

INTERNATIONAL PERSPECTIVES

Cardio-Oncology in Japan

The Rapidly Rising Sun



Toru Oka, MD, PhD,^a Hiroshi Akazawa, MD, PhD,^b Kazuhiro Sase, MD, PhD,^c Kiyohiko Hatake, MD, PhD,^d
Issei Komuro, MD, PhD^b

In Japan, cancer and cardiovascular (CV) disease (CVD) are the first and second leading causes of death, respectively. As the result of long-term lifestyle habits including Western-style diet and sedentary lifestyle, cancer and CVD have emerged as the leading causes of mortality and burden of disease. In the 21st century, the elderly population is rapidly increasing, and we are coping with the unprecedented aging of society. The incidence of both cancer and CVD increases with age, and cancer and CVD comorbidities in elderly patients have become serious concerns in clinical practice. In addition, recent progress in cancer therapy has decreased all-cancer mortality, leading to an increase in the number of cancer survivors (1). As a consequence, CV adverse events owing to cancer therapy have a greater impact on clinical outcome and quality of life in cancer patients and survivors. Under such circumstances, cardio-oncology is increasingly important and attracting a great deal of attention in Japan (2).

CANCER AS THE LEADING CAUSE OF DEATH IN JAPAN

In 2019, the total population of Japan was approximately 126 million, and the population aged over 65

years was 28.4%. The projected cancer incidence was approximately 1.0 million in 2019. The most common cancer site in males is colon/rectum (16%), followed by stomach (15%), lung (14%), prostate (14%), and liver (4%), and in females, breast (21%), followed by colon/rectum (15%), stomach (9%), lung (9%), and uterus (6%) are most common. The geographical disparities in cancer incidence are associated with acquired risk factors such as smoking, salt intake, hepatitis virus infection, and *Helicobacter pylori* infection. There is also an inherited predisposition (3). The Center for Cancer Control and Information Services in the National Cancer Center Japan reported that the number of cancer deaths in Japan was approximately 374,000 in 2018. The leading cancer mortality sites for males were lung (24.0%), stomach (13.2%), colon/rectum (12.4%), pancreas (8.2%), and liver (7.8%), and for females were colon/rectum (15.2%), lung (14.2%), pancreas (11.3%), stomach (9.9%), and breast (9.5%). However, cancer survival is constantly improving in Japan, and the 5-year relative survival rate for all cancer patients was 64.1%. These epidemiological data suggest that 1 in 2 Japanese are diagnosed with cancer during their lifetime, and that 1 in 4 Japanese males and 1 in 7 females will die of cancer.

The incidence of most cancers and CVD increases with age, and elderly cancer patients are more likely to have CV comorbidities (4). It was reported that 8.16% of Japanese cancer patients had CV comorbidities such as atrial fibrillation, ischemic heart disease, heart failure, and venous thromboembolism, and that the ratio of cancer patients with CV comorbidities is projected to further increase, reaching a peak in 2030 to 2034 (5). Moreover, intensive and multimodal cancer therapy can predispose cancer patients to CV toxicities and increase the number of cancer patients who are at risk of CV complications, although it certainly prolongs progression-free survival.

From the ^aDepartment of Onco-Cardiology, Osaka International Cancer Institute, Osaka, Japan; ^bDepartment of Cardiovascular Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan; ^cDepartment of Clinical Pharmacology, Juntendo University, Tokyo, Japan; and the ^dDepartment of Lymphoma/Hematologic Malignancy Center, Mita Hospital, International University of Health and Welfare, Tokyo, Japan.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

Therefore, it is becoming more and more important to manage the CV comorbidities and complications that are associated with both cancer and adverse effects of cancer therapy (2).

PRESENT STATUS OF CARDIO-ONCOLOGY/ ONCO-CARDIOLOGY IN JAPAN

Since the Cancer Control Act was enacted in 2007, the national government has taken the initiative to reduce the burden of cancer and to prolong healthy life expectancy. In order to ensure high-quality medical care for cancer patients nationwide, the government has designed 402 cancer hospitals throughout Japan (Designated Cancer Care Hospitals). However, importance of cardio-oncology had not been recognized even in these Designated Cancer Care Hospitals until 2010. The first Onco-Cardiology unit was launched in the Osaka Medical Center for Cancer and Cardiovascular Diseases (OMCC), the predecessor of the Osaka International Cancer Institute (OICI), in 2010 (2). A special lecture on cardio-oncology given by Dr. Thomas Force (Vanderbilt University Medical Center) at OMCC in the preceding year provided impetus for the establishment of the onco-cardiology unit. The term *onco-cardiology* was chosen in honor of the first onco-cardiology unit in MD Anderson Cancer Center (6), and for the subspecialty of cardiology dedicated to CV management of cancer patients by cardiologists, whereas the term *cardio-oncology* is prevalent in many other countries (2). Shortly after the establishment of the onco-cardiology unit in the OICI, onco-cardiology clinics have become widespread throughout Japan. Further organization of cardio-oncology services is an urgent issue to provide high-quality medical care and to coordinate medical education, training, and research for the management of CV monitoring and management of cancer patients and survivors.

ESTABLISHMENT OF THE JAPANESE ONCO-CARDIOLOGY SOCIETY

During the past decade, cardio-oncology has gained a high degree of recognition in Japan, and symposium sessions focusing on cardio-oncology have been consistently included in the program of scientific meetings of major academic societies in both cardiology and oncology. Pioneers and experts in the field of cardio-oncology have been invited to these meetings. In the Annual Meeting of the Japanese Heart Failure Society 2018, Dr. Thomas M. Suter (University of Bern), the chairperson of the European

Society of Cardiology Council for Cardio-Oncology, delivered a lecture on the present status and future of cardio-oncology. In the Annual Scientific Meeting of the Japanese Circulation Society (JCS) 2019, Dr. Javid Moslehi (Vanderbilt University Medical Center) delivered a lecture on the impact of cardio-oncology research on CV discovery. In the Annual Scientific Meeting of JCS 2020, Dr. Bonnie Ky (University of Pennsylvania School of Medicine), the inaugural editor-in-chief of *JACC: CardioOncology*, delivered a lecture on the management of CV complications in cancer patients. Their participation and sharing of recent achievements was exciting and further helped to promote cardio-oncology in Japan.

With the growing demands of the burgeoning field of cardio-oncology, the Japanese Onco-Cardiology Society (JOCS) was established in October 2017 to provide further opportunities for specialists in cardiology and oncology to exchange views and share common experiences for the purpose of integrating their activities into academic pursuits and implementing quality improvement in cancer therapy (2,4). The mission of JOCS is to contribute to the advancement of cardio-oncology by energizing the interdisciplinary collaborations among cardiologists, oncologists, radiologists, nurses, pharmacists, allied health professionals, researchers in basic, translational, clinical sciences, and drug discovery. Dr. Issei Komuro (University of Tokyo), who is a cardiologist and the immediate past president of JCS, became the inaugural president of JOCS, and Dr. Kiyohiko Hatake (International University of Health and Welfare), who is a hematologist, became the vice-president and the Congress chairperson of the 1st Annual Meeting of JOCS. Currently, JOCS has a membership of more than 600, and the ratio of cardiologists to oncologists/hematologists is approximately 1.5:1. The 1st Annual Meeting of JOCS was held in Tokyo in November 2018, adopting “Harmonization of Heart and Cancer Experts” as the main theme. This meeting welcomed 558 participants and competently provided opportunities for a lively discussion on current status and future direction of cardio-oncology. Dr. Ana Barac (Georgetown University), the immediate past chair of the American College of Cardiology Cardio-Oncology Section, delivered a lecture on the intersection of CV function and cancer treatment. In the 2nd Annual Meeting of JOCS 2019, Dr. Daniela Cardinale (European Institute of Oncology, Milan), delivered a lecture on cardiotoxicity and the role of cardio-oncology. In the 3rd Annual Meeting of JOCS 2020, Dr. Daniel L. Lenihan

(Washington University School of Medicine), the president of the International Cardio-Oncology Society, delivered a lecture on the present and future of cardio-oncology.

FUTURE OF CARDIO-ONCOLOGY IN JAPAN

It is the dawn of a new era for cardio-oncology in Japan, and it is moving upward like the rapidly rising sun. Cardio-oncology has been recognized as a subspecialty with multidisciplinary integration of cardiology and oncology, and there is a growing number of cardio-oncology clinics throughout the country. However, there are many issues to be addressed for solving the unmet needs in cardio-oncology. First of all, the exact incidence, severity, and outcome of treatment-related CV toxicities in cancer patients are unknown. For example, nationwide cohort studies and rigorous post-market surveillance are imperative to estimate the long-term incidence and prognosis of immune checkpoint inhibitors-associated CV complications, because CV immune-related adverse events are rare but potentially life-threatening. Accumulation of evidence from clinical trials and real-world data are needed to establish evidence-based practice for diagnosis, prevention, and treatment of CV complications in cancer patients. It is important to educate cancer specialists as well as cardiologists on the increased probabilities of CV complications in cancer patients. In addition, the molecular mechanisms underlying the pathogenesis of CV toxicities by cancer treatment remain to be defined, in order to inform the development of therapeutic strategies. In 2018, the Stroke and Cardiovascular Control Act was passed in Japan, as the legislative countermeasure against CVD and stroke for raising public awareness and prevention, improving provision systems for health, medical, and welfare services, and promoting research (2,7). In February 2020, researchers of the National Cancer Center, the National Cerebral and Cardiovascular Center, and the National Institute of Health Sciences organized the first cardiotoxicity workshop at the government-affiliated research organizations to initiate an all-Japan effort for the development of cardio-oncology. These nationwide approaches are expected to promote epidemiological, clinical, and basic research to achieve the goals of saving cancer patients and survivors from CV complications. These are the issues not only for Japan, but also for all other countries, and we

would like to work together in the international community for further the development of cardio-oncology.

With the increasing need for standardized clinical practice for cardio-oncology, several guidelines or expert consensus have been developed in the USA and Europe. There are unique epidemiological and clinical features in Japanese cancer patients, which originate from the ethnicity, age distribution, dietary habits, and environment. In addition, there are some differences in the repertoire of drugs available for clinical use in Japan from other countries. For example, the use of low-molecular-weight heparin for the treatment of venous thromboembolism and the use of dexrazoxane for the prevention of anthracycline cardiotoxicity still remain to be approved, because of the lack of clinical evidence among the Japanese population. Under such circumstances, the development of evidence-based practice guidelines which would be more suitable for real-world practice in Japan is urgently needed. The working group consisting of the representatives from JOCS, the Japanese Society of Medical Oncology, JCS, the Japan Society of Clinical Oncology, and the Japanese Society of Echocardiography is currently collaborating to develop the guidelines for risk prediction, screening, prevention, diagnosis, treatment, and long-term surveillance.

The importance of cardio-oncology will definitely continue to increase more and more in Japan, where an epidemic of cancer and CVD is emerging because of the aging of the population. Toward our goal of managing the burden of CV comorbidities and complications in cancer patients, we will energize the interdisciplinary collaborations among cardiologists, oncologists, radiologists, pathologists, specialized nurses, pharmacists, and allied health professionals, and make our utmost efforts to promote basic, translational, and clinical research and improve education program.

AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr. Hiroshi Akazawa, Department of Cardiovascular Medicine, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. E-mail: akazawah-tky@umin.ac.jp. Twitter: [@ToruOka1](https://twitter.com/ToruOka1), [@AkazawaHiroshi](https://twitter.com/AkazawaHiroshi), [@ksase](https://twitter.com/ksase).

REFERENCES

1. Katanoda K, Hori M, Matsuda T, et al. An updated report on the trends in cancer incidence and mortality in Japan, 1958-2013. *Jpn J Clin Oncol* 2015;45:390-401.
2. Kadowaki H, Akazawa H, Ishida J, Komuro I. Cancer therapeutics-related cardiac dysfunction—insights from bench and bedside of onco-cardiology. *Circ J* 2020;84:1446-53.
3. Saika K, Matsuda T. Cancer incidence rates in the world from the Cancer Incidence in Five Continents XI. *Jpn J Clin Oncol* 2018;48:98-9.
4. Okura Y, Ozaki K, Tanaka H, Takenouchi T, Sato N, Minamino T. The impending epidemic of cardiovascular diseases in patients with cancer in Japan. *Circ J* 2019;83:2191-202.
5. Okura Y, Takayama T, Ozaki K, et al. Future projection of cancer patients with cardiovascular disease in Japan by the year 2039: a pilot study. *Int J Clin Oncol* 2019;24:983-94.
6. Yeh ET. Onco-cardiology: the time has come. *Tex Heart Inst J* 2011;38:246-7.
7. Nakayama H, Minematsu K, Yamaguchi T, et al. Approval of Stroke and Cardiovascular Disease Control Act in Japan: comprehensive nationwide approach for prevention, treatment, and patients' support. *Int J Stroke* 2020;15:7-8.