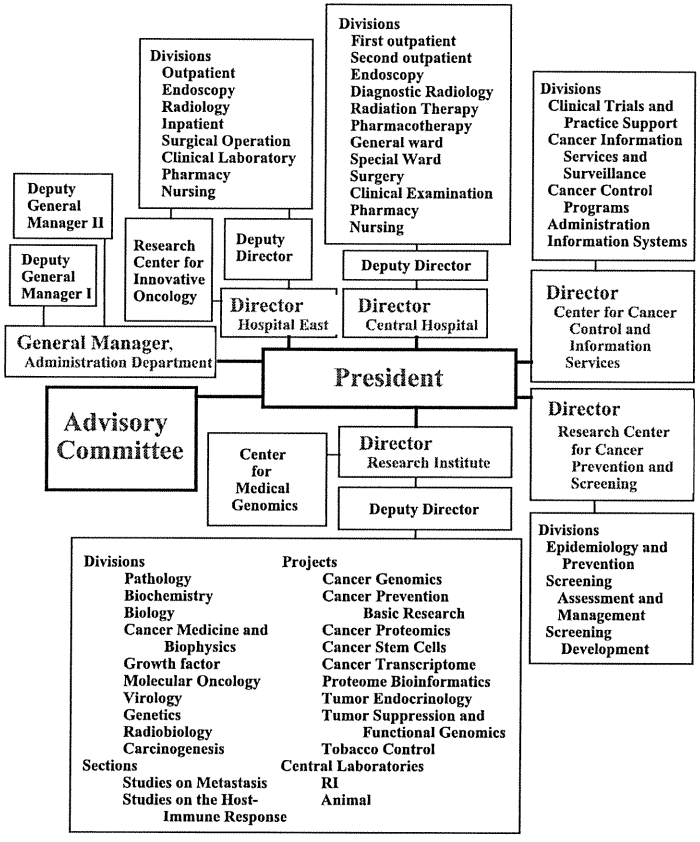
Figure 2. Symbol of the National Cancer Center

administration, hospital, research institute. A second National Cancer Center Hospital east was added in Chiba Prefecture in 1992, with a Research Institute in 1994. This was reorganized to form the Research Center for Innovative Oncology in Hospital East in 2005. Other major additions have been the Research Center for Prevention and Screening (2003) and the Center for Cancer Control and Information Services (2006). Within the NCC complex is also housed the Foundation for Promotion of Cancer Research and its International Lecture Hall, opened in 1985.

The organizational layout of the NCC is illustrated in Text-Figure 1. The President is aided by an advisory committee, made up of leading figures in industry and civil society, and is reported to by a number of Directors.

The administration department is responsible for accounting, statistics, policy-based medical service planning medical affairs and the library. The hospitals are not bound by the traditional department system, rather assuming a structure which allows treatment to be conducted organically. The research institute focuses on three areas, causes and prevention, mechanisms of cancer development and cancer diagnosis and therapy, in addition to the expression profiling conducted in the center for medical genomics.At the research center for innovative oncology, the focus is on imge-guided theapy, new drug development based on cancer specific biology and/or biochemistry, proton therapy and mental and physical supportive care systems.

The Japanese NCC contributes to the work of the World Health Organization in the form of two WHO Collaborating Centers, one established in 1970 for 'Evaluation of Methods of Diagnosis and Treatment of Stomach Cancer', and the other in 1981 for 'Tobacco and Health Programs'. Japan is also one of the Governing Council members of the WHO International Agency for Research on Cancer and the vice-Director of the Research Institute of the NCC traditionally serves as one of its Scientific Council, acting as a liaison with the Agency in Lyon, France.



Text-Figure 1. Organizational Chart of the Japanese National Cancer Center

d) Cooperation with the USA and other countries

In the immediate aftermath of World War II and the dropping of the atomic bombs on Hiroshima and Nagasaki, the American administration in Japan set up a project to investigate the effects of these devastating events on the development of cancer in the exposed populations. In American hands until relatively recently, this has provided abundant evidence of carcinogenity. In a more positive light, the interaction with Japan may have set the scene for a more equal collaboration.

In 1972, Dr Tomizo Yoshida, then serving as director of the Cancer Institute of the JFCR, met with Dr Frank J Rauscehr, Jr, director of the National Cancer Institute (NCI) in the US, to discuss building on the Cooperative Science Program concluded in 1961 between Prome Minister Ikeda and Presdient Kennedy. The result was a meeting in Hakone in 1973 which layed the groundwork for the Japan-US Cooperative Cancer Research Program which was continued ever since. An agreement was drafted between the Japan Society for promotion of Sciences and the NCI and the main focus has been on scientific seminars and exchange of personnel. More recently, large symposia have been organized and specific collaborative research projects launched.

Similar, albeit less official, agreements have also resulted in cooperatiion between Japan and countries of Europe active in cancer control research, and there is now an emphasis on reaching out to scientists in Asia, especially in the immediate vicinity.

History of the Japanese National Cancer Control Program

a) Nationwide Cancer Control Surveillance

Japan's first nationwide cancer control surveillance projects were the three National Cancer Surveys conducted by the Ministry of Health and Welfare in 1958, 1960, and 1962. These were followed by the first national cancer

program, in 1966. The surveys and program shared five common goals (five pillars for cancer control): to promote cancer education, to promote cancer screening, to establish cancer-oriented medical facilities, to train healthcare providers specialized in cancer treatment, and to promote cancer research. Regrettably, a cancer registration system was not included among these goals at the time. Fourth and fifth National Cancer Surveys were further conducted in 1979 and 1989, respectively.

b) Activities of the Research Group for Population-based Cancer Registration and Establishment of the Japanese Association of Cancer Registries (JACR)

In 1975, Dr. Isaburo Fujimoto organized the Research Group for Population-based Cancer Registration in Japan with funds from a grant-in-aid under the National Cancer Research Promotion Program. Meetings of this Group have subsequently been held annually. This research group has been continuing its work, under the direction of five successive chairpersons - Dr Fujimoto himself, followed by Drs Segi Fukuma, Aya Hanai, Akira Oshima, and Hideaki Tsukuma.

Major achievements which can be cited are: 1) two major publications (the "Guideline for Population-based Cancer Registration in Japan" in 1975 (with subsequent revisions) and the "Standardized Methods of Population-based Cancer registry" in 1977 as well as translation into Japanese of "Cancer Registration: Principles and Methods" in 1978; 2) broadening of the scope and coverage of the various registries; 3) preparation of annual cancer statistics on cancer incidences, survival rates by cancer type; 4) publication of the "Guideline for confidentiality in cancer registration schemes" in 1996; 5) provision of training course schedules and lectures for tumor registrars at the National Cancer Center twice a year; 6) promotion of the use of registry data for epidemiological research and the planning and evaluation of the cancer control program of the national and municipal governments in Japan.

In 1959 the Miyagi Tumor Registry was started as the first population-based registry and others soon followed. Cancer registration schemes as part of prefectural cancer control programs were first provided in 1962 by the Health Departments of Aichi Prefecture and of Osaka Prefecture. Thus population-based cancer registries were introduced in many prefectures, even before the enactment of the law on Health and Medical Services for the Aged in 1983. This was the first law to recommend that the prefectures undertake cancer registries to help them anti-cancer programs and evaluate cancer screening programs. The effects of this recommendation were major, as evidenced by the rapid increase in active cancer registries (see Figure 3). However, the data collected and the systems for management differed from prefecture to prefecture so that the Japanese Association of Cancer Registries (JACR) (http://www.cancerinfo.jp/jacr/) was organized in 1992 to promote standardization of the registry process and improve the quality of registry data, holding annual scientific and procedural meetings for this purpose.

As of 2008, 35 out of 47 prefectures and 1 city (Hiroshima city) have implemented population-based

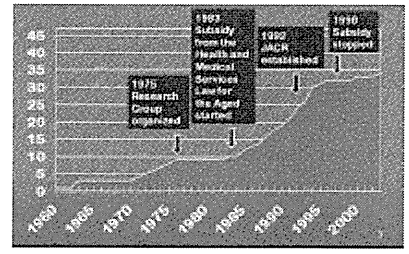


Figure 3. Change in Numbers of Cancer Registries in Japan over Time

cancer registries , which means that over two thirds of the Japanese population is now covered. The problem is with data quality. Because of low completeness (proportion of registered cases out of all new cases is low), data from 22 cancer registries could not be used for estimating nation-wide incidence. Only 7 are considered sufficiently accurate for inclusion in Cancer Incidence in Five Continents, a world-wide data book for cancer incidence issued by International Agency for Research on Cancer (IARC) (see Figure 4).

In 2004, the Japan Surveillance Research group (chaired by Dr Tomotaka Sobue) introduced standard procedures for cancer registry in Japan by selecting a set of 25 standard items for every cancer registry to collect and a standard registry system. However, notification of cancer cases to the population-based cancer registries in Japan is not compulsory for physicians and medical institutions, but rather voluntary. Later, in 2003, a population-based cancer registration was officially reintroduced as a voluntary task in the newly enacted Health Promotion Law. This law requires national and municipal governments to take steps to ascertain details on the onset of lifestyle-related disease such as cancer and cardiovascular disease. At the same time, given the recent concern about the right to privacy, the 2003 Act on the Protection of Personal Information was enacted and this became a barrier for registries to improve their activities. Because of the limited commitment from national government, registration systems at each registry

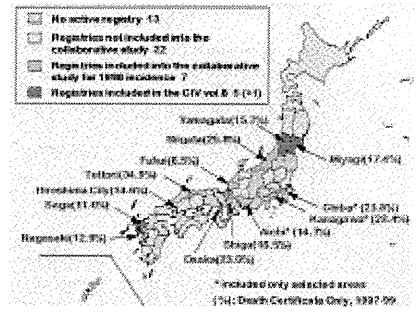
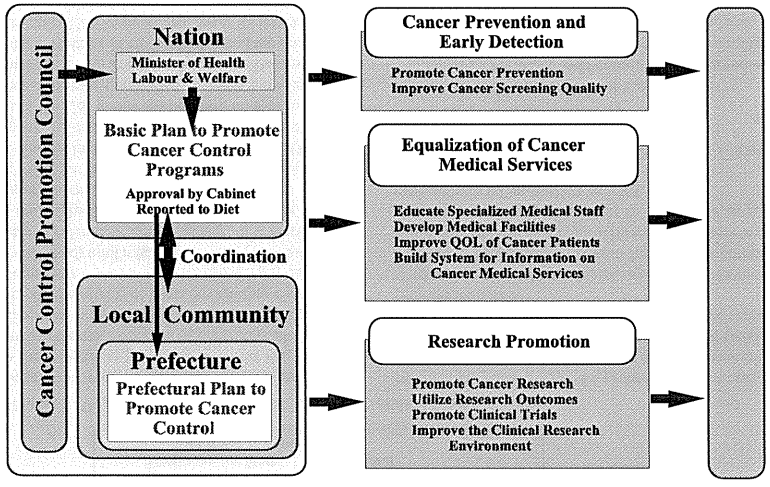


Figure 3. Population-based Cancer Registries in Japan



Text-Figure 2. Concepts Underlying the Japanese Cancer Control Act of 2006, Implemented in 2007

have not been standardized so far.

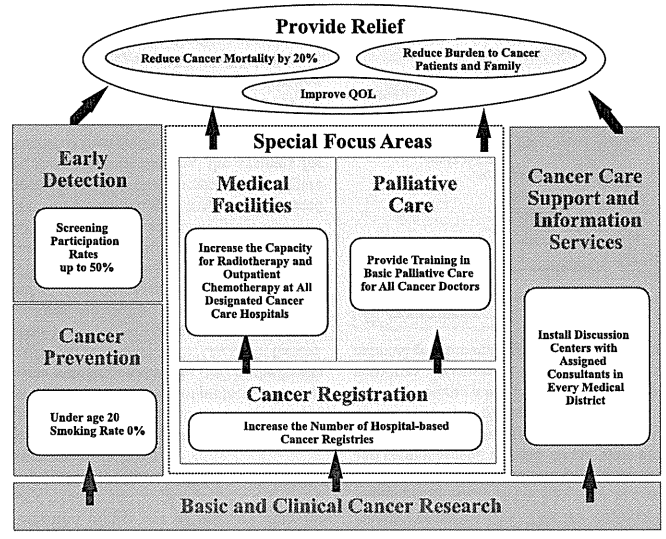
To improve the quality of the data, the Japanese Cancer Surveillance Research Group is now taking steps to standardize the procedures for population-based cancer registries. Because legal support is necessary, the JACR has issued a declaration requesting a legal basis for reporting to cancer registries through the enactment of a "Cancer Registry Law" (a tentative name). There are hopes that this new law, if enacted, will drastically improve the data quality of the cancer registries in Japan. Data on cancer statistics at the national level are available at National Cancer Center website (http://www.ncc.go.jp/index.html).

c) Basic Plan to Promote Cancer Control Programs

One of the landmarks in the history of cancer control in Japan was the decision to provide a subsidy for cancer research by the then Ministry of Health and Welfare in 1963. This was the first official government funding (Joseikin). Cancer became the leading cause of death in 1981 and accepting advice from many quarters the Japanese government under Prime Minister Yasuhiro Nakasone later decided to implement a "Comprehensive 10-year Strategy for Cancer Control" (1984-1993) as a nationwide program to contend with cancer. At the completion of this period a "New 10-year Strategy to Overcome Cancer (1994-2003)" was started, the emphasis in this first 20 year period being on basic research. Next, in 2004, it launched the "Third-Term Comprehensive 10-year Strategy for Cancer Control" to further promote cancer research and disseminate high-quality cancer medical services. The chief aim, with an incremental rise in the level of funding, is to "drastically reduce cancer morbidity and mortality." This latest strategy includes measures not only to fund cancer research, but also measures to prevent cancer, improve the quality of cancer care, promote social support systems, and establish more effective systems for monitoring cancer incidence and survival. Over the last 4 years of the program there has been a rapid increase in the level of yearly funding, from 15 million US$ in 1984, to 33 million in 1994, to 90 million in 2004 and over 200 million in 2007. The organization responsible for overseeing the program is the Japanese Foundation for Promotion of Cancer Research.

The Cancer Control Act approved in 2006 and introduced into law in April 2007 has three basic concepts or areas of activity (see Text-Figure 2): prevention and early detection; equalization of care; and research promotion. Importnatly, it allows patient support groups and other interested parties an official role as members of the Cancer Control Promotion Council, liaising with the Minister.. It also recognizes the cancer registry as one of the most important axes of cancer control activities. The Basic Plan to Promote Cancer Control Programs initiated development in 2007, and covers fiscal years 2007-2011. The overall goals are reducing cancer-associated mortality, reduing the burden on patinets and their families and improvement in QOL. Seven specific fields are covered as indicated in Text-Figure 3, with three special areas of focus: chemotherapy and radiotherapy; palliative care in the early phase of treatment; and promotion of cancer registration.

At the base is cancer research, to support all of the other activities. To expand the network of specialized facilities it has been decided to designate cancer care hospitals, of which there are now 351, as of February 2008 The idea with this newly developed hospital network to provide standardized high-quality cancer care, with provision of essential treatment facilities and palliative care, as well as care support and information services. In order to improve completeness of cancer registration, each of the designated cancer care hospitals is required to



Text-Figure 3. Basic Plan to Promote Cancer Control Programs of the Japanese Ministry of Health, Labour and Welfare

establish and maintain hospital-based cancer registry using standard procedures. The Center for Cancer Control and Information Services (CIS), launched at the National Cancer Center in 2006, is responsible for overseeing all cancer registries in Japan, disseminating information, and developing training and education systems for registrars.

Proportions of cancer patients who can be covered by designated cancer care hospitals varies by prefecture. In rural areas, such as Fukui Prefecture with 0.8 million population, 70% of all new cancer patients are covered by 5 designated cancer care hospitals, so that collecting information from these hospitals can lead to high completeness of population-based cancer registries. On the other hand, in urban areas, such as Osaka Prefecture with 8.8 million population, 11 designated cancer care hospitals cover only 25% of all new cancer patients. Therefore, in these areas, some additional action, such as increasing numbers of designated cancer care hospitals, introducing hospital-based cancer registries into other hospitals or centralize cancer patients into designated cancer care hospitals, will be needed. In addition, legislative action, which makes registration from hospitals obligatory, will be necessary.

In Japan, national programs for cervical and stomach cancer screening were introduced in 1984. Subsequently, such early detection efforts have been added for the lung, liver, colorectal, endometrial and breast cancers. One of the emphases of the Basic Plan is to increase participation rates, with a goal set of 50% of the target populations, with additional stress on the need for better assessment and evaluation. Screening is recommended from the ages of 20 by PAP smear for cervical, 40 by barium X-ray for stomach, 40 by X-ray for lung, 40 by HPV testing for individuals with symptoms for liver, 40 by immuno-fecal occult blood testing for colorectal, 40 by mammography (and to seome extent by clinical breast examination for breast and 40 by tumor marker testing for individuals with symptoms or wishing for screening for endometrial cancers. Basically, the cost for these is covered by medical insurance although since screening is the responsibility of the municipality there may be some variation. This is especially the case for screening for prostate cancer by PSA testing.

The last area is cancer prevention with the emphasis on reducing the smoking prevalence in adolescents and young adults.

d) Japanese Foundation for Promotion of Cancer Research

Housed within the NCC and launched in 1968 as an Association by the Ministry of Health, Labour and Welfare, it changed its status at the suggestion of the then Minister in 1983 to a public Foundation, with permission to receive tax-deductible donations. Its designated roles are to:

1) Provide financial support for basic and clinical cancer research
2) Support development of diagnostic and treatment methodology
3) Assist in international cooperation
4) Provide support for specialist education and training
5) Act to promote research
6) Sponsor the dissemination of accurate information (pamphlets, meetings)
7) Liaise and cooperate with other relevant institutions

Table 2. Japanese Foundation for Promotion of Cancer Research International Symposia

Symposium	Year	Chairperson	Theme
1st	1988	Keiichi Suemasu	Fundamental and Clinical Research in Lung Cancer
2nd	1989	Keiichi Suemasu	Fundamental and Clinical Research in Liver Cancer
3rd	1990	Keiichi Suemasu	Fundamental and Clinical Research in Multiple Cancer
4th	1991	Tadao Kakizoe	Fundamental and Clinical Research in Urinogenital Cancer
5th	1992	Keiichi Suemasu	Fundamental and Clinical Research in Pancreatic and Biliary Tract Cancers
6th	1993	Keiichi Suemasu	Fundamental and Clinical Research in Esophageal Cancer
7th	1994	Nagahiro Saijo	Fundamental and Clinical Research in Lung Cancer
8th	1995	Tadao Kakizoe	Basic and Clinical Research in Colorectal Cancer
9th	1996	Kazuhiro Nomura	Basic and Clinical Research in Brain Cancer
10th	1997	Satoshi Ebihara	Basic and Clinical Research in Head and Neck Cancer
11th	1998	Mitsuru Sasako	Basic and Clinical Research in Gastric Cancer
12th	1999	Kaoru Abe	Basic and Clinical Research in Breast Cancer
13th	2000	Tadao Kakizoe	Cancer Screening - Past, Present and Future
14th	2001	Tadao Kakizoe	Pain Control, Palliative Medicine and Psycho-oncology - Present Status and Future Directions
15th	2002	Tadao Kakizoe	New Horizons in the Diagnosis and Treatment of Hematological Malignancies based on Molecular Genetic Features
16th	2003	Tadao Kakizoe	Recent Advances in Pancreatic Cancer
17th	2004	Tadao Kakizoe	Recent Advances in Gastric Cancer
18th	2005	Tadao Kakizoe	Disputes or Controversies in Prostate Cancer Diagnosis and Treatment
19th	2006	Daizo Saio	Infection, Cancer and Prevention
20th	2007	Mitsuru Sasako	Physiological Changes and QOL of Cancer Patients after Radical Surgery
21st	2008	Hiroshi Ikeda	Modern Radiation Oncology: Innovative Technologies and Translational Research

The Foundation has produced pamphlets on lung, stomach, breast, cervical, liver, prostate, and colon cancers, cancer and diet, cancer statistics, and a series on tobacco control, published with the financial help of the Japanese Lottery Association. For each of the major cancers there is detailed information on prevalence, risk factors, symptoms and early detection (including screening when appropriate), diagnosis, treatment and palliative care. At one time the Founation also published the Japanese Journal of Clinical Oncology but this has now been taken over by Oxford Press. However, a yearly publication of cancer registration statistics is continuing, with detailed explanations of their significance.

The Foundation also makes major contributions to international activities. For example, it sponsors foreign researchers to visit Japan to give lectures or work for longer periods in Japanese research establishments (a total of over 730 in the 25 years of the program so far), and Japanese researchers to visit overseas for the same purpose (over 783). It also provides almost 100 training grants to Japanese research residents every year. Furthermore, there is a yearly International Research Symposium sponsored by the Japanese Bicycle Promotion Society (see Table 2 for details). With the same sponsorship there are numerous public Cancer Prevention Workshops and Lectures, generally performed by researchers from the National Cancer Center, at different communities across Japan. Since 2000, there have also been yearly International Nursing Seminars.

Table 2. Japanese Academic Societies and Research Meetings

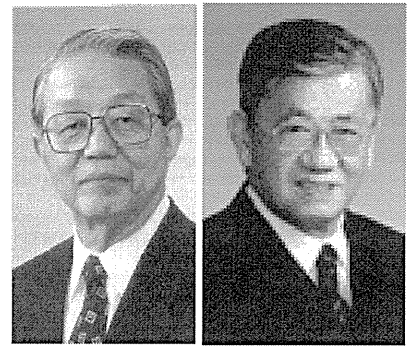
From	Name
1954	Japanese Cancer Association
19?	Japanese Association for Cancer Detection and Diagnosis
	Japanese Gastrointestinal Cancer Screening Association
	Japanese Gynecology Cancer Screening Society
	Japanese Breast Cancer Screening Association
	Japanese Association for Lung Cancer
	Japanese Pediatric Cancer Association
	Japanese Medical Radiology Society
	Japanese Kidney and Urology Patients Prevention
19?	Japanese Association for Cancer Prevention*
19?	Japanese Society of Cancer Epidemiology*
200?	Japanese Society of Cancer Molecular Epidemiology*
19?	Japanese Society of Clinical Oncology
19?	Japanese Society of Medical Oncology
19?	Japanese Palliative Care Association
19?	Japanese Society of Cancer Registries

*Joint yearly meeting

e) Academic Organizations

The number of academic organizations involved with different aspects of cancer control continues to increase (see Table 3), each holding a yearly meeting to exchange information among its members.

The largest is the Japanese Association of Cancer Research with over 16,000 members, which stages a meeting in late October early November. An interesting offshoot of this is the Carcinogenesis-Pathology Research Workshop. Started by Dr Nobuyuki Ito (Photograph 10) as an opportunity for the members of a number of collaborating laboratories to practice their presentations before this meeting in front of a friendly audience, this has subsequently grown with the support of Dr Takashi Sugimura, Emeritus President of the NCC (Photograph 11), to a yearly gathering of all the Japanese groups active in basic toxicological pathology-carcinogenesis research.



Photographs 10 and 11. Drs Nobuyuki Ito and Takashi Sugimura

The Japanese Association meeting is in fact becoming more international and this year many of the the presentations are scheduled to be given in English. A recent development has been to include a UICC symposium, focusing on problems in Asia.

Most of the organizations have their own separate conferences but one important development has been the change staging of joint meetings by the Cancer Prevention, Cancer Epidemiology, and Cancer Molecular Epidemiology groups, generally in July, to allow scientists from different disciplines to interact more positively. Similarly, a number of organizations contribute to the meeting of the Japanese Association for Cancer Detection and Diagnosis.

f) Non-Government Organizations

Princess Takamatsu Cancer Research Foundation

The Princess Takamatsu Cancer Research Fund was established in 1968. Her Imperial Highness Princess Takamatsu devoted much of her life to alleviating the scourge of cancer since the disease took the life of her mother in 1933. She founded the precursor of the present Fund, the "Nadeshiko-kai", with her classmates at Joshi Gakushuin School in 1953. The Fund sponsored various charities and provided financial support for cancer research. Initiatives such as these increased public awareness of cancer and attracted the support of parties with interests similar to those of the Princess.

In her position as Honorary Patroness of the Fund since its inception, Her Imperial Highness Princess Takamatsu maintained a strong influence in matters related to the Fund and was actively involved in its many activities in different fields. It was with a deep sense of regret that the Japanese and international community acknowledged her passing in 2004. In 2001, His Imperial Highness Prince Tomohito of Mikasa became the Fund's Patron.

The objective of the Fund is to contribute to the progress of science and the welfare of mankind through supporting cancer research. At present, it is engaged in the following activities:

With the guidance of Dr Takashi Sugimura as Chairperson of its Scientific Advisory Committee, the International Symposium of the Princess Takamatsu Cancer Research Fund has been held annually in Tokyo every November since 1970 (see Table 3). Invited speakers, each time 20 from abroad and 10 from Japan, are scientists that are considered to be highly productive and at the cutting edge of cancer research. Consequently, the symposia have come to be well regarded among scientists both at home and abroad.

The Lectureship of the Princess Takamatsu Cancer Research Fund was established in 1981. A prominent cancer researcher from abroad is invited every year to present lectures in three places in Japan. These lectures leave a deep impression on attendees and serve to stimulate many young Japanese scientists and students.

Research Grants have been awarded to 12 Japanese scientists each year since 1969, and this support has contributed positively to various fields of cancer research. Each recipient is awarded JP¥2,000,000.

The Princess Takamatsu Cancer Research Fund Prizes are awarded every year to Japanese scientists who have made outstanding contributions to fundamental and clinical research on cancer. Award of the prize is regarded as an enormous honor in the Japanese cancer research community. The Award of Merit, which bears the name of Her Imperial Highness, and JP¥3,000,000 are presented to each recipient. To honor the late Dr Waro Nakahara who was a pioneer of cancer research in Japan and played an important role in establishing of the International Symposium, a special lecture has been presented in his name at every symposium since 1977. The Fund awards a plaque and a prize (JP¥500,000) to honor the lecturer for his or her distinguished research on cancer in the occasion of the symposium.

The Princess Takamatsu Cancer Research Fund and the American Association for Cancer Research AACR

Photograph 12. Princess Takamatsu

Table 3. Princess Takamatsu Cancer Research Fund International Symposia

Symposium Year	Chairperson	Theme
1st (1970)	Waro Nakahara	Recent Advances in Human Tumor Virology and Immunology
2nd (1971)	Waro Nakahara	Topics in Chemical Carcinogenesis
3rd (1972)	Waro Nakahara	Analytic and Experimental Epidemiology of Cancer
4th (1973)	Waro Nakahara	Differentiation and Control of Malignancy of Tumor Cells
5th (1974)	Goro Chihara	Host Defense Against Cancer and Its Potentiation
6th (1975)	Peter N Magee	Fundamentals in Cancer Prevention
7th (1976)	Emmanuel Farber	Pathophysiology of Carcinogenesis in Digestive Organs
8th (1977)	Stephen K Carter	Advances in Cancer Chemotherapy
9th (1978)	Iwao Hirono	Naturally Occurring Carcinogens-Mutagens and Modulators of Carcinogenesis
10th (1979)	Harry V. Gelboin	Genetic and Environmental Factors in Experimental and Human Cancer
11th (1980)	Clyde J Dawe	Phyletic Approaches to Cancer
12th (1981)	Masanao Miwa	Primary and Tertiary Structure of Nucleic Acids and Cancer Research
13th (1982)	Osamu Hayaishi	ADP-ribosylation, DNA Repair and Cancer
14th (1983)	Hirota Fujiki	Cellular Interactions by Environmental Tumor Promoters
15th (1984)	Masanao Miwa	Retroviruses in Human Lymphoma/Leukemia
16th (1985)	Yuzo Hayashi	Diet, Nutrition and Cancer
17th (1986)	Stuart A Aaronson	Oncogenes and Cancer
18th (1987)	Joseph F Fraumeni Jr	Unusual Occurrences as Clues to Cancer Etiology,
19th (1988)	Toshiyuki Hamaoka	Immune System and Cancer,
20th (1989)	Alfred G Knudson Jr	Genetic Basis for Carcinogenesis: Tumor Suppressor Genes and Oncogenes,
21st (1990)	Lars Ernster	Xenobiotics and Cancer: Implications for Chemical Carcinogenesis and Cancer Chemotherapy
22nd (1991)	Curtis C Harris	Multistage Carcinogenesis
23rd (1992)	Richard H Adamson	Heterocyclic Amines in Cooked Foods: Possible Human Carcinogens,
24th (1993)	Setsuo Hirohashi	Molecular and Cellular Basis for Cell to Cell Interaction: its Significance in Cancer
25th (1994)	Kenichi Kobayashi	Hepatitis C Virus and ts Involvement in the Development of Hepatocellular Carcinoma
26th (1995)	Setsuo Hirohashi	Genomic Instability and Carcinogenesis
27th (1996)	Allan H Conney	Fundamentals of Cancer Prevention
28th (1997)	Carlo M Croce	Cancer Genomics
29th (1998)	Isaiah J Fidler	Molecular Basis for Invasion and Metastasis,
30th (1999)	Samuel M Cohen	New Frontiers in Mechanistic Cancer Research in Animal Models
31st (2000)	Setsuo Hirohashi	DNA Methylation and Cancer
32nd (2001)	Ken Yamaguchi	Basic and Clinical Research on Tumor Markers
33rd (2002)	Tadao Kakizoe	Innovative Achievements in Cancer Imaging
34th (2003)	Kumao Toyoshima	Cancer Immunotherapy
35th (2004)	Susumu Nishimura	Challenges & Novel Approaches to Modern Cancer Drug Discovery & Development
36th (2005)	Suketami Tominaga	Developments in Cancer Epidemiology? Prospects for Cancer Control in the Asian Pacific
37th (2006)	Hiroyasu Esumi	Cancer Microenvironments
38th (2007)	Hitoshi Nakagama	Current Challenges in the Understanding and Management of Colon Cancer
39th (2008)	Keiji Wakabayashi	The Metabolic Syndrome and Cancer

furthermore established a Lectureship in 2007 in honor of the late Princess Takamatsu. The aim is to recognize an individual scientist whose novel and significant work has had a far reaching impact on the detection, diagnosis, prevention, or treatment of cancer, and who embodies the dedication shown by Princess Takamatsu to multinational collaboration. The lecturer has the opportunity to present a major lecture during the AACR Annual Meeting, and is awarded US$10,000 along with an appropriate commemorative item (such as a plaque) serving as tangible witness to the singular honor of his/her selection.

The Princess Takamatsu Cancer Research Fund provides annually a grant of JP¥3,000,000 as a financial support to the AACR for the establishment of the Lectureship and also publishes 'Cancer', an annual Japanese publication that describes the activities of the Fund to the general public. The Fund became an affiliate of the International Union against Cancer (UICC) in 1978 and contributes JP¥1,500,000 in membership contributions annually.

Sapporo Cancer Seminar Foundation

In 1979, Dr. Hiroshi Kobayashi, now Professor Emeritus of Hokkaido University, inspired by the academically liberal atmosphere of The Gordon Research Conferences, Santa Barbara, California, the USA, conceived the idea of the Sapporo Cancer Seminar to provide greater opportunities for cancer researchers to share their knowledge in a relaxed but academic atmosphere. His proposal was encouraged by Dr. Takashi Sugimura and supported by Dr. Takeo Yamazaki, then President of the Hokkaido Medical Association, Sapporo, Hokkaido, Japan.

The first SCS was held in Sapporo in 1981, and in 1983 the SCS established itself as a foundation, with the warm support of businesses, pharmaceutical organizations, and the general public. Dr Kobayashi acted in the consideration that research itself is insufficient and there is a greatest urgency that medical specialists, wherever they are working, should have the opportunity to meet each other and discuss methods to combat or prevent the

Table 4. Sapporo Cancer Seminar Foundation - Summer Seminars

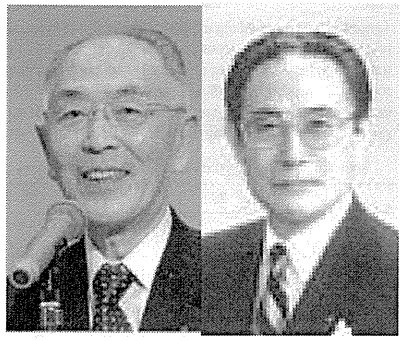
Seminar		Chairperson	Theme
1st Seminar	1981	H Kobayashi	Escape of Tumor Cells from Immune Controls
2nd Seminar	1982	A Makita	Membrane-Associated Alterations in Cancer: Biochemical Strategies
3rd Seminar	1983	Y Sakurai	Biological Responses in Cancer Chemotherapy
4th Seminar	1984	K Fujinaga	Viral Transforming Genes and Oncogenes: Origin, Structure, and Function
5th Seminar	1985	A Yachi	Monoclonal Antibodies: Progress in Cancer Immunobiology and Clinical Application
6th Seminar	1986	T Osato	Viruses, Immunodeficiency, and Human Cancer
7th Seminar	1987	K Aoki	Primary & Secondary Prevention of Cancer
8th Seminar	1988	H Kobayashi	Cancer Progression & Metastasis
9th Seminar	1989	M Hozumi	Cell Differentiation and Cancer Control
10th Seminar	1990	T Ohsato	Recent Topics in Cancer Research
11th Seminar	1991	Y Ikawa	Molecules in Carcinogenic Processes
12th Seminar	1992	N Taniguchi	Oxyradicals and Antioxidative Responses in Cancer
13th Seminar	1993	H Fujiki	Current Strategies of Cancer Chemoprevention
14th Seminar	1994	M Watanabe	Genetic Polymorphisms and Cancer Susceptibility
15th Seminar	1995	F Sendo	Psycho-Neuroimmunology and Cancer
16th Seminar	1996	M Hosokawa	Molecular Mechanisms for Inflammation-promoted Pathogenesis of Cancer
17th Seminar	1997	N Kuzumaki	Cytoskeleton and G proteins in the Regulation of Cancer
18th Seminar	1998	Y Niitsu	Regulation of Machinery for Cancer Cell Growth, Immortality, Apoptosis and Invasion
19th Seminar	1999	Y Nakamura	Cancer Genomics and Molecular Diagnosis
20th Seminar	2000	H Kobayashi	Gene-Environment Interaction and Cancer Prevention
21st Seminar	2001	K Takada	Epstein-Barr Virus and Human Cancer
22nd Seminar	2002	K Imai	Cancer Epigenetics
23rd Seminar	2003	K Imai	Immunology-based Targeting Therapy
24th Seminar	2004	Y Hata	Pharmacogenomics in Cancer Chemotherapy: Recent Advances in ABC Transporters and Genome Analyses
25th Seminar	2005	F Sendo	Toward Personalized Medicine in Cancer and other Life-style Related Disease
26th Seminar	2006	T Seya	Innate Immunity in Cancer and Infectious Diseases
27th Seminar	2007	N Taniguchi	Glycomics; New Perspectives in Cancer Cell Behavior
28th Seminar	2008	K Miyazono	Future problems for medical treatment of cancer

disease. He also was instrumental in establishing the Japanese Association (now Society) for Cancer Prevention in 1994.

The July Seminar (see Table 4) consists of symposia, a poster session with general discussions and meetings. Reports are published in Cancer Research and other world renowned journals. The Winter Seminar (see Table 5) originated as an offshoot of the activities of the Sapporo Cancer Seminar Foundation, with the generous sponsorship of the Foundation for Total Health Promotion, whose President Mitsuo Shikano has continued to be a generous sponsor. Taiho Pharmaceutical Industry Co. Ltd.,

Table 5. Sapporo Cancer Seminar Foundation - Winter Seminars

Seminar		Chairperson	Theme
1st Seminar	1987	Miyazaki Tamotsu	The biomedical characterisitics and control of leukemia cells
2nd Seminar	1988	Uchino Junichi	The biomedical characterisitics and control of liver cancer
3rd Seminar	1989	Suzuki Akira	Lung cancer and mediastinal tumors
4th Seminar	1990	Urushizaki Ichiro	Cancer and the quality of life
5th Seminar	1991	Inoguchi Kiyoshi	The changing nature and prospects for cancer medical treatment
6th Seminar	1992	Abe Hiroshi	Basics and clinic assessment of brain, head and neck tumors
7th Seminar	1993	Orimo Hajime	Pursuing a connection between ageing and cancer
8th Seminar	1994	Kakizoe Tadao	Appropriate countermeasures for intractable (obstinate) cancers
9th Seminar	1995	Kawakami Yoshikazu	Recent topics on adenocarcinoma research of the lung
10th Seminar	1996	Kobayashi Hiroshi	Secondary primary cancer and its prevention
11th Seminar	1997	Katou Hiroyuki	Considering present day cancer-diagnosis, treatment and prevention
12th Seminar	1998	Imai Kouzoh	Considering present day cancer-diagnosis, treatment and prevention
13th Seminar	1999	Abe Shousaku	Considering present day cancer 1999-diagnosis, treatment and prevention
14th Seminar	2000	Toudou Hajime	Considering present day cancer 2000-new challenges
15th Seminar	2001	Inoue Shoichi	Considering present day cancer 2001-prevention, diagnosis and treatment strategy
16th Seminar	2002	Hirata Kouichi	Considering present day cancer 2002-prevention, diagnosis and treatment strategy
17th Seminar	2003	Hata Yoshinobu	Considering present day cancer 2003-prevention, diagnosis and treatment strategy
18th Seminar	2004	Abe Shosaku	Considering present day cancer 2004-prevention, diagnosis and treatment strategy
19th Seminar	2005	Hareyama Masato	Considering present day cancer 2005-prevention, diagnosis and treatment strategy
20th Seminar	2006	Hirata Koichi	Considering present day cancer 2006
21st Seminar	2007	Hosokawa Masao	Future problems for medical treatment of cancer
22nd Seminar	2008	Inoue Shoichi	TGFb signaling and cancer



Photographs 13 and 14. Drs Hiroshi Kobayashi and Eiichi Tahara

under its President Yukio Kobayashi, has also provided assistance since the beginning of the 11th Winter Symposium. The summer seminar deals with basic aspects of cancer research, while the winter seminar, which is scheduled to coincide with Sapporo's Snow Festival, an internationally famous event, concentrates upon cancer-related clinical investigations.

Dr Kobayashi and the Sapporo Cancer Seminar Foundation are also very active in a community-based health promotion project in Sri Lanka focusing on schools and school children (see Photograph 12) .

Hiroshima Cancer Seminar Foundation

As is well-known, Hiroshima was the first city in the world to be struck with an atomic bomb, and the relative risk for hematological malignancies and thyroid cancer is high among the survivors. The goal of the Hiroshima Cancer Seminar Foundation is to promote everlasting peace by contributing to cancer research. Established by Eiichi Tahara (Professor Emeritus, Hiroshima University) (see Photograph 13) in 1992 with the cooperation of Hiroshima Prefectural Government, Hiroshima Financial Circles and Hiroshima Medical Association, the Foundation annually holds an international symposium (see Table 6) to create an opportunity for basic scientists and clinical researchers to exchange ideas on cancer research and cancer therapy. There is a strong focus on molecular biology.

The foundation also supports the activity of many scientific societies related to cancer, including the Japanese Cancer Association. The foundation offers scientific grants for young cancer researchers. Another important task of the Hiroshima Cancer Seminar Foundation is to distribute precise information on the causes and course of cancer as a contribution to cancer prevention. Since a correct understanding of the diagnosis and treatment of cancer is an important aspect of the provision of adequate medical care, a lecture open to the public is held annually.

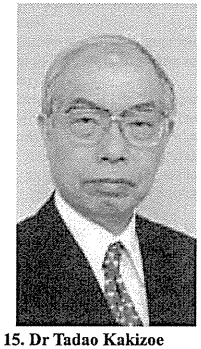
Japan Cancer Society (JCA)

The JCA was established in 1958 to aid the struggle to bring cancer under control, with strong support from the Asahi Shimbun, a leading Japanese newspaper. The first President was Hiroshige Shioda, an influential surgeon and Emeritus Professor of the University of Tokyo, and the present incumbent is Tadao Kakizoe (President Emeritus of the National Cancer Center). Dr Kakizoe himself (see Photograph 14) has long been active in promoting contacts within Asia, for example hosting a meeting of Directors of National Cancer Institutes/Centers to promote interaction. The JCA plays a major role in promoting screening, sponsoring early detection of 280 million people since its foundation. It also operates a 'cancer-hotline' and provides various kinds of free cancer consultation. For example in 2007, more than 14,000 patients and family members had the opportunity to avail themselves of advice from doctors.

To heighten awareness of cancer, the JCA organizes lectures and seminars, contributes to the 'pink-ribbon' fight against breast cancer, produces and distributes pamphlets, posters and DVDs and provides information

Table 6. Hiroshima Cancer Seminar Foundation International Symposia

Symposium	Year	Main Speakers	Theme
1st	1990	T Sugimura and S Waxman	New Approaches to Cancer Therapy
2nd	1992	T Sugimura and CC Harris	Carcinogenesis and Metastasis
3rd	1993	EJ Stanbridge and J Yokota	Tumor Suppressor Genes
4th	1994	T Sugimura and AB Deisseroth	Gene Therapy of Cancer
5th	1995	CB Harley and T de Lange	Telomerase and Cancer
6th	1996	RR Brentani and R Lotan	Cancer-stromal Interactions
7th	1997	IM Verma and F Wong-Staal	Gene Therapy: Application to Disease
8th	1998	JC Barrett and Oshimura	Aging and Cancer
9th	1999	Anna T Meadows and Ed Harlow	Pediatric Tumors and Secondary Cancers
10th	2000	J Quachenbush and T Tsunoda	Gene Diagnosis - Introduction of New Technology
11th	2001	R Grosschedl and PA Jones	Chromatin and Cancer
12th	2002	W K Cavenee and F B Furnari	Molecular Targeting Therapy for Cancer
13th	2003	CC Harris and XW Wang	New Approaches to Identification of Biomarkers for Early Cancer Detection
14th	2004	JP Issa and M Oshimura	Cancer and Epigenetics -Basic Research and Clinical Implications
15th	2005	JA Ajani and A Ohtsu	Current Progress of Cancer Chemotherapy
16th	2006	E Quintana and F Radtke	Cancer Stem Cells
17th	2007	JD Cox and T Ogino	Radiation Therapy for Cancer
18th	2008	NA Wright and RN DuBois	Recent Progress in Pathogenesis and Management of Colorectal Cancer



Photograph 15. Dr Tadao Kakizoe

(http://www.jcancer.jp). It also coordinates and co-sponsors the 'Relay for Life' with the American Cancer Society, a yearly event at six venues across the nation.

Patient Support Groups

There are also a number of patient support groups which are active, particularly for breast cancer survivors, including Gan-to-Tomo-ni Ikiru-kai (Live with Cancer Society) and Akebono-kai (Bringing light) and various Mamma clubs. Some of these have formed an alliance together with the Health Policy Institute of Japan for more effective coordination of their activities.

Present and Future Perspectives

a) National

There is currently an exercise being conducted in the Japanese NCC, comparing the cancer control strategies and programs in countries like the US, Canada, the UK and Korea, for example. Direct comparisons are difficult but in such countries with similar levels of economic development it appears that the amount of financial support may markedly vary. Especially the availability of research funding from NGOs is considerably greater in the Western countries. That said, there is a massive research effort continuing in all areas of cancer control and Japan makes a major contribution to the international literature. A very simple exercise is revealing in this regard. By country name and cancer research as search items, Japan is number 2 in the world with over 26,000 papers listed, behind the USA (187,000), but in front of the UK (23,000), Germany (13,000) and France (10,000).

Regarding cancer registration, great advances have been made and the level of coverage is high, but Japan remains in a relatively difficult position given the lack of any law making registration compulsory. The hospital-based program should facilitate greater accuracy as part of an overall improvement in data collection capacity.

In terms of cancer screening services, Japan is of course very well placed and there is no shortage of either facilities or capacity. The actual screening participation rates, however, for the National Cancer Screening program for 2006 were 22.5% for lung, 18.8% for colorectal, 18.8% for cervical, 12.9% for breast and 12.2% for stomach, the target populations ranging from 22-36 million (unpublished data). Therefore the set task of reaching an overall rate of 50% will not be simple to achieve.

Smoking control has become a major topic with Japan signing the WHO Framework Convention on Tobacco Control but there are difficulties, not least because the Japanese Government is an important shareholder in the Japanese tobacco industry (Assunta and Chapman, 2006).

Regarding health promotion and prevention of cancer, the recent emphasis on early diagnosis and treatment of the metabolic syndrome should eventually have a beneficial influence on the rates for colorectal, breast, endometrial, prostate and other adenocarcinomas generally considered to be related to obesity and lifestyle, but the economic costs will be considerable so that sustainability of a major issue.

b) International

The continued support of WHO and IARC by the Japanese Government makes a considerable contribution to international efforts for cancer control. Furthermore, the large number of International Symposia staged in Japan very much help dissemination of findings of researchers across the globe. The country is perhaps the major international player in this area. Certainly, within Asia Japan is playing the leading role. In addition, financial support from its individual scientists and the Japanese National UICC Committee are the only reason why the Asian Pacific Organization for Cancer Prevention and its journal, the Asian Pacific Journal of Cancer Prevention, have been able to continue operation now for almost ten years.

However, training activities within Japan itself targeting foreigners interested in doing cancer research are relatively limited. There have been no examples of coordination like that between the Korean National Cancer Center and IARC, although one is planned to coincide with the IACR yearly meeting in Yokohama in 2010. The Central Japan Japan Internation Cooperation Agency funded course on 'Community-based Cancer Prevention for the Asian and Pan-Pacific Countries' (Wakai and Matsuo, 2007), organized by Dr Kazuo Tajima of the Aichi Cancer Center (see Table 7) did successfully train almost 90 participants over 10 years from the developing world (see Table 8), but it is unfortunately no longer being offered. Furthermore, the vast majority of those taking part were from Ministries of Health and are no longer working in the field because of the general tendency for revolving from Department to Department in Government. If another such course were to be launched, then it might be advisable to focus more attention on staff of research institutes and universities where there is more likelihood of long-term activity. Such courses are of exceeding importance for nurturing of registration, screening and research capacity within the developing world, also providing the human links for continued collaboration and cooperation.

While Japan is a major financial supporter of the International Atomic Energy Agency in its Programme of Action for Cancer Therapy, it is unfortunately not one of

Table 7. Contents of the JICA Course Program

	Sessions* Lecture	Practice	Contents of practice
Outline of Epidemiology			
Concepts and overview of cancer epidemiology	1		
Cancer control in Japan	1		
Global health policies/trends	1		
Cause and risk	1	1	Calculation
Details of Epidemiology			
Demographic studies	1	1	Calculation
Human ecology	1		
Case-control studies	2	2	Group Discussion and Calculation
Cohort study	1		
HERPACC#	1	1	Observation
Cancer pathophysiology	1		
Diet, nutrition and cancer	2		
Molecular epidemiology	1		
Instruction of reporting skills	2		
Design of intervention trials	1		
Ethical issues	1		
Biostatistics		2	Computer
Aichi cancer registry	1	2	Computer
Osaka registry (Osaka)	1	1	Observation
Cancer Prevention			
Aichi Cancer Center Research Institute and Hospital		1	Observation
Smoking control (Osaka)		1	Group Discussion
Radiation cancer (Hiroshima)		1	Observation
Infection and cancer	1		
H pylori and gastric cancer	1		
Cancer screening	1	4	Observation
Evaluation of screening	1	1	Computer
Occupational health in Japan	2		
Occupational cancer	2		
Primary cancer prevention	1	3	Discussion
Carotenoids as biomarkers	1		
Local public health activity		1	Observation
Main risk factors by site	1		
Health promotion and prevention of lifestyle-related diseases in Japan		1	Observation
Country report		1	Presentation
Cancer prevention and its strategy (Action planning for cancer prevention)	1	3	Personal tuition
		1	Group discussion
		5	Report making
		1	Presentation
Course evaluation			
Weekly		(4)	Report
Mid-term & final		(2)	Discussion
Japanese language lesson			
Total	32	34	

* One lecture 1.5 hours and practice 2.5 hours # Hospital-

the Centres of Excellence or Mentors listed for the WHO Western Pacific Region in which it is located.Clearly, its profile in the world would be greatly improved if minor changes in the emphasis were to be brought about. Then the image of Japan would be more in line with the actual contributions that it has made in the past and will hopefully continue to make in the future.

Table 8.Distribution of Participants

Area	Country	Total
South, SE and NE Asia		
	Bangladesh	2
	Cambodia	1
	China	1
	India	3
	Indonesia	1
	Laos	1
	Malaysia	5
	Mongolia	6
	Nepal	1
	Philippines	3
	Sri Lanka	4
	Thailand	3
	Viet Nam	1
Oceania		
	Fiji	3
	Micronesia	1
	Papua New Guinea	3
	Solomon Islands	3
	Vanuatu	1
Middle and South America		
	Colombia	2
	Costa Rica	2
	Dominica	1
	Dominican Republic	1
	Honduras	1
	Brazil	3
	Ecuador	1
	Paraguay	4
	Uruguay	2
Western Asia		
	Iran	1
	Jordan	1
	Palestine Authority	2
	Turkey	1
Africa		
	Ethiopia	1
	Kenya	1
	Seychelles	1
	Tanzania	1
	Zambia	2
	Zimbabwe	1
East Europe		
	Bosnia-Herzegovina	2
	Lithuania	1
	Romania	1
Total (No. of countries)		76 (40)

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Special reference should be made to earlier historical reviews made by Dr Kunio Aoki (2000, 2001; 2006) and papers by Drs Tomotaka Sobue (2008) and Naoyuki Okamoto (2008), which provided substantial segments of the present review. Grateful thanks are also due to Dr Hiroshi Saito for helpful discussions.

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Epidemiology Note

Cancer Incidence and Incidence Rates in Japan in 2003: Based on Data from 13 Population-based Cancer Registries in the Monitoring of Cancer Incidence in Japan (MCIJ) Project

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The Japan Cancer Surveillance Research Group is involved in cancer monitoring in Japan (1–3). This group estimated the cancer incidence in 2003 as part of the Monitoring of Cancer Incidence in Japan (MCIJ) project, on the basis of data collected from 13 of 31 population-based cancer registries: Miyagi, Yamagata, Chiba, Kanagawa, Niigata, Fukui, Shiga, Osaka, Tottori, Okayama, Hiroshima, Saga and Nagasaki. If data from all 31 registries were used, this would have led to a large underestimation of national cancer incidence because of under-registration. The methods of registry selection, estimation of incidence and the limitations of these methods have been explained in previous studies (4–6). There were two major methodologic changes in the present study: (i) this was the first time we invited all 31 population-based cancer registries in Japan to participate, and from these we selected the 13 cancer registries with high-quality data in order to estimate the national incidence, and (ii) in consideration of timeliness, we did not apply the moving average which calculates the annual mean incidence rates of a year by using preceding and following years, and we used 2003 data alone for the national estimation. Because of the enlargement of the coverage area, Hiroshima prefecture was newly selected as one of the registries with high-quality data for the national estimation, but the other registries remained since the previous estimations. In 2007, we estimated incidences with and without the moving average based on the same registry data to compare the two methods. In conclusion, the estimated incidence without the moving average was comparatively unstable from year to year, but the gaps of the incidence numbers between the two estimations were subtle. These new methods therefore do not bring about changes in the estimated incidence numbers.

The number of incidences, crude rates, age-standardized rates and completeness of registration in 2003 are shown in Table 1, and the age-specific number of incidences and the rates according to sex and primary site are shown in Tables 2 and 3. The total number of incidences in Japan for 2003 was estimated as 620 011 (C00–C96). The time trends of age-standardized incidence rates for the five major sites and male- and female-specific sites in 1975–2003 are shown in Fig. 1 (standard population: the world population) and in Fig. 2 (standard population: the 1985 Japanese model population). The leading cancer site according to the crude and age-standardized incidence rates was the stomach for men and breast for women, as shown in Figs 1 and 2. The apparent increase in age-standardized incidence rates in 2003 is considered to be caused primarily by the development of hospital-based cancer registry in designated cancer care hospitals. The estimated cancer incidence data in Japan by sex, site, 5-year age group and calendar year during the period 1975–2003 are available as a booklet (7) and as an electronic database on the website (http://ganjoho.ncc.go.jp/professional/statistics/statistics.html).

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Table 1. Incidence, completeness of reporting and accuracy of diagnosis in Japan according to sex and primary site, 2003

Primary sites	ICD-10th	Number of incidence	Crude rate*	Age-standardized rate*		Completeness of reporting		Accuracy of diagnosis
				World population	Japanese 1985 model population	DCO/I (%)	I/M	MV/I (%)
Male								
All sites (incl. CIS)	C00–C96, D00–D09	372 374	597.7	288.0	409.8	16.5	1.99	74.8
All sites	C00–C96	364 072	584.3	281.4	400.5	16.8	1.95	74.4
Lip, oral cavity and pharynx	C00–C14	7835	12.6	6.7	9.1	11.7	1.94	81.0
Esophagus	C15	13 658	21.9	10.8	15.1	15.5	1.45	78.3
Stomach	C16	73 798	118.4	57.1	81.1	13.8	2.30	82.4
Colon	C18	35 262	56.6	27.0	38.5	11.9	2.74	82.6
Rectum and anus	C19, C20	21 892	35.1	18.0	24.8	11.1	2.68	84.2
Liver	C22	29 126	46.7	22.7	31.9	25.2	1.25	38.4
Gallbladder etc.	C23, C24	8755	14.1	6.1	9.2	27.2	1.20	46.0
Pancreas	C25	12 511	20.1	9.5	13.7	28.7	1.11	37.0
Larynx	C32	3921	6.3	3.1	4.3	7.3	4.24	88.5
Trachea, bronchus and lung	C33, C34	55 928	89.8	39.6	59.5	24.2	1.34	69.8
Skin	C43, C44	3325	5.3	2.6	3.6	7.1	6.08	90.6
Prostate	C61	40 062	64.3	27.3	41.4	9.5	4.76	85.7
Bladder	C67	12 646	20.3	9.3	13.6	11.1	3.40	84.7
Kidney, renal pelvis, ureter etc.	C64–C66, C68	8217	13.2	6.7	9.3	16.0	2.27	74.3
Brain and nervous system	C70–C72	2571	4.1	3.1	3.5	27.5	2.95	65.3
Thyroid	C73	2023	3.2	2.0	2.6	5.9	4.53	90.2
Malignant lymphoma	C81–C85, C96	12 881	20.7	11.6	15.5	17.0	2.65	79.9
Multiple myeloma	C88–C90	2251	3.6	1.6	2.4	30.6	1.20	65.8
All leukaemias	C91–C95	5606	9.0	5.8	7.0	25.3	1.37	82.9
Female								
All sites (incl. CIS)	C00–C96, D00–D09	269 220	412.2	193.9	260.8	17.1	2.20	73.6
All site	C00–C96	255 939	391.9	179.3	242.5	17.9	2.09	72.4

Continued

Table 1. *Continued*

Primary sites	ICD-10th	Number of incidence	Crude rate[a]	Age-standardized rate[a]		Completeness of reporting		Accuracy of diagnosis
				World population	Japanese 1985 model population	DCO/I (%)	I/M	MV/I (%)
Lip, oral cavity and pharynx	C00–C14	3180	4.9	2.2	2.9	15.0	2.01	76.6
Esophagus	C15	2742	4.2	1.7	2.3	20.0	1.66	69.3
Stomach	C16	36 525	55.9	22.1	31.2	17.9	2.10	78.3
Colon	C18	29 859	45.7	17.4	24.7	15.8	2.30	77.1
Rectum and anus	C19, C20	11 902	18.2	7.9	10.9	13.1	2.43	81.5
Liver	C22	13 535	20.7	7.0	10.4	29.3	1.26	32.8
Gallbladder etc.	C23, C24	10 200	15.6	4.7	7.1	32.3	1.18	40.5
Pancreas	C25	10 371	15.9	5.5	7.9	34.0	1.05	30.1
Larynx	C32	448	0.7	0.3	0.4	3.8	7.34	91.4
Trachea, bronchus and lung	C33, C34	22 817	34.9	12.8	18.4	25.1	1.51	66.5
Skin	C43, C44	4497	6.9	2.5	3.4	9.6	8.52	89.2
Breast (incl. CIS)	C50, D05	45 716	70.0	43.4	56.1	5.6	4.66	90.5
Uterus (incl. CIS)	C53–C55, D06	24 240	37.1	25.5	32.3	7.4	4.57	88.9
Uterus (only invasive)	C53–C55	17 285	26.5	16.1	20.8	10.0	3.26	85.7
Cervix uteri	C53	8674	13.3	8.8	11.3	7.1	3.65	89.4
Corpus uteri	C54	7430	11.4	6.5	8.5	5.6	5.41	89.6
Ovary	C56	7946	12.2	7.2	9.2	17.2	1.88	77.0
Bladder	C67	3713	5.7	1.8	2.7	18.8	2.19	74.5
Kidney, renal pelvis, ureter etc.	C64–C66, C68	4689	7.2	3.0	4.1	18.3	2.38	71.7
Brain and nervous system	C70–C72	2034	3.1	1.8	2.1	24.6	3.10	60.2
Thyroid	C73	6046	9.3	5.6	7.2	7.6	6.17	87.4
Malignant lymphoma	C81–C85, C96	8592	13.2	6.1	8.2	16.8	2.36	80.8
Multiple myeloma	C88–C90	2234	3.4	1.2	1.7	34.4	1.23	62.3
All leukaemias	C91–C95	3951	6.0	3.8	4.3	25.2	1.35	81.0

ICD-10th, International Classification of Disease, 10th Revision; DCO/I, proportion of cases with the death certificate only to incident cases; I/M, number of incidence/number of deaths; MV/I, proportion of microscopically verified cases to incident cases; CIS, carcinoma *in situ*.
[a]Per 100 000 population.

Table 2. Age-specific incidence in Japan according to sex and primary site, 2003

Primary sites	ICD-10th	All ages	Age group (years)																	
			0–4	5–9	10–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85+
Male																				
All sites (incl. CIS)	C00–C96, D00–D09	372 374	401	290	190	416	656	1021	1510	2353	4422	7922	18 940	29 913	44 332	57 691	72 125	63 779	36 791	29 622
All sites	C00–C96	364 072	401	290	190	405	650	1020	1497	2310	4213	7732	18 421	29 054	43 110	56 281	70 601	62 386	36 217	29 294
Lip, oral cavity and pharynx	C00–C14	7835	2	0	2	8	34	39	99	127	117	316	626	924	1180	1342	1220	910	543	346
Esophagus	C15	13 658	0	0	0	0	0	0	0	14	93	317	850	1629	2351	2281	2621	1945	981	576
Stomach	C16	73 798	0	0	0	17	47	70	154	281	878	1741	4439	6714	9286	12 022	14 013	12 042	6472	5622
Colon	C18	35 262	0	3	0	8	18	54	120	204	339	713	1698	2905	4591	5634	7014	5589	3432	2940
Rectum and anus	C19, C20	21 892	0	0	1	8	5	15	83	158	420	709	1582	2564	3380	3828	3652	2925	1445	1117
Liver	C22	29 126	11	2	3	0	19	12	33	82	266	573	1792	2714	4018	5290	6146	4455	2127	1583
Gallbladder etc.	C23, C24	8755	0	0	0	0	0	1	4	23	57	79	294	410	820	1137	1483	1697	1438	1312
Pancreas	C25	12 511	0	0	0	0	14	4	1	41	157	194	727	1081	1666	1880	2247	2119	1365	1015
Larynx	C32	3921	0	0	0	0	19	0	0	6	31	72	229	434	604	713	746	616	304	147
Trachea, bronchus and lung	C33, C34	55 928	0	0	0	1	5	3	68	175	296	820	1944	3549	5091	7296	11 701	11 923	7446	5610
Skin	C43, C44	3325	0	0	3	0	13	42	68	50	46	77	107	148	349	358	572	590	364	538
Prostate	C61	40 062	0	0	0	0	0	0	0	0	9	58	430	1251	3704	6719	9914	9291	4852	3834
Bladder	C67	12 646	7	0	0	10	4	23	32	101	92	229	645	862	1196	1544	2623	2287	1520	1471
Kidney, renal pelvis, ureter etc.	C64–C66, C68	8217	14	5	0	0	26	50	35	70	164	280	648	834	932	1226	1487	1223	760	463
Brain and nervous system	C70–C72	2571	67	111	18	45	85	72	88	84	139	146	230	149	319	313	290	202	105	108
Thyroid	C73	2023	0	3	0	1	34	49	44	126	88	137	245	215	224	188	270	193	117	89
Malignant lymphoma	C81–C85, C96	12 881	12	38	76	96	113	123	175	307	528	680	791	1184	1415	2002	1705	1680	1107	849
Multiple myeloma	C88–C90	2251	0	0	0	0	0	0	4	8	10	33	88	184	240	344	349	450	304	237
All leukaemias	C91–C95	5606	138	94	50	77	73	162	142	81	200	211	319	459	518	795	844	699	390	354
Female																				
All sites (incl. CIS)	C00–C96, D00–D09	269 220	397	219	202	332	821	1909	4996	6722	9210	13 421	19 959	22 867	25 392	28 998	34 319	34 339	29 314	35 803
All site	C00–C96	255 939	397	219	202	315	612	1301	3433	5118	7788	12 156	18 900	21 931	24 287	28 108	33 190	33 601	28 888	35 493

Continued

Table 2. *Continued*

Primary sites	ICD-10th	All ages	Age group (years)																	
			0–4	5–9	10–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85+
Lip, oral cavity and pharynx	C00–C14	3180	0	0	2	18	42	23	33	56	74	100	219	248	332	370	363	468	385	447
Esophagus	C15	2742	0	0	0	0	0	0	1	14	13	123	140	243	250	378	392	335	323	530
Stomach	C16	36 525	0	0	0	2	17	70	234	418	783	1101	1851	2752	3010	4149	5208	5706	4850	6374
Colon	C18	29 859	0	0	0	2	11	36	121	214	346	634	1480	2021	2853	3709	4420	4681	4120	5211
Rectum and anus	C19, C20	11 902	0	0	0	0	0	12	62	120	239	414	852	1162	1444	1511	1695	1602	1264	1525
Liver	C22	13 535	1	0	11	0	0	12	13	10	36	68	246	575	946	1989	2754	2677	2228	1969
Gallbladder etc.	C23–C24	10 200	0	0	0	4	0	0	6	4	44	108	229	337	609	894	1274	1758	2086	2847
Pancreas	C25	10 371	0	0	0	0	0	6	6	33	69	197	394	551	860	1080	1583	1619	1637	2336
Larynx	C32	448	0	0	2	0	0	0	7	2	0	38	2	37	59	83	47	92	39	40
Trachea, bronchus and lung	C33, C34	22 817	5	0	0	5	0	36	35	126	190	417	955	1525	2005	2774	3558	3831	3272	4083
Skin	C43, C44	4497	10	0	10	7	15	13	24	98	56	90	137	168	250	512	441	561	734	1371
Breast (incl. CIS)	C50, D05	45 716	0	0	0	0	29	222	934	1986	3547	5722	6882	5832	5657	4570	3724	3098	2009	1504
Uterus (incl. CIS)	C53–C55, D06	24 240	0	0	0	8	268	835	2479	2529	2299	2167	2432	2876	2030	1557	1609	1360	899	892
Uterus (only invasive)	C53–C55	17 285	0	0	0	2	77	259	988	1114	1146	1408	1978	2557	1791	1377	1531	1291	879	887
Cervix uteri	C53	8674	0	0	0	2	74	223	791	889	870	832	753	879	701	613	600	552	443	452
Corpus uteri	C54	7430	0	0	0	0	3	29	193	203	245	520	1148	1577	997	661	817	606	248	183
Ovary	C56	7946	0	0	20	40	47	150	182	258	412	683	1183	1183	801	695	761	536	488	507
Bladder	C67	3713	0	0	0	0	0	0	2	14	10	42	78	136	197	403	608	659	684	880
Kidney, renal pelvis, ureter etc.	C64–C66, C68	4689	17	8	8	4	2	3	26	25	111	95	348	345	441	559	693	737	593	674
Brain and nervous system	C70–C72	2034	53	27	27	21	9	28	106	43	46	54	79	156	233	223	217	208	225	279
Thyroid	C73	6046	0	0	11	21	89	133	233	325	339	448	715	716	723	591	704	443	225	330
Malignant lymphoma	C81–C85, C96	8592	19	33	13	45	81	86	117	113	217	282	592	637	808	918	1471	1248	969	943
Multiple myeloma	C88–C90	2234	0	0	0	0	0	0	9	11	33	20	81	84	200	215	375	378	368	460
All leukaemias	C91–C95	3951	114	98	32	68	81	44	108	96	97	147	289	321	319	411	483	476	378	389

Table 3. Age-specific incidence rate per 100 000 population in Japan according to sex and primary site, 2003

Primary sites	ICD-10th	All ages	Age group (years)																	
			0–4	5–9	10–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85+
Male																				
All sites (incl. CIS)	C00–C96, D00–D09	597.7	13.5	9.5	6.1	11.6	16.3	22.1	30.8	55.2	111.9	199.2	379.7	661.4	1100.6	1643.2	2488.8	3093.1	3541.0	3954.9
All sites	C00–C96	584.3	13.5	9.5	6.1	11.3	16.2	22.0	30.6	54.2	106.6	194.5	369.3	642.4	1070.3	1603.0	2436.2	3025.5	3485.8	3911.1
Lip, oral cavity and pharynx	C00–C14	12.6	0.1	0.0	0.1	0.2	0.8	0.8	2.0	3.0	3.0	7.9	12.6	20.4	29.3	38.2	42.1	44.1	52.3	46.2
Esophagus	C15	21.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.3	2.4	8.0	17.0	36.0	58.4	65.0	90.4	94.3	94.4	76.9
Stomach	C16	118.4	0.0	0.0	0.0	0.5	1.2	1.5	3.1	6.6	22.2	43.8	89.0	148.4	230.5	342.4	483.5	584.0	622.9	750.6
Colon	C18	56.6	0.0	0.1	0.0	0.2	0.4	1.2	2.5	4.8	8.6	17.9	34.0	64.2	114.0	160.5	242.0	271.0	330.3	392.5
Rectum and anus	C19, C20	35.1	0.0	0.0	0.0	0.2	0.1	0.3	1.7	3.7	10.6	17.8	31.7	56.7	83.9	109.0	126.0	141.9	139.1	149.1
Liver	C22	46.7	0.4	0.1	0.1	0.0	0.5	0.3	0.7	1.9	6.7	14.4	35.9	60.0	99.8	150.7	212.1	216.1	204.7	211.3
Gallbladder etc.	C23, C24	14.1	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.5	1.4	2.0	5.9	9.1	20.4	32.4	51.2	82.3	138.4	175.2
Pancreas	C25	20.1	0.0	0.0	0.0	0.0	0.3	0.1	0.0	1.0	4.0	4.9	14.6	23.9	41.4	53.5	77.5	102.8	131.4	135.5
Larynx	C32	6.3	0.0	0.0	0.0	0.0	0.5	0.0	0.0	0.1	0.8	1.8	4.6	9.6	15.0	20.3	25.7	29.9	29.3	19.6
Trachea, bronchus and lung	C33, C34	89.8	0.0	0.0	0.0	0.0	0.1	0.1	1.4	4.1	7.5	20.6	39.0	78.5	126.4	207.8	403.8	578.2	716.7	749.0
Skin	C43, C44	5.3	0.0	0.0	0.1	0.0	0.3	0.9	1.4	1.2	1.2	1.9	2.1	3.3	8.7	10.2	19.7	28.6	35.0	71.8
Prostate	C61	64.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2	1.5	8.6	27.7	92.0	191.4	342.1	450.6	467.0	511.9
Bladder	C67	20.3	0.2	0.0	0.0	0.3	0.1	0.5	0.7	2.4	2.3	5.8	12.9	19.1	29.7	44.0	90.5	110.9	146.3	196.4
Kidney, renal pelvis, ureter etc.	C64–C66, C68	13.2	0.5	0.2	0.0	0.0	0.6	1.1	0.7	1.6	4.1	7.0	13.0	18.4	23.1	34.9	51.3	59.3	73.1	61.8
Brain and nervous system	C70–C72	4.1	2.3	3.6	0.6	1.3	2.1	1.6	1.8	2.0	3.5	3.7	4.6	3.3	7.9	8.9	10.0	9.8	10.1	14.4
Thyroid	C73	3.2	0.0	0.1	0.0	0.0	0.8	1.1	0.9	3.0	2.2	3.4	4.9	4.8	5.6	5.4	9.3	9.4	11.3	11.9
Malignant lymphoma	C81–C85, C96	20.7	0.4	1.2	2.4	2.7	2.8	2.7	3.6	7.2	13.4	17.1	15.9	26.2	35.1	57.0	58.8	81.5	106.5	113.4
Multiple myeloma	C88–C90	3.6	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.3	0.8	1.8	4.1	6.0	9.8	12.0	21.8	29.3	31.6
All leukaemias	C91–C95	9.0	4.6	3.1	1.6	2.1	1.8	3.5	2.9	1.9	5.1	5.3	6.4	10.1	12.9	22.6	29.1	33.9	37.5	47.3
Female																				
All sites (incl. CIS)	C00–C96, D00–D09	412.2	14.1	7.5	6.8	9.7	21.4	42.6	104.0	159.9	235.7	339.5	397.2	492.1	594.0	744.7	991.9	1211.3	1479.0	1904.4
All site	C00–C96	391.9	14.1	7.5	6.8	9.2	16.0	29.1	71.5	121.8	199.3	307.5	376.1	471.9	568.1	721.8	959.2	1185.2	1457.5	1887.9

Continued

Table 3. *Continued*

Primary sites	ICD-10th	All ages	Age group (years)																		
			0–4	5–9	10–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85+
Lip, oral cavity and pharynx	C00–C14	4.9	0.0	0.0	0.1	0.5	1.1	0.5	0.7	1.3	1.9	2.5	4.4	5.3	7.8	9.5	10.5	16.5	19.4	23.8
Esophagus	C15	4.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.3	3.1	2.8	5.2	5.8	9.7	11.3	11.8	16.3	28.2
Stomach	C16	55.9	0.0	0.0	0.0	0.1	0.4	1.6	4.9	9.9	20.0	27.9	36.8	59.2	70.4	106.5	150.5	201.3	244.7	339.0
Colon	C18	45.7	0.0	0.0	0.0	0.1	0.3	0.8	2.5	5.1	8.9	16.0	29.5	43.5	66.7	95.2	127.7	165.1	207.9	277.2
Rectum and anus	C19, C20	18.2	0.0	0.0	0.0	0.0	0.0	0.3	1.3	2.9	6.1	10.5	17.0	25.0	33.8	38.8	49.0	56.5	63.8	81.1
Liver	C22	20.7	0.0	0.0	0.4	0.0	0.0	0.3	0.3	0.2	0.9	1.7	4.9	12.4	22.1	51.1	79.6	94.4	112.4	104.7
Gallbladder etc.	C23, C24	15.6	0.0	0.0	0.0	0.1	0.0	0.0	0.1	0.1	1.1	2.7	4.6	7.3	14.2	23.0	36.8	62.0	105.2	151.4
Pancreas	C25	15.9	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.8	1.8	5.0	7.8	11.9	20.1	27.7	45.8	57.1	82.6	124.3
Larynx	C32	0.7	0.0	0.0	0.1	0.0	0.0	0.0	0.1	0.0	0.0	1.0	0.0	0.8	1.4	2.1	1.4	3.2	2.0	2.1
Trachea, bronchus and lung	C33, C34	34.9	0.2	0.0	0.0	0.1	0.0	0.8	0.7	3.0	4.9	10.5	19.0	32.8	46.9	71.2	102.8	135.1	165.1	217.2
Skin	C43, C44	6.9	0.4	0.0	0.3	0.2	0.4	0.3	0.5	2.3	1.4	2.3	2.7	3.6	5.8	13.1	12.7	19.8	37.0	72.9
Breast (incl. CIS)	C50, D05	70.0	0.0	0.0	0.0	0.0	0.8	5.0	19.4	47.3	90.8	144.8	137.0	125.5	132.3	117.4	107.6	109.3	101.4	80.0
Uterus (incl. CIS)	C53–C55, D06	37.1	0.0	0.0	0.0	0.2	7.0	18.7	51.6	60.2	58.8	54.8	48.4	61.9	47.5	40.0	46.5	48.0	45.4	47.4
Uterus (only invasive)	C53–C55	26.5	0.0	0.0	0.0	0.1	2.0	5.8	20.6	26.5	29.3	35.6	39.4	55.0	41.9	35.4	44.2	45.5	44.3	47.2
Cervix uteri	C53	13.3	0.0	0.0	0.0	0.1	1.9	5.0	16.5	21.2	22.3	21.0	15.0	18.9	16.4	15.7	17.3	19.5	22.4	24.0
Corpus uteri	C54	11.4	0.0	0.0	0.0	0.0	0.1	0.6	4.0	4.8	6.3	13.2	22.8	33.9	23.3	17.0	23.6	21.4	12.5	9.7
Ovary	C56	12.2	0.0	0.0	0.7	1.2	1.2	3.4	3.8	6.1	10.5	17.3	23.5	25.5	18.7	17.8	22.0	18.9	24.6	27.0
Bladder	C67	5.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.3	1.1	1.6	2.9	4.6	10.3	17.6	23.2	34.5	46.8
Kidney, renal pelvis, ureter etc.	C64–C66, C68	7.2	0.6	0.3	0.3	0.1	0.1	0.1	0.5	0.6	2.8	2.4	6.9	7.4	10.3	14.4	20.0	26.0	29.9	35.9
Brain and nervous system	C70–C72	3.1	1.9	0.9	0.9	0.6	0.2	0.6	2.2	1.0	1.2	1.4	1.6	3.4	5.5	5.7	6.3	7.3	11.4	14.8
Thyroid	C73	9.3	0.0	0.0	0.4	0.6	2.3	3.0	4.9	7.7	8.7	11.3	14.2	15.4	16.9	15.2	20.3	15.6	11.4	17.6
Malignant lymphoma	C81–C85, C96	13.2	0.7	1.1	0.4	1.3	2.1	1.9	2.4	2.7	5.6	7.1	11.8	13.7	18.9	23.6	42.5	44.0	48.9	50.2
Multiple myeloma	C88–C90	3.4	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.3	0.8	0.5	1.6	1.8	4.7	5.5	10.8	13.3	18.6	24.5
All leukaemias	C91–C95	6.0	4.0	3.4	1.1	2.0	2.1	1.0	2.2	2.3	2.5	3.7	5.8	6.9	7.5	10.6	14.0	16.8	19.1	20.7

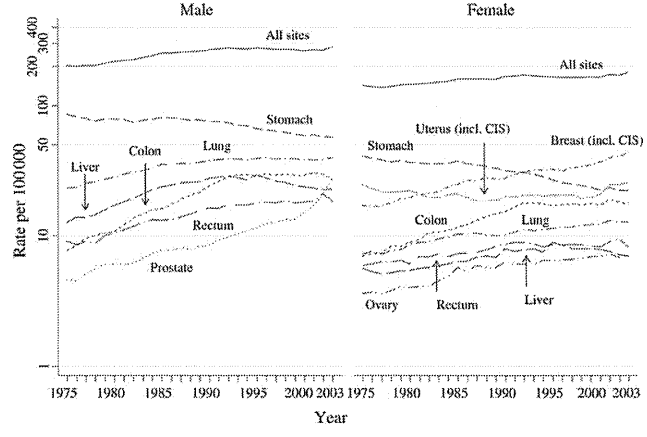

Figure 1. Trends of age-standardized cancer incidence rates for five major sites and specific sites for each sex (standard population: the world population). CIS, carcinoma *in situ*.

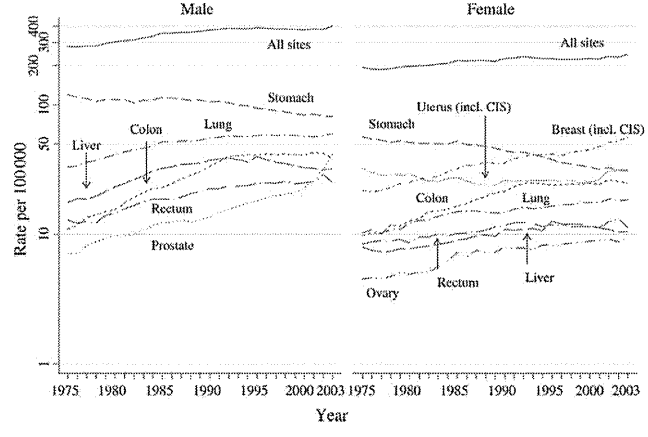

Figure 2. Trends of age-standardized cancer incidence rates for five major sites and specific sites for each sex (standard population: 1985 Japanese model population)

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Conflict of interest statement

None declared.

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Statistical Data

Secular Trends in Neuroblastoma Mortality Before and After the Cessation of National Mass Screening in Japan

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ABSTRACT

Background: In 2003, the Japanese government halted the national mass screening program for neuroblastoma (NB), which had been running since the mid-1980s. It is not known whether the NB mortality rate subsequently increased or decreased.

Methods: Utilizing vital statistics data from 1980 through 2006, we analyzed the secular trends in NB mortality by using cancer of the adrenal gland as a surrogate. We examined the validity of this substitution by comparing the results with data from death certificates. Using a joinpoint regression model, we examined the trends in age-specific mortality rates by calendar year and cumulative mortality rates by birth year. The cumulative mortality rate was analyzed for age under 1 or 2 years for infants born after the cessation of the mass screening program.

Results: The number of deaths from cancer of the adrenal gland was closely correlated with the number of deaths from NB. Significant decreases in the mortality rate were observed from 1980 through 2006 by calendar year for those aged under 1 year, 1 to 4 years, and 5 to 9 years. The cumulative mortality rates by birth year also significantly decreased from the 1980 birth cohort. Although the cumulative mortality rates under the age of 2 appear to have increased after the 2003 birth cohort, the change was not statistically significant.

Conclusions: No significant increase in the NB mortality rate was detected after the cessation of the mass screening program in Japan. However, continuous monitoring is still needed to fully evaluate this health policy decision.

Key words: mass screening; mortality; neuroblastoma

INTRODUCTION

Studies conducted in Germany and in the province of Quebec, Canada showed that screening infants for neuroblastoma (NB) did not result in lower NB mortality.[1,2] Although a large number of epidemiological studies have been conducted in Japan, the findings regarding the effectiveness of NB screening have been inconsistent.[3–8] Clinical studies have reported that a considerable fraction of NB patients whose disease was detected by mass screening had favorable outcomes, which suggests the possibility of over-diagnosis.[9–14] In 2003, the Japanese government halted the national mass screening program—which had been in place since the mid-1980s for infants aged 6 months—because of the potential for over-diagnosis and the lack of evidence for its effectiveness in reducing NB mortality.[15] Most local municipalities in Japan stopped the program during the following year. It is not known whether the NB mortality rate increased or decreased after this national change. Therefore, we analyzed secular trends in NB mortality in Japan before and after the cessation of the national mass screening program.

METHODS

As is the case in most countries, the Japanese government collects vital statistics data, in which the causes of death are classified according to the International Classification of Diseases (ICD). NB mortality cannot be directly identified in this classification because deaths attributable to NB are coded based on the organ affected, and are grouped together with deaths due to other cancers affecting the same organ.[16] Two different methods have been adopted to address this issue. The first approach (hereafter referred to as method-1) is to extract the data on deaths due to cancer of the candidate sites, inspect the relevant individual death certificates, and identify NB

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deaths based on the description of the cause of death or the histological type.[16] The second approach (hereafter referred to as method-2) is to use deaths from cancer of the adrenal gland as a surrogate index.[17]

Method-2 is less accurate than method-1 because NB can occur at sites other than the adrenal gland, and because other histological types of cancer can occur in this organ. Method-1 requires official permission for the use of unpublished vital statistics data, whereas method-2 uses only published vital statistics data, at least for the years after the ICD version 10 was applied.

The present study used method-1 to analyze data from the year 2006. We obtained individual mortality data from the vital statistics, with official permission, according to the following criteria: year of death = 2006; age at death = 0 to 14 years; cause of death (ICD) = malignant neoplasms of mediastinum (ICD-9 164.2, 164.3, 164.9; ICD-10 C38.1, C38.2, C38.8), connective and soft tissue (ICD-9 171.0, 171.2, 171.3, 171.4, 171.5, 171.6, 171.7, 171.8, 171.9), peripheral nerves and autonomic nervous system (ICD-10 C47.0, C47.1, C47.2, C47.3, C47.4, C47.5, C47.6, C47.8, C47.9), retroperitoneum and peritoneum (ICD-9 158.0, 158.8, 158.9; ICD-10 C48.0, C48.1, C48.2, C48.8), adrenal gland (ICD-9 194.0; ICD-10 C74.0, C74.1, C74.9), or other/ill-defined sites (ICD-9 195.0, 195.1, 195.2, 195.3, 195.4, 195.5, 195.8; ICD-10 C76.0, C76.1, C76.2, C76.3, C76.4, C76.5, C76.7, C76.8). Then, we inspected individual death certificates for the extracted data, and identified NB deaths based on the recorded causes of death or histological types. This process was performed by one of the authors (K. K.) and was confirmed by another author (K. Y., a pediatrician). For the data from 1980 through 2001, we obtained data on NB deaths from previous reports[16,18] that had used a method identical to the present method-1 for extracting and identifying NB deaths. Thus, in the present study, data on the number of NB deaths based on method-1 were available for the years from 1980 through 2001, and for the year 2006. We could not apply method-1 to the time period from 2002 through 2005 because a previous application to use death certificates for research had been rejected,[19] and the document storage period had expired by the time of our application.

For method-2, we calculated the age-specific number of deaths from adrenal gland cancer, based on officially obtained individual mortality data from the vital statistics. The criteria for data collection were as follows: year of death = 1980 to 2006; age at death = 0 to 14 years; cause of death (ICD) = malignant neoplasms of the adrenal gland (ICD-9 194.0; ICD-10 C74.0, C74.1, C74.9).

To validate method-2, we calculated the Pearson correlation coefficient between the number of NB deaths and the number of adrenal gland cancer deaths, using data from 1980 through 2001, and from 2006.

We obtained population data from the published vital statistics and calculated the age-specific mortality rate by calendar year for cancer of the adrenal gland. For the age-specific mortality rate, age was stratified into the following 4 groups: 0 years, 1 to 4 years, 5 to 9 years, and 10 to 14 years. We also calculated the cumulative mortality rate by birth year, by summing the 1-year age-specific mortality rate according to each birth year.[20] The number of deaths according to each age and each birth year was used as the numerator for the 1-year age-specific mortality rate. The denominator was the number of births (for age younger than 1 year) or the population for each age (for 1 year or older). The most recent birth year that we analyzed was 2005 for the cumulative mortality rate under 1 year of age, 2004 for 2 years of age, 2003 for 3 years of age, and 2002 for 4 years of age.

For the statistical analysis, we used a joinpoint regression model,[21] implemented in the Joinpoint Regression Program (version 3.3.1) developed by the US National Cancer Institute. This method describes changes in data trends by connecting several different line segments on a log scale at joinpoints. The analysis starts with the minimum number of joinpoints (that is, 0, representing a straight line) and tests for the model fit with a maximum number of joinpoints. A Monte Carlo permutation method is used for tests of significance. In addition, the annual percent change (APC) for each line segment and the corresponding 95% confidence interval (CI) were estimated. In the statistical analysis, the number of deaths was assumed to follow a Poisson distribution. The maximum number of joinpoints was set at 3, the minimum number of observations from a joinpoint to either end of the data was set at 2 (including the end and joinpoint), and the minimum number of observations between 2 joinpoints was set at 4 (including the joinpoints).

RESULTS

Table 1 shows the secular trends in the age-specific number of deaths, according to the 2 methods. Although method-1 tended to yield slightly larger numbers than method-2, the secular trends were similar. The Pearson correlation coefficients between the annual numbers of deaths according to the 2 methods were close to 1 (1.00 for 0–14 years, 0.96 for <1 year, 0.98 for 1–4 years, 0.96 for 5–9 years, and 0.73 for 10–14 years; all 5 correlation coefficients were significantly different from 0 [number of data points = 23, $P < 0.001$]). In 2006, 45 deaths from cancer of the adrenal gland were observed, one of which was non-NB (malignant pheochromocytoma). In comparison, 45 NB deaths were identified by the inspection of death certificates from 2006, of which 1 case occurred at a site other than the adrenal gland (retroperitoneum).

Table 2 shows the results of the joinpoint analysis. Significant decreases in the age-specific mortality rate were observed from 1980 through 2006 by calendar year for those aged less than 1 year, 1 to 4 years, and 5 to 9 years. The cumulative mortality rates by birth year also significantly

Table 1. Numbers of deaths due to neuroblastoma (NB) and adrenal gland cancer from 1980 to 2006

Calendar year[a]	1) Number of deaths from NB identified by individual death certificates[b]					Calendar year[a]	2) Number of deaths from cancer of the adrenal gland[c]				
	0–14 years	<1 year	1–4 years	5–9 years	10–14 years		0–14 years	<1 year	1–4 years	5–9 years	10–14 years
1980–1982	381	28	209	119	25	1980–1982	338	22	194	103	19
1983–1985	329	31	174	102	22	1983–1985	294	28	150	94	22
1986–1988	280	15	132	101	32	1986–1988	249	15	119	88	27
1989–1991	221	10	109	81	21	1989–1991	207	8	106	74	19
1992–1994	178	11	72	77	18	1992–1994	171	8	68	76	19
1995–1997	185	16	67	78	24	1995–1997	181	14	65	79	23
1998–2000	147	9	55	59	24	1998–2000	139	8	53	56	22
2001–2003	(N.A.)	(N.A.)	(N.A.)	(N.A.)	(N.A.)	2001–2003	116	6	49	42	21
2004–2006	(N.A.)	(N.A.)	(N.A.)	(N.A.)	(N.A.)	2004–2006	123	7	55	45	16
2001, 2006	86	4	38	29	15	2001, 2006	84	4	38	27	15

[a]Consecutive 3-year periods from 1980 to 2006 were pooled. Two years (2001 and 2006) were also pooled.
[b]The numbers of NB deaths between 1980 and 2001 were obtained from previous reports (Hanawa et al, 1990 and Hayashi et al, 2004), and the numbers of NB deaths in 2006 were counted by one of the authors (K. K.).
[c]Deaths due to cancer of the adrenal gland were defined by codes in the ICD: 194.0 for 1980–1994, C74.0, C74.1, and C74.9 for 1995–2006.
N.A.: Not available

Table 2. Results of joinpoint regression analysis for the secular trends in adrenal gland cancer mortality

A) Age-specific mortality rate, by calendar year

	Number of joinpoints	Line segment		Annual % change	95% confidence interval	
		Start	End		Lower	Upper
0 year old	0	1980	2006	−3.6[a]	−5.8	−1.4
1–4 years old	0	1980	2006	−4.1[a]	−5.0	−3.3
5–9 years old	0	1980	2006	−1.1[a]	−2.0	−0.1
10–14 years old	0	1980	2006	1.4	−0.4	3.2

B) Cumulative mortality rate, by birth year[b]

	Number of joinpoints	Line segment		Annual % change	95% confidence interval	
		Start	End		Lower	Upper
<1 year old	0	1980	2005	−3.0[a]	−5.4	−0.5
<2 years old	0	1980	2004	−3.4[a]	−5.3	−1.4
<3 years old	0	1980	2003	−4.3[a]	−5.7	−2.8
<4 years old	0	1980	2002	−4.1[a]	−5.2	−2.9

[a]Annual % change is statistically significant from zero.
[b]The analyzed most recent birth year was 2005 for age <1 year, 2004 for <2 years, 2003 for age <3 years, and 2002 for age <4 years.

decreased from the 1980 birth cohort. Figure 1 shows the trends in the age-specific mortality rate. The mortality rates for 1 to 4 years of age in 2004 and 2006 were high, but no significant increase or joinpoint was detected around this time. Figure 2 shows the trends in the cumulative mortality rate. The cumulative mortality rate under the age of 2 for the 2004 birth cohort was considerably higher than the cumulative mortality rate for the past several birth cohorts. However, this change was not detected as a significant joinpoint.

DISCUSSION

We examined the secular trends in the mortality rate for NB, using mortality for cancer of the adrenal gland as a surrogate index, and found no significant increase before or after the cessation of the Japanese national mass screening program. We confirmed the validity of this surrogate method by examining the correlation between the numbers of deaths from the 2 cancers. Nationwide mass screening had previously been performed for infants aged 6 months, and the participation level was high (ranging from 84% to 90% in the period from 1990 through 2001). Because the most recent year of death that we analyzed was 2006, any increase in the age-specific mortality rate associated with the cessation of mass screening in 2003 would have been expected to occur among children aged 1 to 4 years. However, we did not observe any significant increase or joinpoint in the mortality rate among this age group around this time. It is possible that the time elapsed since the cessation of mass screening was still too short to detect any increase in mortality for this age group, which

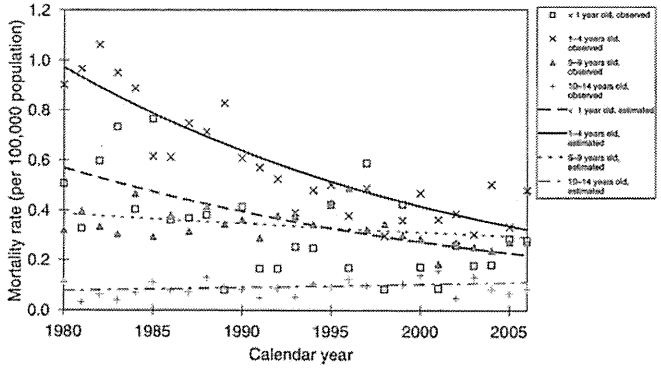

Figure 1. Annual trends in age-specific mortality rate for cancer of the adrenal gland, by calendar year

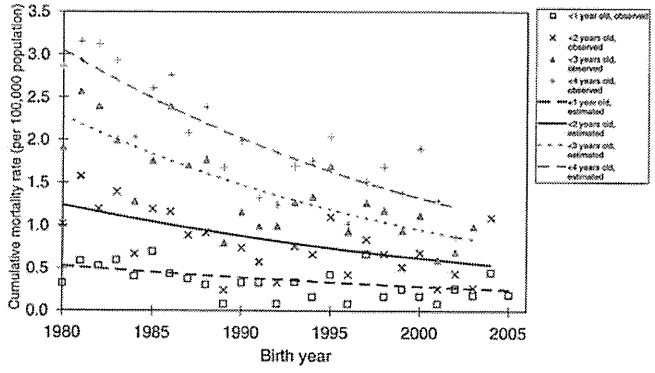

Figure 2. Annual trends in cumulative mortality rate for cancer of the adrenal gland, by birth year. Note: The most recent analyzed birth year was 2005 for age <1 year, 2004 for age <2 years, 2003 for age <3 years, and 2002 for age <4 years

included both screened and unscreened individuals, even at the end of our observation period.

The cumulative mortality rate according to birth year was a more direct index to examine the effect of the cessation of the mass screening program. It decreased significantly throughout the observed birth years, and the birth year 2003 was not detected as a significant joinpoint. However, these results should be interpreted with caution because the analyzed range of birth years and ages was limited after the cessation of the mass screening program. In consideration of the time from diagnosis to death, we should assume that any increase in the mortality rate for infants born after the cessation could occur later than the end of our observation period.

There are several Japanese municipalities that continued mass screening for NB after 2003. However, the number of such municipalities is very small, and our results did not change when we excluded the prefectures to which these municipalities belong (ie, Hokkaido, Kanagawa, Niigata, Shizuoka, Kyoto, Osaka, and Kumamoto).

We found a high correlation between the number of deaths from NB and the number of deaths from adrenal gland cancer, with the former slightly and consistently higher than the latter (Table 1). This tendency was in agreement with a previous report, in which approximately 90% of NB deaths were attributable to cancer of the adrenal gland, and almost all of the cancers that occurred at this site were NB.[16] One death due

to non-NB cancer in the adrenal gland was included among the data for 2006, but this was considered to be an unusual case.

The effect of the cessation of the mass screening program for NB should be verified by monitoring the trend in incidence.[22] Studies have reported the trends in NB incidence and mortality before and after the start of a national mass screening program, based on data from a population-based cancer registry.[3,5] Additional similar studies need to be conducted, and should include a sufficient observation period after the cessation of the program.

In conclusion, no significant increase in the NB mortality rate was detected after the cessation of the national mass screening program in Japan. However, continuous monitoring is still needed to evaluate further this health policy decision.

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タバコと発がん

片野田耕太*

要　旨

・タバコは，予防可能な最大のがんのリスク要因である。
・タバコの煙に含まれる発がん物質は，体内の代謝過程で活性化され，DNA 付加体を形成し，遺伝子変異を引き起こす。
・タバコとがんとの関連について，能動喫煙によるリスク上昇だけでなく，禁煙後のリスク低下，受動喫煙など，さまざまな側面から疫学的な証拠が蓄積されてきた。
・能動喫煙と因果関係が確立されているがん種は，口腔，鼻腔・副鼻腔，咽頭，食道，胃，肝臓，膵臓，喉頭，肺，子宮頸部，膀胱，腎臓(腎盂，腎細胞)のがん，および骨髄性白血病である。これらの多くは，継続的な禁煙によりリスクが低下する。
・日本人において，非喫煙者に対する現在喫煙者のリスクは，肺がんでは男女とも 3〜4 倍，喉頭および尿路のがんでは男性で 5 倍以上である。
・日本人のがん死亡に占める喫煙の寄与(人口寄与危険割合)は，男性で 30%強，女性で 5%前後である。
・受動喫煙と肺がんとの因果関係は確立されており，リスク上昇は 20〜30%である。

はじめに

タバコは，予防可能な最大のがんのリスク要因である。1950 年代に喫煙と肺がんとの関連を示す疫学研究の結果が初めて報告されて以来，タバコとがんとの関連については，能動喫煙だけでなく，禁煙によるリスク低下，受動喫煙など，さまざまな側面から研究が行われてきた。今日では，タバコとの因果関係が確立されているがん種は 10 を超える。

以下，タバコとがんとの関連について，トピックごとに最近の知見をまとめる。

タバコによる発がんの仕組み

タバコの煙の中には，タバコ自体に含まれるものだけでなく，不完全燃焼に伴って生じる化合物を含めて約 4,000 種類の化学物質が含まれているといわれる。その中には，多環芳香族炭化水素化合物やニトロソアミン類をはじめとする発がん物質が 60 種類以上含まれている[1]。発がん物質の多くは，体内で代謝される際に活性型に変化した後，DNA と共有結合をして DNA 付加体を形成する。この DNA 付加体が，DNA 複製の際に遺伝子の変異を引き起こす。こうした遺伝子変異が，がん遺伝子やがん抑制遺伝子などに蓄積することによって，細胞ががん化すると考えられている[2]。

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表1　日本人における喫煙者のがんの相対リスク

がん種	日本の三つのコホート研究の併合解析による相対リスク*		日本の疫学研究のメタアナリシスによる相対リスク†	
	男性	女性	男性	女性
全がん	2.0 [1.8：2.1]	1.6 [1.4：1.8]	1.6 [1.6：1.7]	1.3 [1.2：1.4]
口唇・口腔・咽頭	2.7 [1.5：4.8]	2.0 [0.7：5.7]	—	—
食道	3.4 [2.3：5.1]	1.9 [0.7：4.9]	—	—
胃	1.5 [1.3：1.8]	1.2 [0.9：1.6]	1.8 [1.5：2.1]	1.2 [1.1：1.4]
肝・肝内胆管	1.8 [1.5：2.2]	1.7 [1.2：2.5]	—	—
膵臓	1.6 [1.2：2.1]	1.8 [1.3：2.6]	—	—
喉頭	5.5 [1.3：23.1]	N.A.	—	—
肺	4.8 [3.9：5.9]	3.9 [3.1：4.9]	4.4 [3.9：4.9]	2.8 [2.4：3.2]
子宮頸部	—	2.3 [1.3：4.1]	—	—
腎盂を除く腎臓	1.6 [0.8：3.1]	0.6 [0.1：4.5]	—	—
膀胱	6.7 [2.4：18.5]	1.7 [0.7：4.2]	—	—
腎盂・尿管・膀胱	5.4 [2.5：11.6]	1.9 [0.8：4.1]	—	—
骨髄性白血病	1.5 [0.7：2.8]	1.0 [0.3：3.1]	—	—

＊：現在喫煙者の非喫煙者に対する死亡相対リスク（年齢調整），出典；文献[4,5]，†：出典；文献[6~8]
N.A.：死亡数が少数のため算出不可
［ ］内は95%信頼区間

能動喫煙とがん

1．喫煙によるリスク上昇

2002年，国際がん研究機関（IARC）は「ヒトへの発がんリスク評価に関するモノグラフ」（以下，モノグラフ）第83巻において，喫煙とタバコ煙のヒトに対する発がん性を評価した[1]。その結果，喫煙とタバコ煙は，もっとも強い「グループ1：ヒトに対して発がん性がある」と判定された。この報告書は，喫煙と因果関係が認められるがん種として，口腔，鼻腔・副鼻腔，咽頭，食道，胃，肝臓，膵臓，喉頭，肺，子宮頸部，膀胱，腎臓（腎盂，腎細胞）のがん，および骨髄性白血病をあげている。これらの因果関係の評価は，2004年にまとめられた米国公衆衛生総監（Surgeon General）報告書でも，ほぼ同じ内容となっている[3]。

表1は，これらのがん種について，日本の三つのコホート研究の併合解析[4,5]，および日本の疫学研究のメタアナリシスによる[6~8]，喫煙による各種がんの相対リスクをまとめたものである。現在喫煙者の非喫煙者に対する全がんのリスクは，男性で1.5～2倍，女性で1.5倍前後である。男性では肺，喉頭，および尿路のがんで4～7倍と高く，次いで口唇・口腔・咽頭および食道がんが3倍前後である。女性では男性より全体的に相対リスクが低く，現在喫煙者の非喫煙者に対するリスクは肺がんで3～4倍，口唇・口腔・咽頭および子宮頸部のがんで約2倍，その他のがん種では2倍未満である。

全がん死亡に占める喫煙（現在喫煙および過去喫煙）の人口寄与危険割合（当該死因の死亡のうち喫煙が原因だと考えられる割合）は，年齢調整では男性39%，女性5%[4]，多変量調整では男性33%，女性3%（女性は現在喫煙のみ）であり[9]，男性の全がん死亡の30%強，女性の全がん死亡の5%前後は喫煙が原因だと考えられる。同様に肺がんでは，男性肺がん死亡の約70%，女性肺がん死亡の約20%は喫煙が原因だと推計されている[4]。

日本人における現在喫煙者の非喫煙者に対する相対リスクは肺がんでも3～5倍だが，欧米人を対象とした研究では10倍を超える相対リスクが報告されている[10]。喫煙による日本人の肺がん相対リスクが欧米人に比べて低い理由には，①日本人の方が喫煙者の曝露量が小さい（喫煙開始年齢が遅い，1日喫煙本数が少ないなど），②喫煙によるリスク増加が比較的小さい腺がんの割合が日本人で大きい，③日本人の方が非喫煙者の肺がん死亡率が高い（受動喫煙レベルが高い，非喫煙者に喫煙経験者が誤分類されているなど），④遺伝的な感受性が異なる，などが指摘されている。ただし，②については，近年米国の肺がん罹患率は男女とも扁平上皮がんの減少傾向が顕著で腺がんの割合が増加している[11]。

喫煙との関連が明らかではないがん種として，大腸がんがある。IARCモノグラフおよび米国公衆衛生総監報告書とも，喫煙と大腸がんとの間に因果関係があると判定するための科学的証拠は不十分であると結論づけている[1,3]。一方，2008年に能動喫煙と大腸がんとの関連について，大規模なメタアナリシスの結果が報告された[12]。この論文は，喫煙と大腸がん罹患および死亡との間に有意な関連を認め，大腸がんのリスク上昇が有意になるには喫煙年数が30年以上必要であると報告している。

日本人を対象とした疫学研究の系統的レビューでは，喫煙と大腸がんとの関連は「可能性がある（possible）」という弱い評価となっている（4段階中，「確実である」，「ほぼ確実である」に次ぐ3番目）[13]。この結果は上記のメタアナリシスの結果と一見矛盾するようではあるが，上記のメタアナリシスでも，対象地域別の解析においてアジアではリスク比が1に近い[12]。また，結腸がんより直腸がんが強く喫煙と関連しているという結果において両研究は一致している。

喫煙による大腸がんリスク上昇の生物学的機序としては，ポリープの発生過程，進行過程，およびがん化過程にそれぞれ関与する*APC*（*adenomatous polyposis coli*），*ras*，*p53*などの遺伝子が喫煙により変異を起こす可能性が考えられている。

喫煙との関連が否定的とされているがん種として乳がんがある。IARCモノグラフおよび米国公衆衛生総監報告書とも，喫煙と乳がんとの関連に否定的な結論を出している[1,3]。日本の疫学研究の系統的レビューの結果でも，喫煙と乳がんとの関連は「可能性がある」という弱い評価にとどまる[14]。タバコ煙に含まれる物質やその影響が喫煙者の乳腺組織に到達する可能性が指摘されている一方，喫煙者ではエストロゲンレベルが低下するという報告もあり，喫煙と乳がんとの関連についてはリスクの上昇と低下の双方の生物学的機序が考えられ，いずれも確定的ではない。

2．禁煙によるリスク低下

表2は，IARCが2007年に行った禁煙後のリスク低下についての評価をまとめたものである[15]。禁煙後リスクが低下するとされたがん種は，口腔，食道，胃，膵臓，喉頭，肺，子宮頸部，腎細胞，膀胱のがんで，うち喉頭および子宮頸部のがんは禁煙後のリスク低下が早い。子宮頸部のがんは禁煙後非喫煙者のレベルまでリスクが急速に下がるが，他の多くのがん種では非喫煙者のレベルまでリスクが下がるのに20年以上かかる。

また，肺がんは禁煙後長期間経っても非喫煙者のレベルまでリスクが下がらない。ただ，禁煙後の肺がんリスクの低下は，40歳代および50歳代はもちろん，60歳代で禁煙した場合でも認められるため[16]，比較的高齢の喫煙者においても禁煙によるメリットは確実にある。

禁煙後に疾病リスクが低下するかどうかは，喫煙と疾病との因果関係の判定に重要である。ただ，もし喫煙による遺伝子変異が発がん過程の初期に関与していた場合，喫煙をやめた後に他の要因でがん化の過程が進むことも考えられる。

受動喫煙とがん

1．国際機関などの報告

1980年代後半以降，IARC，米国学術会議（National Research Council；NRC），米国環境保護庁（Environmental Protection Agency；EPA）などが科学的証拠に基づいて受動喫煙を肺がんのリスク要因として認め始めた。2002年のIARCモノグラフ第83巻は，受動喫煙について，もっとも強い「グループ1：ヒトに対して発がん性がある」と判定している[1]。受動喫煙と疾患との関連について比較的最近まとめられた報告書