Challenges for Future Cancer Research

“Complete Cure, Prevention, and Living with Cancer - Cancer Research in Collaboration with Patients and Society”

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Cancer has been the leading cause of death in Japan since 1981. There are concerns that the number of cancer deaths will grow with the rapidly increasing number of elderly people in Japan. The 3rd-term Comprehensive 10-year Strategy for Cancer Control has been underway since 2004, and it is scheduled to end in March 2014. During this period, the Cancer Control Act was established, in 2006. According to the Basic Plan to Promote Cancer Control Programs, which was revised in 2012, the government should set a new strategy for cancer research. An Advisory Council on Future Cancer Research has compiled a report with the slogan “Complete cure, prevention, and living with cancer - Cancer research in collaboration with patients and society.” Research issues to be addressed are as follows: 1) clarification of the true nature of cancer; 2) development of new drugs for unmet medical needs; 3) development of new patient-friendly medical technologies; 4) establishment of new standard therapy; 5) research focusing on life-stage and the characteristics of cancer such as childhood cancer, cancer in elderly, refractory cancer and rare cancer; 6) cancer prevention and/or early detection methods; 7) research aimed to establish a society in which both patients and survivors can live well with good survivorship; and 8) promotion and dissemination of cancer control activities.

Key words: Cancer Control Act, Basic Plan to Promote Cancer Control, cure, prevention, living with cancer

Cancer has been the leading cause of death in Japan since 1981, and some 360,000 people died from cancer in 2011. Around 750,000 people were diagnosed with cancer in 2008. It is estimated that one in two persons will develop a cancerous condition within their lifetimes. There are concerns that the number of cancer deaths will grow with the rapidly increasing number of elderly people. The Comprehensive 10-year Strategy for Cancer Control was launched in 1984. The 3rd-term Comprehensive 10-year Strategy for Cancer Control has been underway since 2004, and it is scheduled to end in March 2014.

During the aforementioned period, the Cancer Control Act was approved in 2006, and the Basic Plan to Promote Cancer Control Programs was implemented in 2007. The government should set a new comprehensive 10-year strategy for cancer control according to the revised Basic Plan in collaboration with relevant ministries and the public. In this article, future cancer research desirable for a new cancer control strategy will be discussed.

Present status of cancer in Japan

After the end of the World War II, mortality resulting from infectious diseases such as tuberculosis and pneumonia decreased rapidly, while there was an increase in mortality arising due to lifestyle-related diseases, including cancer and heart disease\(^1\). The number of cancer deaths in
2011 was 360,000, and the death rate per 100,000 was 280, accounting for 30% of all deaths (Figure 1a). However, the age-adjusted mortality rate of cancer has decreased since late 1990s (Figure 1b). This suggests that the increase in crude mortality rate may have been caused by the aging of the population. The number of male cancer deaths was 1.5 times greater than that of female cancer deaths. In terms of cancer sites, lung was the leading site (24%) for males, followed by stomach (15%), colon/rectum (12%), liver (9%), and biliary pancreas (7%). The leading site for females was colon/rectum (15%), followed by lung (14%), stomach (12%), pancreas (10%), and breast (9%), respectively.

The age-adjusted incidence rates of all cancers are still increasing. Among major cancer sites, stomach cancer and liver cancer have been decreasing. The incidence rates of prostate cancer in males and breast cancer and lung cancer in females are increasing. Given the difference in age-adjusted rates between mortality and incidence for all cancers, it is expected that the number of cancer survivors will increase even further in the future. The age-specific incidence rates for all cancers are increasing among old age groups. In addition, the prevalence of cancer is rising sharply among the rapidly increasing elderly population, raising concern that the number of cancer deaths will grow. Meanwhile, whereas the five-year survival rate for all patients with cancer from 1993 to 1996 was 53.2%, the figure climbed to 56.9% for the 2000-2002 period, showing a trend toward improvement that was probably due to early detection and improvement of treatment.

Outline of cancer research as cancer control

Progress on cancer control in Japan has mainly come about through a focus on basic cancer research. The Comprehensive 10-year Strategy for Cancer Control, with the slogan "Clarification of the nature of cancer," was launched in 1984, and the New 10-year Strategy to Overcome Cancer, with the slogan "Overcoming cancer through clarification of the nature of cancer," commenced in 1994. Under the slogan "Dramatic reduction in cancer morbidity and mortality," the 3rd-term Comprehensive 10-year Strategy for Cancer Control has been underway since 2004, and it is scheduled to end this fiscal year (Figure 2).

During the aforementioned period, the Cancer Control Act was established in 2006, and progress has been made on national cancer control in accordance with the Basic Plan to Promote Cancer Control Programs (hereinafter referred to as the...
"Basic Plan"), which reflects the opinions of patients, their families, and the public. The Basic Plan was revised to incorporate the following statements as our overall goal in June 2012, and it has been implemented in a comprehensive and systematic manner.

**Future cancer research for a new cancer control strategy**

As the 3rd-term Comprehensive 10-year Strategy for Cancer Control is due to end in March 2014, the government should set a new comprehensive strategy for cancer research that clarifies the desirable future direction. An Advisory Council on Future Cancer Research was established by the Ministry of Health, Labour and Welfare (MHLW), the Ministry of Education and Science (MEXT), and the Ministry of Economy, Trade and Industry (METI). The Advisory Council produced recommendations below from the perspective of a desirable future direction for cancer research, as summarized in Figure-3.

In consideration of the above, the Advisory Council on Future Cancer Research (hereinafter referred to as the "Advisory Council") was established for the purpose of discussing and making decisions about a new comprehensive strategy for cancer research to clarify the desirable future direction and specific research areas. The Advisory Council held its first meeting on April 15, 2013, and it has held a total six meetings to date. The meetings produced the following recommendations from the perspective of a desirable future direction for cancer research.

1) Research to clarify the true nature of cancer

It is necessary to clarify the molecular mechanism of carcinogenesis, such as resistance to treatment. There is also a need to identify intervention points for appropriate and innovative treatments and prevention based on an understanding of the mechanisms involved in order...
to establish cancer prevention measures and develop medical care. These require not only identification and analysis of individual cancer-related molecules but also recognition that cancer is a destruction of a system consisting of individual molecules. The following cancer characteristics should be clarified from the perspective of interaction between cancer and hosts (patients): pathological characteristics; biochemical and metabolic characteristics; immunological characteristics; and biological characteristics, including diversity and plasticity such as stemness of cancer cells. This will provide a deeper understanding of the true nature of cancer as it relates to the fundamentals of life phenomena. Based on the obtained findings, prevention or treatment methods that could potentially inhibit the occurrence and progress of cancer should be developed. To achieve this, it is important to generate new research approaches through active integration of knowledge and technologies from various fields (e.g., stem cell biology, including with regard to iPS cells). It is also important to generate world-leading, high-quality knowledge on cancer.

(Specific research areas)
i. Research to clarify the causes of cancer, including identification of unknown internal and external factors behind cancer, and the mechanism of maintenance of phenotypes in cancer cells

ii. Research to clarify the mechanism of development and progress of cancer based on biological characteristics of cancer cells, including invasion and metastasis

iii. Research to clarify the dynamics of cancer in an individual based on biological and pathological characteristics including diversity and plasticity of cancer cells/tissues, focusing primarily on clinical pathological conditions such as metastasis, recurrence, and acquisition of treatment
iv. Research to clarify the true nature of cancer through integration of advanced life sciences such as iPS cell research, genome biology, and stem cell biology with other advanced fields, including imaging engineering, computational science, materials science, physics, engineering, and information science

v. Empirical research on new concepts relating to the nature and dynamics of cancer cells/tissues, including with regard to cancer stem cells, cancer microenvironments, and circulating tumor cells, and research on application of such concepts to cancer treatment

vi. Research to explore and identify innovative targets for prevention and treatment of cancer based on clarification of the causes and the true nature of cancer, and research to promote clinical application of the results

vii. Research to clarify the basis of the characteristic biological nature of cancer, including childhood cancer, cancer in the elderly, and rare cancers

2) Research on the development of new drugs for unmet medical needs

In new drug development, research to overcome the current "drug-lag" ("development lag") should be strongly promoted. In addition, research and development of diagnostic agents and treatment drugs that contribute to Japan-originated individualized treatment and development of new treatments, including immune therapy and gene therapy, should be encouraged. Promotion of development of these drugs is required in order to address unmet medical needs.

Reverse translational research should be promoted for the aforementioned purpose through the combination of tumor pathology, which is highly developed in Japan, with multilayer comprehensive molecular analysis technology, including genome/epigenome analysis, which is being optimized for clinical specimens, and advanced collection/analysis of clinical information. It is also necessary to continuously promote effective generation and growth of medical "seeds" (new ideas and technologies for research and development) for cancer treatment in pursuit of innovative drug targets identified through academic research based on clarification of the true nature of cancer.

Collaboration among industry, government, and academia should be further consolidated. Meanwhile, in order to eliminate the so-called "valley of death" in drug discovery and development, translational research should be promoted to a much greater extent, and ongoing support for practical application should be provided for drug discovery research, mainly from application research through nonclinical studies, utilizing the Drug Discovery Support Network.

Furthermore, mainly in areas in which progress with private-sector-led research is difficult, support should be provided for clinical trials, including investigator-initiated clinical trials that are conducted at medical sites; e.g., clinical research core hospitals, which are well equipped to conduct clinical research.

(Specific research areas)

i. Research to explore and identify drug candidates

ii. Research to help drug candidates progress to clinical trials

iii. Clinical research aimed at practical application of off-label-use drugs and unapproved drugs, mainly for refractory or rare cancers, which have been used in standard treatments in the U.S.A. and European countries but for which there has not been sufficient evidence in Japan.

iv. Clinical research aimed at practical application of therapeutic drugs contributing to individualized treatments such as cancer diagnostics, including companion diagnostics, and molecularly targeted agents

v. Clinical research aimed at practical application of new therapeutic agents in immune therapy, gene therapy, etc.

vi. Clinical research aimed at practical application of drugs for supportive therapy

3) Research on the development of new patient-friendly medical technologies

Patient-friendly medical technologies include technology for detecting cancer in the early, curable stage, technology to allow minimally invasive treatment that imposes a low physical burden, and drug-delivery technology to increase the rates of response to treatment and to decrease adverse reactions. From this perspective, in the develop-
ment of new medical technologies it is important to promote development of the following: medical devices, including imaging technology to allow early detection of cancer that has become refractory due to difficulties with early detection; surgical treatments with high radical curability to allow minimal-invasive treatment with minimal discomfort to patients; innovative, next-generation medical devices incorporating Japan’s most advanced technologies, such as robotics; radiation therapy, such as particle beam radiotherapy and next-generation X-ray radiotherapy; and endoscopy. Establishment of a drug delivery system that can help minimize adverse reactions is also important for improving patient QOL.

In addition, it is necessary to conduct higher-quality clinical trials in order to solve "device-lag" problems. There is a need to organize a system for implementing research through cross-disciplinary collaboration among medical, engineering, and other fields, so as to orchestrate high-quality domestic elemental technologies.

(Specific research areas)

i. Research on the development of cancer detection methodologies, including innovative biomarkers and advanced imaging diagnostic technologies, to enable early diagnosis of cancer that is currently difficult to detect in early stages, metastasis, and recurrence.

ii. Research on the development of molecular imaging through a combination of imaging technology and biomarkers

iii. Research aimed at practical application of innovative radiation therapy technologies, including radiation therapy, particle beam radiotherapy, and next-generation X-ray radiotherapy, based on results of research designed to clarify the mechanism of radiation injury and repair

iv. Research aimed at making surgery more advanced and minimally invasive through application of advanced technologies

v. Research aimed at advancing complete cure-oriented treatment through utilization of regenerative therapy to restore functions

vi. Research on the development of a drug delivery system to control distribution of a drug within the body by devising novel administration methods and drug formulations

4) Research to develop new standard treatments

Since multidisciplinary treatments using appropriate combinations of surgical treatment, radiation therapy, pharmacotherapy, and other treatments can provide the most therapeutic effects, it is important to promote multicenter clinical trials in order to develop standard treatments built through the most appropriate combinations of these treatments, and to develop individualized treatments. It is particularly necessary to promote clinical trials for the development of individually optimized treatments that incorporate the perspectives of individualization and stratification through utilization of molecular information such as genomes. In order to efficiently promote research in small patient populations targeted for individualized treatment, it is necessary to promote the establishment of an implementation system for nationwide multicenter clinical trials at medical sites such as designated cancer care hospitals. Meanwhile, it is essential for Japan to actively participate and play a leading role in international collaborative research activities, with a particular focus on Asia. It is also necessary to promote clinical trials and evaluate therapeutic effects in a scientific manner for immune therapy and gene therapy, which are expected to become new treatment approaches.

Furthermore, development of evidence-based standard treatments should be promoted, including supportive therapies aimed at improving safety and QOL during and after treatment, as well as the efficacy of treatment. For new development of supportive therapies, research on the establishment of methods for determination of therapeutic effects should be promoted at the same time.

(Specific research areas)

i. Multicenter clinical research on the development of standard treatments that are further optimized for individual patients and populations with the purpose of improving treatment efficacy.

ii. Multicenter clinical research on the development of standard treatments aimed at improving treatment safety and QOL.

iii. Research on the development of supportive therapies, including palliative care, nutritional care, and rehabilitation therapy for patients with cancer, and on the development of methods for
determining the effects of such therapies
iv. Multicenter clinical research to confirm the efficacy of supportive therapies

5) Prioritized research areas focusing on life stages and characteristics of cancer

(1) Research on childhood cancer
Childhood cancer, which is the leading cause of death due to disease in children, can occur over a broad age range, from infancy through adolescence to young adulthood, and it includes various rare types of cancer. Research on treatment development, focusing on such diversity, should be conducted. There is also a requirement for clinical research aimed at the early practical application of unapproved drugs and off-label-use drugs. In order to promote research effectively, it is necessary to establish a research network based primarily on pediatric cancer base hospitals, and to reinforce the support system for clinical research.

(Specific research areas)
   i. Clinical research aimed at practical application of therapeutic agents (unapproved drugs and off-label-use drugs) for childhood cancer
   ii. Research on the development of new treatments aimed at increasing the cure rates for refractory childhood cancer
   iii. Research on the development of treatments for childhood cancer aimed at improved treatment safety and QOL
   iv. Research on clarification and development of cancer treatment in the adolescent and young adult (AYA) age group

(2) Research on cancer in the elderly
With regard to cancer in the elderly, it is necessary to develop prevention, diagnosis, and treatment methods that are appropriate to the particular characteristics of elderly patients, including decreased physical function, other comorbid conditions, and increased individual differences due to advanced age. It is also necessary to promote research on clarification of the biological features of cancer development in the elderly.

We must also promote clinical trials for the development of combination treatments aimed at achieving complete cures that are most suitable for the elderly and clinical trials for the development of supportive therapies to maintain and improve QOL.

(Specific research areas)
   i. Research to clarify the characteristics of cancer in the elderly, including from a biological perspective
   ii. Clinical research to develop standard treatments that are most suitable and more effective for the elderly
   iii. Clinical research to develop standard treatments, including supportive case that are most suitable and more effective for the elderly and help to maintain QOL
   iv. Research incorporating regenerative therapies for restoring functions that are specific to the elderly

(3) Research on refractory cancer
While the 5-year survival rate has improved to around 60% across all cancer patients, it is becoming an urgent issue to improve response rates for patients with refractory cancer, such as pancreatic cancer. Alongside promotion of research aimed at overcoming the "development lag" for off-label-use drugs and unapproved drugs, it is necessary to strongly promote research aimed at developing Japan-originated treatments. With regard to cancer that becomes refractory due to difficulties in early detection, it is necessary to develop innovative technologies for diagnostic methods to detect the presence of cancer. At the same time, we need to further promote research on clarification of the characteristics of cancer, such as invasion and metastasis, as a first step toward overcoming continued resistance to treatment of metastatic/recurrent cancers.

(Specific research areas)
   i. Clinical research aimed at practical application of off-label-use drugs and unapproved drugs for refractory cancers
   ii. Research on the development of new treatments for refractory cancers for which effective treatments have not yet been developed.
   iii. Research on the development of cancer detection methods, including innovative biomarkers and advanced imaging diagnosis, for cancer conditions for which early detection is currently difficult
iv. Research on the development of new treatments focusing on characteristics of cancer such as metastasis and recurrence

(4) Research on rare cancers
To date, research sources have mainly been invested in the five major types of cancer. Private sector–led research into rare cancer entails difficulties, and it is necessary to actively address the development of treatments for such rare cancers, which includes research aimed at overcoming the "development lag" issue for off-label-use drugs and unapproved drugs. Rare cancers include sarcoma, malignant brain tumor, oral cancer, and adult T-cell leukemia. There is also a need to for research on the types of cancer that are seen more frequently in Asia (including Japan) than in other regions, taking into consideration the roles played by particular national characteristics in cancer onset. It is important to promote development of research that focuses on individual types of cancer, utilizing as a basis accumulated information on rare cancers. In so doing, it is vital to bear in mind that knowledge and findings obtained from such research on rare cancers can also be applied to many other types of cancer.

(Specific research areas)
i. Clinical research aimed at practical application of off-label-use drugs and unapproved drugs for rare cancers
ii. Research on the development of new treatments for rare cancers for which private sector–led research progresses with difficulty
iii. Research on the development of new treatments for types of cancer that are characteristically seen in Asia (including Japan)
iv. Research on clarification of causes, prevention, early detection, treatments, and practical application of information provision, focusing on particular types of cancer, such as hereditary tumors
v. Biostatistics research aimed at securing the scientific validity of various types of analysis that involve small numbers of cases
vi. Research on the development of animal models of rare human cancers and research on evaluation of the validity of evidence through the use of models

6) Research on cancer prevention and/or early detection methods
Regarding prevention and early detection of cancer, there is a need to develop new methods that can be easily and widely used. At the same time, cancer risk factors, including fixed risk factors (e.g., genetic factors) and variable risk factors (e.g., lifestyle, infection, and environmental factors), should be appropriately stratified and individualized through exploration of unknown causative factors and utilization of existing research achievements, so as to establish methods that are optimized for individuals and, ultimately, to enable individual implementation.

In order to achieve this, it is necessary to promote large-scale epidemiological research to validate the efficacy of preventive intervention, based on empirical evidence extracted through basic research, small-scale observational studies, and intervention studies. Because it is expected that direct inhibition of the molecular mechanisms underlying the onset of cancer will become the mainstream approach, research that utilizes biological specimens obtained before the onset of cancer or from clinical sites should be promoted.

With regard to early detection, we need to promote observational studies or intervention studies in order to accumulate evidence, and large-scale epidemiological research to validate the efficacy of new methods that can be easily and widely used and those that incorporate the perspectives of stratification and individualization.

(Specific research areas)
i. Research aimed at identification, stratification, and individualization of individual cancer risks, including genetic information, presence/absence of infection, contracting of diseases, lifestyle–related factors such as smoking (including passive smoking), dietary habits, exercise, and working/living environments
ii. Research on the development of risk reduction methods suitable for individual cancer risks
iii. Research on the development of diagnostic technologies for use in medical examinations
iv. Large-scale epidemiological research aimed at practical application of cancer prevention methods and new medical examination methods
7) Research aimed at the establishment of a society in which survivors can live well with good survivorship

In order to establish a society in which survivors can live well with good survivorship, it is necessary to focus on various issues such as psychophysiological disorders and social factors that could be causes or relevant factors nationwide, including with regard to patients, their families, healthcare professionals, and the general public. It is also necessary to conduct research aimed at overcoming such issues and ameliorating relevant factors, as well as research on health promotion in cancer patients, including measures to prevent recurrence and/or complications. Moreover, it is necessary to further promote research on the role of cancer education and research on the role of provision of information to and consultation/support for the public, for the acquisition of accurate knowledge regarding cancer epidemiology, prevention, diagnosis, and treatments.

(Specific research areas)

i. Research on health maintenance and promotion for patients and their families, and on psychophysiological and social issues

ii. Research on the role of the cancer care delivery system, including widespread use of palliative care, home care, and standard treatments, and on adequate allocation of medical resources

iii. Research on provision of information on cancer and consultation/support for those affected by cancer, including cancer education for the public

8) Research on effective promotion and assessment of cancer control activities

Because well-evidenced measures effective for prevention, early detection, diagnosis, and treatment have not been sufficiently disseminated in practice, research to close the gap is required.

Improvement of the cancer research system

To promote effective progress in research, it is essential to have a thorough grasp of the needs of the public, including cancer patients. Furthermore, we must have an accurate understanding of overall progress on cancer research in Japan and other countries. Only then can we properly plan and execute research projects and establish research plans and endpoints, and only then can we conduct intermediate and post-study evaluations. Ongoing follow-ups are important and, to ensure that meaningful results are produced from cancer research, concerted efforts by the government to create a research system are essential.

Conclusion

Future research areas to be addressed in order to construct a new strategy for cancer research have been discussed in this paper. Research for prevention and early detection of cancer should be promoted to reduce the number of cancer patients – a number that is expected to increase explosively in the near future. We should develop new cure-oriented and patient-friendly medical technologies based on the nature of cancer through basic research to develop the most suitable medical care for elderly patients with cancer. In order to establish a society in which survivors are able live well with cancer, it is necessary to conduct research on psychophysiological and social issues. Cooperation with patients and society will be essential to maximize research efficacy.

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