



update

Summer
Volume 24, Issue 1, 2013

News and Views

Radiation Effects Research Foundation

Hiroshima and Nagasaki, Japan



Hiroshima
Nagasaki



Table of Contents

From the Editors	1
RERF News	
Report on the 40th Scientific Advisory Committee Meeting, 2013	1
RERF's Third Public Lecture for Citizens Held in Hiroshima	4
Biosample Center Newly Established at RERF	5
HICARE Dispatches RERF Chairman and Others to Radiation Exposure Medical Care Seminar in Korea	5
Dr. Warren Muir of NAS Retires—New Executive Director of RERF-support Division Appointed, by Evan B. Douple and Roy E. Shore	6
Students from the U.S. BCA and Dr. Charles J. Camarda of NASA Visit RERF.....	7
U.S. Journalism Students Visit RERF to Learn about Radiation for Reporting on Fukushima.....	8
Staff News	8
Visiting Student Researcher	11
Award Received by RERF Scientist	12
RERF Receives Health, Labour and Welfare Minister's Certificate of Appreciation	13
Conference and Workshop Reports	
RERF International Workshop: Heavy Structural Shielding, by Harry M. Cullings	13
RERF Hosts International Workshop on Radiation and Cardiovascular Disease, by Waka Ohishi....	17
Second International Academic Conference on Radiation Health Risk Management in Fukushima	18
Interdisciplinary Education Intensive Course: A Special Training Program for Recovery from Nuclear Accidents, by Ritsu Sakata	19
Science Articles	
Impact of Smoking on Mortality and Life Expectancy in Japanese Smokers: A Prospective Cohort Study, by Ritsu Sakata.....	21
Unrepairable DNA Double-strand Breaks That Are Generated by Ionizing Radiation Determine the Fate of Normal Human Cells, by Asao Noda	23
Translocations in Spleen Cells from Adult Mice Irradiated as Fetuses Are Infrequent, but Often Clonal in Nature, by Yoshiaki Kodama	24
Association between Chronic Kidney Disease and Cardiovascular Disease Risk Factors in Atomic Bomb Survivors, by Nobuko Sera	26
Human Interest Notes	
A Farewell Note with Reflections on the Last Five Years, by Evan B. Douple	28
Reflections on My Retirement, by Kazue Imai	29
Facts and Figures	
LSS Survivors with Unknown Doses, by Harry M. Cullings.....	30
RERF's Views on Residual Radiation.....	31
Research Protocol and Publications	
Research Protocol Approved in May 2012–April 2013	32
Recent Publications	32

Cover photographs: Liquid nitrogen tanks used to store biosamples (left); see page 5
Public lecture for citizens (right); see page 4

This newsletter is published twice a year by the Radiation Effects Research Foundation (RERF; formerly the Atomic Bomb Casualty Commission), established in April 1975 as a private, nonprofit Japanese foundation. It is supported by the government of Japan through its Ministry of Health, Labour and Welfare and by the United States through its Department of Energy (DOE), in part by DOE contract DE-HS0000031 with the National Academy of Sciences. RERF became a public interest incorporated foundation on April 1, 2012.

RERF conducts research and studies—for peaceful purposes—on medical effects of radiation and associated diseases in humans, with a view to contributing to maintenance of the health and welfare of the atomic-bomb survivors and to enhancement of the health of all humankind.

Editor-in-Chief: Harry M. Cullings, Chief, Department of Statistics

Technical Editor: Fumie Maruyama, Public Relations & Publications Office

Editorial Policy

Contributions to RERF Update receive editorial review only and do not receive scientific peer review. The opinions expressed herein are those of the authors only and do not necessarily reflect RERF policies or positions.

Contact: Mailing address: RERF Public Relations & Publications Office, 5-2 Hijiyama Park,
Minami-ku, Hiroshima 732-0815 Japan
Telephone: 81-82-261-3131; Facsimile: 81-82-263-7279
Internet: <http://www.rerf.jp/>

From the Editors

Welcome to this issue of *Update*. The rainy season, expected to continue until at least the end of June, is upon us here in Japan. In contrast with the rain's constancy, this has been a time of change in terms of personnel, not only at RERF, but also at the U.S. National Academy of Sciences (NAS) and the U.S. Department of Energy (DOE).

RERF recently saw the retirement of Dr. Evan B. Douple, who had been the Associate Chief of Research and the Editor-in-Chief of *Update* since the beginning of 2008. Reflections on his time at RERF until his retirement are included herein. Upon Dr. Douple's retirement, I (Harry M. Cullings) assumed the post of Editor-in-Chief and hope to continue *Update*'s timely, engaging, and informative qualities. I owe a debt of gratitude to Dr. Douple for his careful stewardship during his years overseeing the publication. My task is made easier with the able assistance of the Technical Editor Fumie Maruyama and the staff of the Public Relations and Publications Office, headed by Jeffrey L. Hart.

Two new staff members have been hired in the Statistics Department, including Dr. Young Min Kim, whose introduction appears in this issue, and Dr. Reid D. Landes, who will join RERF in July. Dr. Daisuke Haruta was hired on April 1 as a research scientist at the Clinical Studies Department in Nagasaki. Dr. Kazue Imai retired from the Radiobiology/Molecular Epidemiology Department and offers her thoughts in this issue. There has also been a transition at NAS, with the retirement of Dr. Warren R. Muir, who was succeeded by Dr. Gregory H. Symmes, a change that is touched on in this issue. Dr. Joseph F. Weiss retired from DOE after many years of dedicated service

to the management of RERF's operations, with the new Program Manager for RERF being Dr. Isaf Al-Nabulsi.

I have been associated with NAS since I began working in 1998 for the Committee on Dosimetry for the RERF as a post-doctoral fellow in the



Harry M. Cullings, PhD

DOE program at the University of Pittsburgh, which included my first visit to RERF. I returned to RERF in 1999 as a research scientist in the Statistics Department and have been here continuously for almost 14 years, having become the Chief of the Statistics Department in 2010. We hope you will enjoy this issue, which has a new look but is packed with the usual news and an increased number of science articles, with a short piece on RERF's new Biosample Center and in-depth articles on two recent workshops that were held at RERF.

Harry M. Cullings
Editor-in-Chief

Fumie Maruyama
Technical Editor

Report on the 40th Scientific Advisory Committee Meeting, 2013

The 40th Scientific Advisory Committee (SAC) review of RERF's research activities was held on March 4–6, 2013, at our Hiroshima facility. The SAC consists of 10 scientists, five each from Japan and the United States. The co-chairs this year were Dr. Shunichi Yamashita and Dr. John J. Mulvihill. Dr. Yoichi Gondo of RIKEN BioResource Center joined the SAC with the expiration of the term of Dr. Katsushi Tokunaga. To aid this review, two additional experts were appointed temporarily to the SAC—Dr. Hiroshi Sasaki, Kanazawa Medical University, and Dr. Andrew J. Einstein, Columbia

University Medical Center. Their insights were extremely valuable, and it was a great pleasure for us to work with these outstanding scholars.

RERF Chairman Dr. Toshiteru Okubo opened the meeting and provided a warm welcome to all. In reviewing the past year, he mentioned there had been eight retirements and four newly hired scientists, for a net loss of four. Since 2004, there has been an 18% loss of general staff due to mandated reductions. He also indicated that the Information Technology Department has introduced a virtual desktop system, migration to virtual servers,

increased network security, and improved access by mobile devices.

Next, Vice Chairman Dr. Roy E. Shore spoke on responses to SAC recommendations and on new research achievements. In response to the 2012 SAC recommendations, RERF has proposed policies to improve database and biosample access both internally and externally; we have planned a workshop on DNA sequencing with experts from Japan and abroad; we conduct open meetings regarding research protocols and share research protocol reviews as a way to educate young investigators; we have provided advice and materials to Fukushima investigators for the development and procedures of their large-scale cohort and have helped them focus their scientific and public-health questions; we established a comprehensive Bio-sample Center; we instituted new procedures to ensure that study datasets will be documented and permanently stored; we have encouraged investigators to apply for external grants; because of strong community concerns, we have spent much time and effort to analyze our disease data in relation to possible radiation exposures from A-bomb fallout; and we have developed collaborations with several experts in bioinformatics.

RERF investigators published papers in several high impact journals during FY2012, such as the *British Medical Journal*, *PLoS One*, *FASEB Journal*, *Radiology*, and *Radiation Research*. A few substantive highlights of our research publications are: Regarding radiation exposure and cancer, we published a major analysis of updated data on leukemias and lymphomas¹; an update on thyroid cancer risk²; an analysis of radiation, lifestyle factors, and urothelial cancer risk³; an analysis of radiation, smoking, and various histologic subtypes of lung cancer⁴; and the first evidence for the involvement of *ALK* gene rearrangements in radiation-associated thyroid cancer.⁵ Regarding noncancer diseases and conditions, papers were published on radiation and cataract surgery incidence⁶; radiation and risk for subtypes of stroke⁷; radiation, chronic kidney disease and cardiovascular risk factors⁸; and the impact of smoking on mortality and life expectancy.⁹ Other published reports considered radiation and systemic markers of inflammation¹⁰; an RERF international workshop on radiation effects on somatic and germline mutations¹¹; improved estimation of A-bomb doses to human organs¹²; and the use of tooth enamel for gamma and neutron biodosimetry.¹³

RERF scientists have continued their active involvement on international radiation-protection and risk-assessment committees, such as the ICRP (International Commission on Radiological Protection), UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation), WHO (World Health Organization), and NCRP (National

Council on Radiation Protection & Measurements). They also gave a number of invited lectures abroad and have numerous collaborations with investigators at various institutions in Japan, Europe, America, and Asia.

Turning to the 2013 SAC report, a brief statement of the key general recommendations is as follows:

- More high-quality publications in international English language journals are essential for the continued success of RERF. An examination of citation impact factors would also be useful.
- Decisions about organizational structure are needed, with regard to future hiring and purchase of large equipment.
- The SAC highly values the efforts of RERF to date in support of activities related to Fukushima. This unfortunate tragedy represents an ideal opportunity for delivery of the RERF “product” and “know-how” in that it represents transfer of RERF scientific knowledge and process knowledge (such as consideration of low-dose radiation health effects and long-term follow-up) to a pressing public concern.
- Greater attention should be given to the global impact of RERF. Good beginnings are well underway with international collaborations, participation in international policy agencies, and large research collaborations.
- Since the new Articles of Incorporation now permit receiving donations and philanthropy to augment the mission and effectiveness of RERF, the SAC urges explorations of the use and potential of this new possibility.
- The SAC applauds the effort to consolidate and inventory all biologic specimens.
- For junior investigators, the SAC recommends a program of training for professional radiation career development.

Selected highlights of the departmental recommendations include:

- Clinical Studies Department: Research on radiation and noncancer diseases should be continued, and strengthened by seeking active participation of world-leading experts from inside and outside Japan as well as recruiting young researchers.
- Radiobiology/Molecular Epidemiology Department: The idea of applying an ontology-type approach to the genome-wide genetic variant data is encouraged, as a similar approach has been highly successful in extracting biological meaning from gene-expression studies.

- Genetics Department: Continue to explore the potential use of whole-genome DNA sequencing (WGS). This will help in focusing expectations regarding WGS, framing essential scientific questions, and providing more accurate assessment of concomitant costs.
- Epidemiology Department: Analyses of mortality and cancer incidence among the F₁ (children of the atomic bomb survivors) cohort and those exposed *in utero* are particularly relevant and important to publish as soon as possible.
- Statistics Department: The dosimetry changes and their impact on the basic Life Span Study cancer risk estimates should be completed as soon as possible so that questions about their possible effect can be settled. Also it is critical that the issue of radioactive fallout exposures receives both scientific and public-relations attention.

In summary, the SAC highlighted the unique role RERF plays in determining radiation risks and the potential for valuable continued studies. The committee urged the prompt development and publication of new results regarding issues of scientific and public-health concern and suggested ways to address new technological challenges in the basic sciences.

RERF Scientific Advisors

Dr. Shunichi Yamashita, *Co-Chairperson*, Vice President, Fukushima Medical University

Dr. John J. Mulvihill, *Co-Chairperson*, Children's Medical Research Institute/Kimberly V. Talley Chair in Genetics; Professor of Pediatrics; Head, Section of Genetics, University of Oklahoma Health Sciences Center

Dr. Kiyoshi Miyagawa, Professor, Laboratory of

Molecular Radiology, Center for Disease Biology and Medicine, Graduate School of Medicine, The University of Tokyo

Dr. Kazuo Sakai, Director, Research Center for Radiation Protection, National Institute of Radiological Sciences

Dr. Kazuo Tajima, Director, Aichi Cancer Center Research Institute

Dr. Yoichi Gondo, Team Leader, Mutagenesis and Genomics Team, RIKEN BioResource Center

Dr. Sally A. Amundson, Associate Professor of Radiation Oncology, Center for Radiological Research, Columbia University Medical Center

Dr. Marianne Berwick, Distinguished Professor and Chief, Division of Epidemiology, Associate Director, Population Sciences, University of New Mexico

Dr. David G. Hoel, Distinguished University Professor, Department of Medicine, Medical University of South Carolina, and Principal Scientist, Exponent, Inc.

Dr. Michael N. Cornforth, Professor and Director of Biology Division, Department of Radiation Oncology, University of Texas Medical Branch

Special Scientific Advisors

Dr. Hiroshi Sasaki, Professor, Department of Ophthalmology, Kanazawa Medical University

Dr. Andrew J. Einstein, Victoria and Esther Aboodi Assistant Professor of Medicine, Division of Cardiology; Director, Cardiac CT Research, Columbia University Medical Center

References

1. Hsu, W.-L., Preston, D., Soda, M. *et al.* The incidence of leukemia, lymphoma and multiple myeloma among atomic bomb survivors: 1950-2001. *Radiat. Res.* **179**, 361-382, (2013).



Participants of the 40th Scientific Advisory Committee meeting held at Hiroshima RERF

2. Furukawa, K., Preston, D., Funamoto, S. *et al.* Long-term trend of thyroid cancer risk among Japanese atomic-bomb survivors: 60 years after exposure. *Int. J. Cancer* **132**, 1222-1226 (2012).
3. Grant, E. J., Ozasa, K., Preston, D. L. *et al.* Effects of radiation and lifestyle factors on risks of urothelial carcinoma in the Life Span Study of atomic bomb survivors. *Radiat. Res.* **177**, 86-98 (2012).
4. Egawa, H., Furukawa, K., Preston, D. *et al.* Radiation and smoking effects on lung cancer incidence by histological types among atomic bomb survivors. *Radiat. Res.* **178**, 191-201 (2012).
5. Hamatani, K., Mukai, M., Takahashi, K. *et al.* Rearranged anaplastic lymphoma kinase (ALK) gene in adult-onset papillary thyroid cancer amongst atomic bomb survivors. *Thyroid* **22**, 1153-1159 (2012).
6. Neriishi, K., Nakashima, E., Akahoshi, M. *et al.* Radiation dose and cataract surgery incidence in atomic-bomb survivors, 1986-2005. *Radiol.* **265**, 167-174 (2012).
7. Takahashi, I., Abbott, R. D., Oshita, T. *et al.* A prospective follow-up study of the association of radiation exposure with fatal and non-fatal stroke among atomic bomb survivors in Hiroshima and Nagasaki (1980-2003). *BMJ Open* **2**, e000654, doi:10.1136/ (2012).
8. Sera, N., Hida, A., Imaizumi, M. *et al.* The association between chronic kidney disease and cardiovascular disease risk factors in atomic bomb survivors. *Radiat. Res.* **179**, 46-52 (2013).
9. Sakata, R., McGale, P., Grant, E. J. *et al.* Impact of smoking on mortality and life expectancy in Japanese smokers: a prospective cohort study. *Br. Med. J.* **345**, (e7093) (2012).
10. Hayashi, T., Morishita, Y., Khattree, R. *et al.* Evaluation of systemic markers of inflammation in atomic-bomb survivors with special reference to radiation and age effects. *FASEB J.* **26**, 4765-4773 (2012).
11. Kodama, Y., Noda, A., Booth, C. *et al.* International workshop: Radiation effects on mutation in somatic and germline stem cells. *Int. J. Radiat. Biol.* **88**, 501-506 (2012).
12. Cullings, H. M. Recommended improvements to the DS02 dosimetry system's calculation of organ doses and their potential advantages for the Radiation Effects Research Foundation. *Radiat. Protect. Dosim.* **149**, 2-14 (2012).
13. Nakamura, N., Hirai, Y., Kodama, Y. Gamma-ray and neutron dosimetry by EPR and AMS, using tooth enamel from atomic-bomb survivors: A mini review. *Radiat. Protect. Dosim.* **149**, 79-83 (2012).

RERF's Third Public Lecture for Citizens Held in Hiroshima

On Saturday, December 1, RERF held its third public lecture program for citizens at the Memorial Hall in the basement of the Hiroshima Peace Memorial Museum's East Building, from 14:00 to 16:30. About 150 people attended. This open lecture program was first held in 2010 to promote exchange between citizens and RERF by providing readily understandable information to the general public including A-bomb survivors about research achievements obtained at RERF over the years and health effects from radiation. The program has been held every year since then.

Following opening remarks by Chairman Toshiteru Okubo, Mr. Kazumi Matsui, Mayor of Hiroshima and the event's invited guest, extended his greetings. Two lectures followed. First, Dr. Kotaro Ozasa, Chief of the Department of Epidemiology, delivered a lecture titled "Long-term Health Effects of Radiation," explaining the progress and results of RERF's follow-up studies of A-bomb survivors, persons exposed *in utero*, and A-bomb survivors' children. Next, Dr. Yoichiro Kusunoki,

Chief of the Department of Radiobiology/Molecular Epidemiology, in his lecture titled "Mechanistic



Dr. Kotaro Ozasa, Chief of Department of Epidemiology, giving a lecture during the third public lecture program

Study of Health Effects of Radiation,” briefed the audience on research into the mechanisms of radiation effects on health and the significance of such mechanisms, as well as the changes to immune function brought about by radiation exposure.

Thereafter, a question-and-answer session was

held on the basis of audience questions collected after each of the lectures. Not all of the many questions could be responded to in the time available, and thus several audience members remained in the hall eagerly asking questions even after the conclusion of the event.

Biosample Center Newly Established at RERF

RERF’s Biosample Center, newly established and officially incorporated into the foundation’s organizational structure on April 1, 2013, aims at integrated management in a systematic and accessible manner of RERF’s blood, urine, and other biosamples obtained from A-bomb survivors. About 980,000 biosamples currently in the custody of RERF were previously cryopreserved and managed at individual research departments. Now, RERF will keep all biosamples together under centralized management at the Biosample Center. The Center will be able to respond to requests for data from outside research institutions in the future by forming databases of such individual epidemiological data as age, sex, radiation dose, exposure conditions at the time of bombings, and subsequent incidence information, linking that information to the aforementioned biosamples, and then anonymizing the data.

Center facilities were established in both Hiroshima and Nagasaki, with Chief Scientist Dr. Kazunori Kodama assuming the post of Biosample Center Director and taking charge of both facilities. The facilities have seven staff (a research scientist,

five technical staff, including two full-time members, and an administrative worker) in Hiroshima and eight staff (a vice director, a research scientist, five technical staff, and an administrative worker) in Nagasaki. In fiscal 2013, RERF will proceed with organization of the biosamples and maintenance of databases with a view to initiating full-scale operations of the Center in fiscal 2014.



Dr. Toshiteru Okubo (right), Chairman, and Dr. Kazunori Kodama, Chief Scientist and Director of the Biosample Center, affixing the Center nameplate

HICARE Dispatches RERF Chairman and Others to Radiation Exposure Medical Care Seminar in Korea

On February 19, for the first time, the Hiroshima International Council for Health Care of the Radiation-exposed (HICARE) convened the “Radiation Exposure Medical Care Seminar” in Korea. Among a total of four participants dispatched by HICARE from Japan were two RERF representatives: Dr. Toshiteru Okubo, RERF Chairman and HICARE President, and Dr. Kazunori Kodama, RERF Chief Scientist and HICARE Executive Secretary. Held in Seoul, the seminar was designed for physicians, nurses and other medical personnel who engage in providing health care for A-bomb survivors in Korea.



Chairman Toshiteru Okubo (center) and Chief Scientist Kazunori Kodama (second from left) at the seminar in Seoul

HICARE has organized similar seminars in the U.S. and Brazil, but this is the first seminar staged jointly overseas with the Nagasaki Association for Hibakusha's Medical Care (NASHIM), which has experience hosting seminars and training sessions for Korean physicians and others.

The other two participants were Dr. Koichi Tanigawa, Professor in the Department of Emergency and Critical Care Medicine at the Hiroshima University Graduate School of Biomedical Sciences and HICARE Executive Secretary, and Dr. Yasushi Miyazaki, Professor at the Nagasaki University Graduate School of Biomedical Sciences and NASHIM Operating Committee member, both of whom presented lectures at the seminar. They spoke about the latest findings from health-effects studies of A-bomb survivors in Hiroshima and Nagasaki, and discussed responses to the Fukushima Dai-ichi nuclear power plant accident.

Approximately 3,000 A-bomb survivors reside in Korea. However, 67 years have passed since the atomic bombings, and these survivors are aging. One goal of the seminar was to foster an environment that ensures appropriate medical care for A-bomb survivors on a consistent basis. Another

goal was to respond to the heightened consciousness in Korea about health effects from radiation against the backdrop of the nuclear accident in Fukushima. To accomplish these goals, HICARE and NASHIM approached the Korea Institute of Radiological Medical Sciences (a national radiological research institute) and the Korean Red Cross for help in organizing the seminar. The four HICARE representatives visited these institutes before and after the seminar to exchange views about the possibility of enhanced collaboration and to establish collaborative systems such as for the acceptance of trainees from Korea.

As part of the national government's support operations for A-bomb survivors living outside Japan, Nagasaki Prefecture and Nagasaki City began dispatching a medical team to Korea to provide consultation twice a year, starting in 2004. Dr. Masazumi Akahoshi, former Chief of the Department of Clinical Studies in Nagasaki, often participated in the medical team on behalf of RERF (refer to a separate article by Dr. Akahoshi regarding this project in *RERF Update* Vol. 20, Issue 2, 2009).

Dr. Warren Muir of NAS Retires—New Executive Director of RERF-support Division Appointed

**Evan B. Douple, former Associate Chief of Research
Roy E. Shore, Vice Chairman**

Scientific support for RERF has been provided by the National Academy of Sciences (NAS) and the National Research Council (NRC) component of the National Academies since the establishment of the Atomic Bomb Casualty Commission (ABCC) following the request signed by President Truman 67 years ago. That support and involvement has been a key element in providing independent scientific leadership and guidance. The office at NAS responsible for recruiting U.S. scientists to work at RERF or to serve as advisors to RERF resided initially in the Institute of Medicine's Medical Follow-up Agency, later in the NRC's Board on Radiation Effects Research (BRER), and currently in the Nuclear and Radiation Studies Board (NRSB). The NRC's Division on Earth and Life Studies (DELS) oversees Academy work in the environmental, life, and chemical sciences, including that of NRSB and previously BRER. The first Executive Director of DELS, Dr. Warren R. Muir, recently retired

after 12 years in that position.

Dr. Muir was recently described by NAS President Ralph Cicerone as "a creative and energetic



From right, Dr. Warren R. Muir, Dr. Kevin D. Crowley (NAS), Dr. Shelley A. Hearne (RERF Councilor), Dr. Roy E. Shore, and Dr. Evan B. Douple at the time of the June 2010 Board of Directors meeting in Nagasaki

leader who has been a strong advocate for the role of science in the development of public policy.” He has been a strong supporter of RERF and annually attended the RERF Scientific Advisory Committee or Board of Councilors meetings. Warren championed RERF’s mission and sought to increase its public visibility. He was particularly interested in the humanitarian aspect of the RERF study since he frequently pointed out that the scientific results potentially could benefit the survivors and all of humanity. That interest was probably influenced by his personal “extracurricular” work for peace in a project in Northern Ireland and another in Cyprus—where he has devoted considerable energy and time leading two nonprofit organizations that promote trust, understanding, and friendship between teenage leaders from the divided communities in the two locations. Warren retired from NAS to his home in New Hampshire and sends his best wishes for the future success of RERF. We at RERF will miss him.

However, we are glad for continued strong support under new leadership. After a nationwide search, Dr. Gregory H. Symmes was appointed as Warren’s successor early in 2013. He was viewed as a popular choice by many of Dr. Symmes’ NAS colleagues, who were familiar with Greg’s strong

work ethic, pleasant and soft-spoken style, shrewd judgment, and broad scientific experience. He received his BA *summa cum laude* in geology from Amherst College and his PhD in geology from Johns Hopkins University. Greg first joined the NRC in 1995 and has directed NRC programs



Gregory H. Symmes, PhD

and studies on a wide range of science and technology policy issues. He had risen to the position of Deputy Executive Director of DELS when he was selected to be Warren’s successor. Dr. Symmes especially appreciated his first visit to RERF to attend the Scientific Advisory Committee meeting in March of this year where he was able to receive an overview of RERF’s studies and an update of the most recent findings. He is looking forward to providing assistance to RERF through DELS’ oversight of the NRSB and its Director, Dr. Kevin Crowley, and to making himself available should special RERF needs arise.

Students from the U.S. BCA and Dr. Charles J. Camarda of NASA Visit RERF

On November 20, two teachers and eight students from Bergen County Academies (BCA), a high school located in the U.S. state of New Jersey, visited the Hiroshima Laboratory, led by teachers from the Hiroshima Prefectural Kokutaiji Senior High School, as part of the “Super Science High Schools” project of the Ministry of Education, Culture, Sports, Science and Technology (MEXT). The group was accompanied by Dr. Charles J. Camarda, of the U.S. National Aeronautics and Space Administration (NASA), who was visiting Hiroshima. After receiving briefings on RERF and RERF’s recent research achievements from Mr. Takanobu Teramoto, RERF Executive Director, and Dr. Roy E. Shore, RERF Vice Chairman, respectively, the visitors listened to an explanation by Dr. Yoichiro Kusunoki, Chief of the Department of Radiobiology/Molecular Epidemiology, about mechanistic research into radiation-associated disease development and also watched a demonstra-

tion of a cell sorter (laboratory equipment used for instant analysis of blood cell properties and DNA statuses at the cellular level, and for high-speed extraction of targeted cells).



BCA students watching cell sorter demonstration by Dr. Yoichiro Kusunoki (far left)

U.S. Journalism Students Visit RERF to Learn about Radiation for Reporting on Fukushima

On March 13, two journalism students from Indiana University (IU), located in Bloomington, Indiana, visited the Hiroshima Laboratory. Yao Xiao and Megan Jula belonged to a student group from an IU international reporting class that had traveled to Japan to learn about the atomic bombings of Hiroshima and Nagasaki and how RERF's research has been utilized in Fukushima.

Yao and Megan interviewed Drs. Eric Grant and Hiromi Sugiyama of the Epidemiology Department about RERF's findings and were provided with an abbreviated facility tour. In Hiroshima, in the days before their RERF visit, the two interviewed Mr. Steven Leeper, then Chairperson of the Board of Directors of the Hiroshima Peace Culture Foundation and former member of RERF's Hiroshima Local Liaison Council, and toured the Peace Memorial Museum as well as met with several A-bomb survivors. In Tokyo, at the start of their trip, their itinerary included meeting with Fukushima refugees.

After returning to Indiana, both wrote to RERF about their experience, emphasizing how much they enjoyed Japan and the importance of the infor-

mation obtained at RERF to the writing of their stories. RERF strives to accommodate requests for cooperation in educational activities. We wish Yao and Megan the best with their projects and look forward to seeing how their RERF experience plays out in their future careers. We hope their visit inspires others to contact RERF for information related to radiation's health effects.



Students, at left, listening to explanation about radiation's health effects

Staff News

As reported in *Staff News* in the last issue (Vol. 23, Issue 2, 2012), **Evan B. Douple**, Associate Chief of Research, and **Nori Nakamura**, Chief Scientist, both retired as of December 31, 2012. Dr. Douple, who served at RERF for five years as a staff member of the National Academy of Sciences (NAS), returned to Washington, D.C., where he recently was awarded at a retirement dinner for his 20 years of work at NAS. Dr. Nakamura was reappointed as Consultant to the Department of Genetics effective January 1 of this year. **Yuko Hirai**, Chief of the Cytogenetics Laboratory, Department of Genetics, and **Kazue Imai**, Associate Senior Scientist, Department of Radiobiology/Molecular Epidemiology (RME), retired under the mandatory age limit as of December 31. Dr. Hirai was reappointed as Adjunct Specialist (research scientist) effective January 1, in order to continue research at the Cytogenetics Laboratory. Although Dr. Imai returned to Tokyo, she was appointed as Consultant to the RME Department as of January 1. Research Scientist **Eiji Katsurada**, Department of Clinical Studies (Hiroshima), resigned upon

term expiration as of March 31, and **Masazumi Akahoshi**, Chief, Department of Clinical Studies (Nagasaki), resigned effective March 31. Dr. Akahoshi assumed the position of Deputy Director at Keiju Hospital of the healthcare association Wakokai as of April 1, and was also reappointed as Consultant to the RERF Department of Clinical Studies effective May 1.

On the other hand, four new research scientists were hired at RERF. **Young Min Kim** joined the Department of Statistics as a research scientist as of February 12. **Daisuke Haruta** joined the Department of Clinical Studies (Nagasaki) as a research scientist, and **Masayuki Hidaka** and **Yiqun Hu** joined the Departments of Genetics and RME, respectively, as postdoctoral scientists effective April 1.

Kazunori Kodama, Chief Scientist, was concurrently appointed on April 1 as Director of the Biosample Center, newly established as of the same date (see related article on page 5). **Tomonori Hayashi**, Assistant Chief of the RME Department, and **Misa Imaizumi**, Chief of the Divisions of

Radiology and Clinical Laboratories (Nagasaki), were concurrently appointed as research scientists of the Center on April 1.

In April every year, RERF presents awards to employees for their long-term service. This year, 19 employees were awarded in Hiroshima and 10 in Nagasaki. Among them, **Eiji Nakashima**, Assistant Chief, Statistics Department, and **Michiko Yamada**, Chief, Division of Health Examinations, Department of Clinical Studies (Hiroshima), were awarded for 30 years of service. **Asao Noda**, Assistant Chief, Genetics Department, was awarded for his 10 years of service.

The abovementioned four new research scientists introduce themselves in the following section:

Young Min Kim, PhD

I started working for the Department of Statistics as a research scientist on February 12, 2013. I was born in Seoul, the Republic of Korea. I studied statistics at Yonsei University for bachelor's and master's degrees and obtained a PhD last year at Iowa State University in the USA. My dissertation topic was nonparametric methods such as bootstrap and empirical likelihood methods for dependent data. I also studied kernel-based nonparametric estimation and regression methods. Before I joined RERF, I worked for the Department of Biostatistics, University at Buffalo (UB), State University of New York as a post-doctoral associate. I have developed statistical methodologies for Exact Tests using nonparametric Bayesian methods and quantile regression applied to analysis of biomarker data.

Dr. Randolph Carter, a former research scientist of and currently a consultant to the RERF Statistics Department, as well as a professor at the Department of Biostatistics, UB, introduced me to RERF, and Dr. Harry Cullings, the Statistics Department Chief, visited UB and told students and me in more detail about RERF's work. I then applied for the position here. There were several reasons I was interested in RERF: 1) I had been interested in radiation effects and nuclear issues since I was a freshman at Yonsei University. However, I could not be involved in those topics when I was studying statistics. RERF will give me a chance to now do research related to these fields. 2) I had focused on the development of theoretical statistical methodologies, not on statistical application, before I joined RERF. Since RERF is one of the biggest such institutions in the world and has a lot of data, I can work with such real data and contribute to RERF research with my background in various statistical



Young Min Kim

methodologies. 3) RERF is in Japan, which is close to my home of Korea. That means my parents are relatively close. 4) In addition, I am interested in learning new cultures, in particular, Japanese culture, because I am a fan of Japanese *manga*, books, and TV dramas. Thirteen years ago when I was a university student, I thought that someday I would learn Japanese. And now, this appears to be the time, finally, to do so.

I am honored to have the opportunity to carry on the research mission of RERF as a statistician and develop statistical methodologies related to RERF projects. I would like to get to know the people at RERF as soon as possible, and I look forward to listening to everyone's advice and guidance regarding my research and life in Hiroshima, Japan. I appreciate your support in advance.

Daisuke Haruta, MD, PhD

My name is Daisuke Haruta, and I joined the Department of Clinical Studies at RERF in Nagasaki as a research scientist on April 1, 2013. After graduating from Oita University School of Medicine in 2002, I worked at the Department of Cardiovascular Internal Medicine (formerly the 3rd Internal Medicine Department) of Nagasaki University. I then worked as a cardiovascular specialist at the Nagasaki Atomic-bomb Survivors Hospital, Nagasaki Neurological Medical Center, Usa-Takada Hospital, and other Nagasaki University-affiliated hospitals. In 2007, I started studying as a graduate student at Nagasaki University as I continued to work. While in graduate school and working as an internist, I conducted an epidemiological study of arrhythmia-related symptoms (Brugada syndrome and early repolarization syndrome) for four years as a visiting research fellow at RERF. For this study, I spent over a year reading 50 years' worth of ECG recordings of about 6,000 A-bomb survivors. I can still recall those days being impressed by the long-term participation of A-bomb survivors in the health examination program and the tremendous efforts made by RERF staff to accumulate data. Each of the medical charts I reviewed contained the life stories of A-bomb survivors. During those four years, I was able to experience the hardship of conducting research and the joy of publishing a paper in a journal. These experiences were invaluable to me. I would like to take this opportunity to express my sincere appreciation again to Dr. Masazumi Akahoshi, former Chief of the Department of Clinical Studies in Nagasaki, and other RERF staff members for their support and cooperation.



Daisuke Haruta

At just about the same time that I completed graduate school, the Great East Japan Earthquake struck. Since the earthquake, much attention has been focused on the Fukushima Dai-ichi nuclear power plant accident and the health effects from radioactive substances released as a result of the accident. This prompted me to think that I might be able to make a contribution to society different from my usual role as a physician engaging in medical treatment in a clinical setting. For this reason, I feel highly motivated to continue research at RERF, a long-standing research organization where I feel privileged to work as a research scientist. Being a novice in this field, my abilities are limited; however, I am determined to make utmost efforts to contribute to the further development of RERF research. I look to all of you for your guidance and support.

Masayuki Hidaka, PhD

Greetings to the staff of RERF. My name is Masayuki Hidaka, and I joined the Laboratory of Cytogenetics in the Department of Genetics on April 1 this year.

I completed my doctoral program at the Graduate School of Frontier Sciences, the University of Tokyo, in March 2010. In the doctoral program, I investigated DNA damage responses, such as DNA repair, apoptosis, and cell cycle, using a radiation-sensitive mutant RIC1 strain of Japanese killifish, as well as ATM (-/-) or p53 (-/-) killifish. This became the focus of my PhD research. After completing the doctoral program, I conducted research on new virus-based cancer therapies at the Department of Neurosurgery, the University of Tokyo Hospital. I also examined the physical and chemical properties of pharmaceutical drugs and their effects on the immune complement system at the National Institute of Health Sciences.

After obtaining my PhD, I moved away from radiation research. However, the Fukushima nuclear power plant accident in March 2011 made me want to contribute to society through research in the field of radiobiology. In thinking of possible ways to have an opportunity to do this, I came up with the idea of being certified as a senior radiation protection supervisor. I passed the examination in 2012. When I informed Prof. Hiroshi Mitani, my mentor at the graduate school, of my new qualification, he kindly suggested to me that I apply for a research position at RERF. Guided by fate, I joined RERF.

The first scientific meeting I attended after I started engaging in research was the annual meet-



Masayuki Hidaka

ing of the Japan Radiation Research Society, held in Hiroshima in 2005. I probably have a predestined affinity to Hiroshima. Every day since I began living in Hiroshima, I have felt thankful to the local residents, who have been very hospitable and kind to me. The RERF staff have also been kind to me, and thanks to their support, I have been able to make a promising start. I intend to make efforts to deepen my understanding of radiation effects, first by having a deep understanding of the significance of my studies, and then by making steady progress, step by step, to convey the outcome of the studies to society, with the aim of contributing to “global happiness.” I look to all of you for your guidance and support.

Yiqun Hu, PhD

I am from Hubei province of the People’s Republic of China. The name of the province means “north of the lake,” referring to its position north of Lake Dongting, a large lake located in neighboring Hunan province. The climate in Hubei is similar to that in Hiroshima, with four distinct seasons. Summers are hot and humid, with punishing temperatures of 40°C or above famously associated with Wuhan, the provincial capital. The city of Wuhan feels like a furnace in the summer.

After graduating from my university in China with a bachelor’s degree in dentistry, I came to Japan in 2007 to start my study abroad. It has been almost five-and-a-half years since I first arrived in Hiroshima, and I still remember that I had many troubles in my studies and daily life my first year in Hiroshima. But all of the Japanese people I met were so kind to me. There was a volunteer who taught me Japanese every week for free. I learned about Japanese language and culture from her. The most wonderful thing was that I met a very lovely Japanese couple, who invited me to their home and fed me Japanese home cooking. Sometimes we went out together to see the sights of Hiroshima. I will cherish those memories in my heart forever. Since Hiroshima is the first city that I lived in after leaving Hubei, I consider it my second home.

After one year as a research student at Hiroshima University, I started my PhD course under the advisors Prof. Katsuyuki Kozai (Pediatric Dentistry) and Prof. Motoyuki Sugai (Oral Bacteriology), finishing the program in 2012. Since the work of my PhD program focused on application of bacterial cell wall hydrolase for prevention of disease, I have had for some time an interest in the field of molecular epidemiology. Therefore, I wanted to continue my research in Japan even after graduation, espe-



Yiqun Hu

cially in the field of epidemiology. Thanks to the help I received from Dr. Tomonori Hayashi, Assistant Chief, Department of Radiobiology/Molecular Epidemiology (RME), I now have the opportunity to continue my research as I had hoped.

I am very grateful and fortunate to be accepted as a postdoctoral scientist at this prestigious institute of RERF. RERF has long enjoyed a good reputation in epidemiology. Thus, it will be exciting for

me to do research with RERF's renowned scientists. It is also my great honor to have the opportunity to learn many research ideas from them. I just recently joined the Immunology Laboratory in the RME Department on April 1. It will take time before I am able to accomplish my mission of contributing to RERF's future. In closing, I would like to thank all of RERF's staff and scientists, who have accepted me warmly!

Visiting Student Researcher

Ms. Seung Hyun Hong, Research Scientist at the National Cancer Center, Korea, underwent training at the Departments of Radiobiology/Molecular Epidemiology (RME) and Genetics for a period of about two months, from January 7 to February 22, 2013. The following is her self-introduction and remarks about her training at RERF.

Seung Hyun Hong

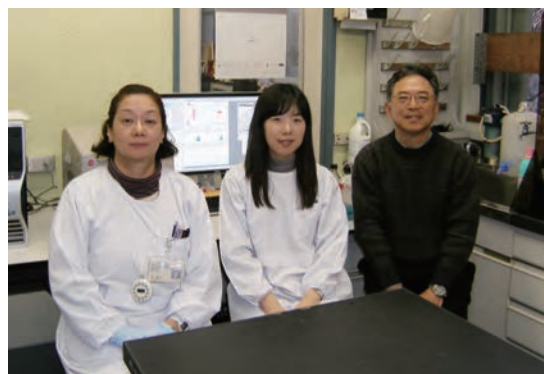
I am a research scientist at the Cancer Genomics Branch, National Cancer Center in Goyang, Korea. Korea is a wonderful country with four different seasons, each of them beautiful with vastly different scenery. There are very many wonderful places in Korea, among them Jeju Island, which is registered as a UNESCO World Heritage Site.

I studied molecular biology at university. I also finished my master's degree in life and pharmaceutical sciences in 2011 and then joined our laboratory at the National Cancer Center. I studied about the effects of radiation exposure and DNA damage on carcinogenesis and immune function. I was recommended to participate in the scientific exchange program at RERF by Dr. Joo Young Kim, Director of the Radiation Therapy Center of the National Cancer Center. I would like to thank RERF for giving me an opportunity to participate in this training.

During my two-month stay, I trained in various experiments such as the effects of radiation exposure on immune function, *HLA* (*human leukocyte*

antigen) genotyping and FISH (fluorescence *in situ* hybridization) assay at RME and the Department of Genetics. It was a valuable experience for me to study and work at RERF, and I feel that the experience will play a very important role in my future studies.

I am very grateful for the chance I was given here at RERF and would like to express my appreciation to the research scientists and administrative staff who have helped me during my stay in Hiroshima, especially Dr. Tomonori Hayashi, Assistant Chief of RME, who served as my supervisor.



Ms. Seung Hyun Hong (center) with Dr. Tomonori Hayashi (far right), Assistant Chief of RME, and Ms. Misae Sora, Assistant Chief of Technicians, in front of the Immunology Laboratory's flow cytometer

Award Received by RERF Scientist

Upon Receiving the Incentive Award for Young Researchers at the 24th Meeting of the Japan Geriatrics Society Chugoku-district Branch

**Ikuno Takahashi, Research Scientist
Department of Clinical Studies, Hiroshima**

At the 24th meeting of the Japan Geriatrics Society Chugoku-district Branch, held in Hiroshima on November 24, 2012, I was presented with the incentive award for young researchers.

It has already been suggested that high levels of height loss compared to an individual's height in youth are associated with increased risk for cardiovascular disease mortality, but the mechanisms behind the effects of height loss on cardiac blood vessels are still unknown. Meanwhile, studies conducted by other research institutes recently reported that changing patterns of blood flow (pulse wave) in longitudinal blood vessels (large arteries) in the trunk of the body strained the heart and were associated with liability to cardiovascular disease. Consequently, we reviewed the association between the augmentation index, which measures pulse wave changes, and height loss based on the RERF's Adult Health Study (AHS). Our research suggested the possibility that height loss might cause pulse wave changes. Based on the relevant results, my presentation, "Review of effects of height loss on the cardiovascular system," was awarded at the aforementioned meeting.

Age-related changes in the physique are inevitable. In cases where people are prone to life-threatening disease (cardiovascular disease) due to changes in the physique, however, methods of preventing such disease represent an important issue. To solve this problem, it is necessary to determine the mechanisms behind the effects of change in the physique upon the cardiovascular system. However, there is a tendency to deal separately with multiple diseases observed in one person: for example, spinal deformity/fracture causing height loss is categorized into the field of orthopedics, and cardiovascular disease into the field of internal medicine. For the purpose of deepening understanding and discovering new aspects of the mechanisms behind disease, it will become increasingly necessary to pay attention to the big picture.



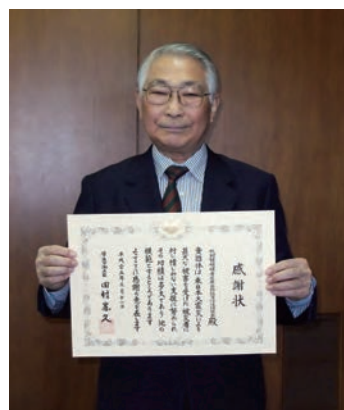
Dr. Ikuno Takahashi, Research Scientist, with her award

The AHS has been utilized in the study of various aspects of abnormalities in different organs to examine the effects of radiation exposure on human health. Without the understanding and cooperation of the AHS participants, it would have been impossible to implement the globally-unique AHS study methods. As demonstrated by the research described above, it might be said that AHS is an important study not only for assessment of radiation effects but also for elucidation of unknown mechanisms behind disease. The study I presented at the Japan Geriatrics Society would not have been possible without AHS, and I believe that the branch society appreciated this point, leading to their presentation of the award to me. I would like to express my heartfelt appreciation for support from the Departments of Clinical Studies in Hiroshima and Nagasaki, the Department of Information Technology, and the many others who contributed, in addition to cooperation of the AHS participants. I hope to make further efforts to play a role in the distribution of information from RERF.

RERF Receives Health, Labour and Welfare Minister's Certificate of Appreciation

RERF recently received a certificate of appreciation from the Health, Labour and Welfare Minister for its contributions to the Ministry of Health, Labour and Welfare (MHLW) Health Service Bureau's projects related to the March 2011 Great East Japan Earthquake. On April 22, 2013, Mr. Hisayuki Dehara, Chief, Atomic Bomb Survivors Support Division, Health and Welfare Affairs Bureau, Hiroshima Prefecture visited RERF and presented the certificate on behalf of the national government to Dr. Toshiteru Okubo, RERF Chairman. The certificate, dated March 11, 2013, the second anniversary of the disaster, was awarded to 1,458 organizations in recognition of their cooperation in disaster victim support activities managed by MHLW's Health Policy Bureau, Health Service Bureau, Pharmaceutical and Food Safety Bureau, and Labour Standards Bureau, among others. Information about RERF's support activities is available in the second issue of *RERF Update*

2011. An updated report of our support activities is also available on the RERF website at <http://www.rerf.jp/fukushimaRERF.pdf>.



Chairman Toshiteru Okubo holding the Health, Labour and Welfare Minister's certificate of appreciation

RERF International Workshop: Heavy Structural Shielding

On February 4 and 5, 2013, an international workshop was held at RERF on radiation dose calculation for survivors who had heavy structural shielding. Heavy structural shielding refers to concrete buildings or underground air-raid shelters. Nearly all of the air-raid shelters were located in Nagasaki and consisted of tunnels dug into the side of a hill, or other, similar underground spaces. The dosimetry systems DS86 and DS02 do not contain modules for calculating the structural shielding of survivors in such situations, and those survivors have therefore been considered to have unknown doses, which represent missing values for dosimetric variables in RERF analyses. (Regarding the more general issue of unknown doses, see the *Facts and Figures* article in this issue of *Update* on page 30.) The calculation of shielding for heavy or underground structures involves special problems that do not occur with light wooden structures such as houses, for which the shielding is calculated by DS86 and DS02. In light of this situation, the RERF Dosimetry Committee decided to hold a workshop to discuss these problems and the feasibility of calculating doses for such survivors.

Harry M. Cullings, Chief Department of Statistics

Opening remarks were given by Dr. Kazunori Kodama of RERF, and Dr. Stephen D. Egbert of Science Applications International Corporation (SAIC) provided a key lecture for the workshop. Dr. Satoru Endo of Hiroshima University and Dr. Tetsuji Imanaka of the Kyoto University Reactor Research Center served as discussants. Presentations were also made by a number of RERF researchers and staff, including Mr. Tadaaki Watanabe, Mr. Tomoaki Yamashita, Mr. Takashi Oda, Mr. Hiroshi Fuchi, and Dr. Harry M. Cullings. The workshop concluded with detailed discussions and a hands-on demonstration of the models and tools used at RERF in the 1960s to produce "Globe" (spherical coordinates) data on the shielding of survivors in concrete buildings.

Mr. Watanabe reviewed the categories of survivors with unknown doses, Mr. Oda reviewed detailed data on concrete buildings, and Mr. Fuchi reviewed detailed data on air-raid shelters. Of 7,070 survivors in the Life Span Study (LSS) with unknown dose, an estimated 3,729 were in either concrete buildings (2,114) or air-raid shelters (1,615). There were at the time 24 concrete build-

ings in Hiroshima and 37 in Nagasaki, but many buildings contained only a few survivors, whereas a few contained many survivors. In regard to feasibility of dose calculation, almost all of the concrete buildings in Hiroshima have floor plans available, but very few of the survivors in those buildings have shielding histories that depict their location within the buildings: 979 of 1,272 survivors in concrete buildings in Hiroshima were in buildings with floor plans, but only 218 of those 979 have shielding histories. In Nagasaki, a larger fraction of survivors have shielding histories but far fewer of the concrete buildings have floor plans: 255 of 842 survivors were in buildings with floor plans, and 166 of those 255 have shielding histories. In the case of air-raid shelters, detailed floor plans and

architectural drawings may not be necessary for dose calculation, but few survivors have shielding histories depicting their location within the shelter: 1,488 of the 1,615 survivors in air-raid shelters were in Nagasaki, and only 247 of those 1,488 have shielding histories. The table indicated below gives details for individual buildings in terms of the existence of floor plans and the numbers of survivors with and without shielding histories.

Doses in concrete structures vary greatly depending on the exact position of survivors within the structure for which the doses are calculated. In order to calculate doses to survivors in a heavy-shielding structure, the dosimetry system would need to calculate “shielded fluences”: numbers of neutrons and gamma rays in categories of energy

Table. Details of occupants in concrete buildings

Bldg No.	Hiroshima			Nagasaki		
	Floor plan*	SH**	No SH	Floor plan	SH	No SH
1	1	3	0	0	38	6
2	1	2	1	1	13	1
3	1	3	5	0	1	0
4	1	7	10	1	10	3
5	1	1	1	0	2	0
6	1	1	1	1	6	0
7	1	25	21	1	2	1
8	1	33	16	0	2	1
9	1	50	41	1	4	1
10	0	2	5	1	2	0
11	1	5	15	0	2	1
12	1	2	2	1	2	3
13	1	13	147	0	2	0
14	1	4	9	0	4	2
15	1	0	4	0	6	3
16	0	0	2	0	1	0
17	1	6	87	0	50	7
18	0	0	10	0	39	15
19	0	2	33	0	7	0
20	1	1	86	0	1	0
21	1	49	207	1	74	61
22	1	1	97	0	19	22
23	1	0	23	0	6	4
24	0	0	118	0	11	6
25				0	4	1
26				1	33	15
27				0	1	0
28				0	26	5
29				0	45	20
30				1	4	3
31				1	7	0
32				1	6	1
33				1	3	0
34				0	1	4
35				0	2	20
36				0	6	36
37				0	11	45
“Others”	0	8	113	0	2	100
Total	19	218	1,054	13	455	387

*1 = floor plan available, 0 = no floor plan; **Shielding History (gives location within building)

and direction, at various locations in the structure. There are two main problems, essentially matters of practicality, in calculating shielded fluences within concrete buildings. One problem is that heavy shielding requires a more difficult calculation: because so few of the neutrons and gamma rays impinging on the building pass through to create dose in the more heavily shielded interior locations of interest, it may require very large amounts of computer time, accurate geometries, and sophisticated biasing (putting more effort on those portions of the incident fluences that lead to the majority of the shielded fluences in the locations of interest) to do calculations with acceptable accuracy and precision. The other problem is that, unlike the Japanese houses considered by the dosimetry systems, each concrete building and each air-raid shelter is unique, which means it is necessary to build a detailed computational model and do a suite of calculations for each building or shelter. Furthermore, because the shielded fluences in a heavy structure depend so acutely on the exact survivor location within the structure, additional problems, discussed below, arise in calculating dose estimates for survivors.

Dr. Egbert gave an extensive review of the kinds of computational programs and related software that are available for such calculations. He began by illustrating the dosimetry method used in the current system and then reviewing two important papers from 1992 in which doses were calculated for the occupants of two concrete school buildings in Nagasaki.^{1,2} These papers used methods much like those that would be used in a contemporary calculation and illustrated a number of important principles that would apply directly to the problems under consideration by RERF.

There are two basic computational approaches to the shielding calculation: Monte Carlo and discrete ordinates. Monte Carlo works by creating “particle histories” of neutrons and gamma rays, using rules of probability to propagate individual,

imaginary neutrons or gamma rays through the shielding. Because neutrons can be captured or scattered in interactions that produce gamma rays, neutron scattering may give rise to new gamma rays according to certain probabilities. Monte Carlo is “an approximate solution to an exact problem”: it can handle a very detailed model of the building, but very few histories end up delivering dose at the location of interest, and it is difficult to obtain enough such histories at any location, let alone to map out the dose environment in the entire building. The discrete-ordinates approach works by partitioning the building into imaginary cells that constitute a “spatial mesh” and calculating differential flows of neutrons and gamma rays through the mesh. It is “an exact solution to an approximate problem”: it provides solutions in every location defined by the center of a cell in the spatial mesh, but it is difficult to make the mesh fine enough to include sufficient detail of the building’s structure and it is also difficult to avoid computational artifacts such as “ray effects.” Dr. Egbert reviewed software packages of each method and also hybrid approaches that combine them.

Dr. Cullings reviewed several concerns relating to the statistical properties of dose estimates that appear to be possible for survivors in heavy shielding, particularly in concrete buildings, assuming that the computational problems can be solved, i.e., assuming that sufficient funding is available for acceptably precise estimates at *known locations* within a building. Many of the concrete buildings were at distances from the bombs where the unshielded dose was well above lethal levels, such that shielded doses inside the buildings could span a large range from sublethal to supralethal levels. For example, the doses inside the Chinzei School calculated by Rhoades *et al.*¹ ranged from 0.2 Gy or less at positions deep in the first floor to well above 30 Gy near the windows on the second floor, and the dose gradients as a function of location within the building are correspondingly steep. As a consequence, the fact of survival contains information about the survivor’s likely position within the building and the corresponding dose: the more lethal the dose in a given location, the less likely it is that a person who survived was in that location. For survivors who lack shielding histories to document their position (location within the building), it may be difficult or impossible to obtain a reliably unbiased estimate of dose—for example, a simple spatial average over a building containing lethal



RERF International Workshop: Heavy Structural Shielding held at Hiroshima RERF

or supralethal doses in some areas would clearly be a biased overestimate. Even for survivors with shielding histories, the positional uncertainty may result in substantial dose uncertainty. In the case of the doses calculated by Rhoades *et al.*,¹ who had extremely good position information, the estimated positional uncertainty was between 30 and 90 cm in each of two horizontal directions, and the corresponding dose uncertainty was between about 3% and 56%, although almost all estimates had uncertainty of less than 30%.

In some sense a concrete building is a microcosm of the entire city, given the range of doses possible in the building and the dose uncertainty due to positional uncertainty, and there would be a need for a method to account for that dose uncertainty as is currently available for other survivors with “known” doses. There are few if any buildings that have enough surviving occupants with shielding histories to allow the dose estimates of the survivors in a building to serve as a useful estimate of the frequency distribution of doses among all possible survivors in that building. Furthermore, such estimates would be clouded by the positional uncertainty of the survivors with shielding histories, and the need to assume that the survivors with shielding histories would have the same spatial distribution as the full complement of all survivors from a building in which the occupants, including those who did not survive, were evenly distributed throughout all occupiable parts of the building. As these are likely to be untenable conditions and assumptions, one would need to consider something such as a Bayesian approach for the survivors without shielding histories. Both that approach and the method of accounting for dose uncertainty among those *with* shielding histories would have to rely on additional information such as the median lethal dose estimated by Levin *et al.*,² with the attendant concerns about the accuracy of that estimate and the caveat that it applies only to survivors without any concomitant injury from heat or blast trauma.

Mr. Watanabe and Mr. Oda provided a demonstration of the spherical-coordinates projector and related tools that were used in the 1960s, with scale models of the buildings and shelters, to collect “Globe” data on the shielding in various directions for survivors in heavy shielding. Those data were used in the tentative dosimetry system T65D to calculate doses, although they were considered “rough estimates” by Dr. J. S. Cheka of Oak Ridge National Laboratory in the U.S.,³ who was a leading dosimetry physicist associated with the effort, and were considered not to be reliably accurate by Mr. Seymour Jablon.⁴ The ensuing discussion clarified that, unfortunately, there is no apparent way to use the Globe data for survivors in concrete buildings, because each such building is unique. There-

fore, we cannot do something analogous to what was done in DS86 and DS02 in using Globe data for survivors who were outside but near wooden houses. To devise a similar method for concrete buildings, we would calculate the doses for various positions in a model concrete building and then use the Globe data for those positions and for survivors in actual concrete buildings to relate the cases of the actual survivors to positions in the model building. However, we cannot make a model concrete building that capably represents all of the various buildings of interest.

A further general discussion on feasibility of dose calculation was held. Dr. Egbert pointed out that calculations would require detailed structural data for a building, including the thickness of walls and floor slabs, the dimensions and locations of windows, the details of any other massive structures such as pillars and beams, and the elemental compositions of all the related materials. It appears that work on the heavy shielding problem may continue with performance of calculations for some example buildings to evaluate feasibility.

I would like to thank the participants of the workshop, especially Dr. Egbert, and Dr. Douglas E. Peplow of Oak Ridge National Laboratory for granting permission for Dr. Egbert to use his instructional materials on shielding calculation, the members of the RERF Master File Section who prepared detailed materials and excellent illustrations of the available data, and the members of the Departments of Statistics and Epidemiology, as well as others at RERF who supported the workshop. Dr. George D. Kerr, an important investigator in this area, was unfortunately not able to attend the workshop, but we would like to recognize his contributions to work on this problem over the years, starting with work he did with Globe data and T65D.

References

1. Rhoades WA, Childs RL, Ingersoll DT. Radiation exposure inside reinforced concrete buildings at Nagasaki. *Health Phys.* 63: 510-21; 1992.
2. Levin SG, Young RW, Stohler RL. Estimation of median human lethal radiation dose computed from data on occupants of reinforced concrete structures in Nagasaki, Japan. *Health Phys.* 63: 522-31; 1992.
3. ABCC Interoffice Memorandum dated 22 September 1970, from Mr. M. Usagawa of the Statistics Department to Mr. Yoshida, re revision of CD#575: code for globe operation for subjects exposed inside concrete building on class of estimating dose.
4. Jablon S. ABCC Technical Report No. 23-71: Atomic bomb radiation dose estimation at ABCC. Atomic Bomb Casualty Commission, Hiroshima and Nagasaki, Japan, 1971.

RERF Hosts International Workshop on Radiation and Cardiovascular Disease

**Waka Ohishi, Acting Chief
Department of Clinical Studies, Hiroshima**

The RERF Department of Clinical Studies, with the help of the Cardiovascular Disease (CVD) Working Group, hosted a two-day international workshop titled “Radiation and Cardiovascular Disease” on February 5 and 6, 2013, in the auditorium of the Hiroshima RERF.

Recent results of the Life Span Study (LSS) have showed that increased mortality risk from heart disease and stroke is associated with radiation dose. Looking at the risk by subtype showed no significant association with ischemic heart disease, cerebral infarction, cerebral hemorrhage, or subarachnoid hemorrhage, whereas significant associations between radiation dose and hypertensive heart disease, rheumatic heart disease, and heart failure were observed. In addition, increased risk of myocardial infarction has been observed in the Adult Health Study (AHS), for example, among female survivors exposed to over 2 Gy at less than 40 years of age. Although no consistent trend has been observed with regard to stroke, recent reports indicate that the risk of hemorrhagic stroke increases with radiation dose in both males and females.

Based on this background, experts in relevant fields in Japan and abroad, along with RERF research scientists, made presentations at the workshop to discuss the following questions: What is consistent or inconsistent in the study results for radiation-associated CVD? What mechanisms are important for radiation-associated CVD at high- and low-dose exposures? What are the measurable indicators for evaluation of radiation-associated CVD? Which statistical methods are useful for evaluating radiation-associated CVD risk?

On the first day of the workshop, Dr. Fred A. Mettler, Jr. (Clinical and Emeritus Professor, Department of Radiology, University of New Mexico) offered a broad-based review of findings and problems pertaining to radiation risk and cardiovascular disease. He spoke from the viewpoint of general concepts and studies of radiation therapy, radiation workers, A-bomb survivors, and animal experiments. Subsequently, Dr. Kotaro Ozasa (Chief, RERF Department of Epidemiology) gave a lecture titled “Epidemiological Studies of Cardiovascular Disease in the LSS”; Dr. Peter Jacob (Acting Director, Institute of Radiation Protection, Helmholtz Zentrum München) presented “Radiation Dose Responses of LSS Cardiovascular Disease Mortality”; and Dr. Nobuhiko Ban (Professor,

Tokyo Healthcare University) offered “Considerations for Dose Response of Radiation-related Cardiovascular Disease.” The session sparked active discussion about the importance of dose-response evaluation by subtype and period, and about how to assess dose response by taking risk factors into consideration.

During the afternoon session, Dr. Steven E. Lipshultz (Professor, Leonard M. Miller School of Medicine, University of Miami) delivered a lecture titled “Cardiomyopathy Following Radiation Exposure in the Childhood Cancer Survivor Cohort.” He explained study results (including his own) based on vast amounts of data from long-term follow-up of a childhood cancer survivor cohort (considering, for example, heart disease risk by subtype and the effects on growth hormones by cranial irradiation). Dr. Ikuno Takahashi (Research Scientist, RERF Department of Clinical Studies) then presented “Overview of Studies on Cardiovascular Disease in the AHS” and Dr. Fiona Stewart (Associate Professor, Netherlands Cancer Institute) considered “Biological Mechanisms of Radiation-induced Cardiovascular Disease.” Discussion during this session focused on different biological mechanisms of radiation-induced cardiovascular diseases for high-dose exposure as opposed to low-dose exposure, whole body exposure as opposed to local/cranial exposure, and various cardiovascular disease subtypes. Participants emphasized that more appropriate markers (examinations and biomarkers) need to be selected, taking the aforementioned biological mechanisms into consideration, in order to correctly assess radiation-induced cardiovascular disease risk.

On the second day, following a lecture by Dr. Toru Nabika (Professor, Shimane University School of Medicine) on “Genetic Analysis of Stroke-prone Spontaneously Hypertensive Rats (SHRSP)—a Genetic Model Rat of Stroke,” Dr. Norio Takahashi (Consultant, RERF Vice Chairman’s Office) presented “Animal Study for Radiation and Cardiovascular Disease in RERF.” Dr. N. Takahashi’s study uses SHRSP hypertensive rats at RERF and is conducted in collaboration with Dr. Yasuharu Niwa (Associate Senior Scientist, RERF Department of Radiobiology/Molecular Epidemiology). A significant finding from the study indicated that a correlation was observed between radiation exposure (1–4 Gy) and cardiovascular disease development based on the SHRSP

rat model, with characteristic histopathology in the brain, heart, and other organs of the irradiated rats. This result served to focus attention on the importance of research at lower dose ranges.

The concluding session was an overall discussion debating future directions for RERF's cardiovascular disease studies. The two-day discussions were summarized by Drs. Kazunori Kodama, Kotaro Ozasa, Masazumi Akahoshi, and Roy E. Shore. The speakers, chairpersons, and others are now preparing a meeting report, which will be submitted to an international journal.

The workshop was held with the support of the International Exchange Program Fund from the Japanese Ministry of Health, Labour and Welfare, and organized through cooperation with many of RERF's staff members, not only from the Department of Clinical Studies but also from other research departments and the Secretariat. I would

like to take this opportunity to express my sincere appreciation for the support and cooperation that made this workshop possible.



International Workshop on Radiation and Cardiovascular Disease held at Hiroshima RERF

Second International Academic Conference on Radiation Health Risk Management in Fukushima

The second International Academic Conference on Radiation Health Risk Management in Fukushima was held in the city of Fukushima over a period of three days, February 25–27, 2013. The conference was hosted by Fukushima Medical University, with cooperation from the Fukushima prefectural government and the Radiation Protection/Risk Management Group, Subcommittee of Clinical Medicine, Science Council of Japan. The conference objectives were to invite specialists both inside and outside of Japan to report on topics related to radiation's health risks, including information on efforts taking place in Fukushima and results of related studies conducted throughout the world, and to foster scientific discussion about such issues. The conference was attended by about 460 specialists from nine nations, including the USA, Russia, Germany, and Japan, and from international organizations and universities, including the World Health Organization (WHO), United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), International Atomic Energy Agency (IAEA), International Commission on Radiological Protection (ICRP), Fukushima Medical University, Hiroshima University, and Nagasaki University.

On the first day of the conference, four sessions were held. In Session 1, "Initial Medical Response to the Fukushima Nuclear Accident," Dr. Koichi Tanigawa, Professor at Hiroshima University, delivered a report on radiation emergency medical issues. In Session 2, "Current Actions of the

Fukushima Health Management Survey," representatives of Fukushima Medical University reported a portion of data analysis results obtained through four in-depth examinations/surveys (thyroid screening, health examinations, survey of pregnant women and nursing mothers, and survey of mental care and lifestyles). In Session 3, "Coordination and Cooperation with Domestic Members (1)," Dr. Kazunori Kodama, RERF Chief Scientist, made a presentation titled "Support for Fukushima Provided by the Radiation Effects Research Foundation." In Session 4, "Coordination and Cooperation with Domestic Members (2)," Dr. Toshiteru Okubo, RERF Chairman, served as one of the co-chairs.

On the second day of the conference, in Sessions 5–8, presentations were made regarding actions in response to the earthquake in Fukushima by international organizations, and the experience gained from the Chernobyl nuclear power plant accident by researchers from abroad, followed by a comprehensive discussion of the conference proceedings. On the last day, Dr. Shigenobu Nagasaki, Professor Emeritus at Nagasaki University (and former RERF Chairman), delivered a keynote lecture on the theme "Mission and Responsibility of the Scientific Society in Japan after the Fukushima Accident." Session 9, "Radiation Health Risk Management," was followed by the summary discussion titled "Implications of the Fukushima Accident and Suggestions for Future Actions," concluding the three-day conference.

Interdisciplinary Education Intensive Course: A Special Training Program for Recovery from Nuclear Accidents

**Ritsu Sakata, Associate Senior Scientist
Department of Epidemiology, Hiroshima**

A two-day interdisciplinary education intensive course, “Radiation biology and medicine overlooking the moment of radiation exposure throughout the lifetime,” a special human resource training program for recovery from nuclear accidents, was held on March 18 and 19 at the RERF Hiroshima Laboratory. This program is supported by the Ministry of Education, Culture, Sports, Science and Technology and comprises a series of intensive courses held as part of a larger recovery project initiated in FY2012. It is intended to train specialists who have an extensive and deep understanding of the causal relationship between radiation damage and health effects and can contribute to society. The program covers the following four subcategories in the fields of radiobiology and medicine: 1) radiation protection and radiation emergency medical care, 2) epidemiology and cancer therapy, 3) individual responses, and 4) molecular responses. Six universities, including Kyoto University, as well as the Institute for Environmental Sciences and three other research institutes participate in this program, and RERF was responsible for providing an intensive course on epidemiology in the subcategory of epidemiology and cancer therapy. Those who enroll in the program can choose intensive courses and international symposiums they wish to participate in from the list of courses and symposiums on the program’s webpage. These courses and symposiums are intended mainly for students, graduate students, and young researchers.

Although the courses require no admission fees, and travel and lodging expenses are paid from the program’s fund, in designing the course schedule, we had no idea about the type or number of participants who would register, due to the non-accredited nature of the course. In early March, when we learned that there would be 13 participants with varied backgrounds, from university sophomores to first year doctoral students, with backgrounds in engineering, science, and medical science, we wavered about the focus of the course. Also, three scientists who had registered as program lecturers would participate in the RERF course to deepen

their understanding in fields outside of their areas of expertise and also to foster questions and discussions among participants.

Despite the unfortunate rain, the course began successfully, with the opening address by Dr. Toshiteru Okubo, RERF Chairman. On the first day in Session 1, “Methods and results of epidemiological studies of atomic bomb survivors,” Dr. Kotaro Ozasa, Chief, Department of Epidemiology, lectured on the history of the RERF studies of A-bomb survivors, including the Life Span Study (LSS), and their results. Dr. Ritsu Sakata then provided an explanation of technical terms used in Dr. Ozasa’s talk, to facilitate participants’ understanding of the lectures that followed. Dr. Hiromi Sugiyama, Acting Chief, Tumor and Tissue Registry Office, Department of Epidemiology, and Dr. Eric Grant, Assistant Chief, Department of Epidemiology, talked about studies of *in utero* survivors and children of A-bomb survivors, respectively. Session 2, “Epidemiological research methods enabling such studies,” on the morning of the second day comprised three lectures: “Introduction to epidemiology” by Dr. Ozasa, “Risk assessment” by Dr. Sakata, and “Factors that could distort the true picture” by Dr. Atsuko Sadakane, Associate Senior Scientist, Department of Epidemiology. The intent of these three lectures was to familiarize the participants with epidemiology, the field that forms the basis for the technical terms introduced in Session 1. Because these two sessions, presented in a day and a half, covered about one-third of the contents generally provided in a six-month course, the participants may not have fully understood what was being explained. In Session 3, “Interface between animal experiments and epidemiological studies,” on the afternoon of the



Participants of the interdisciplinary education intensive course held at Hiroshima RERF

second day, Dr. Nori Nakamura, Consultant, RERF Department of Genetics, lectured on the challenges involved in this interface. The topic of biodosimetry was covered by Dr. Satoshi Tashiro, Professor, Hiroshima University, Dr. Yoshiaki Kodama, Chief, RERF Department of Genetics, and Dr. Yuko Hirai, Adjunct Specialist (research scientist), RERF Department of Genetics, in their lectures on methods based on dicentric chromosomes, chromosome translocations, and electron spin resonance (ESR), respectively. The topics in this session were probably the most familiar to the participants, but they did not ask many questions, perhaps because of the mental fatigue from the previous sessions over the past one-and-a-half days. This somehow worried us, but we found out later, to our relief, that they had remained after the lectures, asking questions to Dr. Nakamura and Dr. Hirai with intense interest.

We also realized the difficulty of organizing such an event. For example, although the Project Secretariat had asked participants to bring their lunch, half of them did not, due to the unique course format provided by each of the institutes of the program, so they had to go down Hijiyama Hill in the rain for lunch. Also, some participants had not made hotel reservations prior to their arrival. Yet, the participants, who voluntarily registered in the program, were highly motivated to learn and did their best to understand the lectures despite their fast pace, even managing to ask questions. Twelve participants attended the reception held on the evening of March 18, and actively communicated with each other and the lecturers. I was impressed by their motivation and sincerely hope that more students and researchers will specialize in radiation research.

Impact of Smoking on Mortality and Life Expectancy in Japanese Smokers: A Prospective Cohort Study*

Ritsu Sakata

Department of Epidemiology (Hiroshima), RERF

*This article is based on the following publication:

Sakata R, McGale P, Grant EJ, Ozasa K, Peto R, Darby SC. Impact of smoking on mortality and life expectancy in Japanese smokers: A prospective cohort study. *BMJ* 2012; 345:e7093 (doi: 10.1136/bmj.e7093)

Introduction

Previous studies have found that smoking increased the risk of morbidity and mortality from many diseases in the Japanese as in other populations. However, such studies revealed that the magnitude of risk in Japan was smaller than that in Europe and the U.S., but the reason for that result is unclear. We examined the impact of smoking on overall mortality and average life expectancy in the Life Span Study (LSS).

Explanation

1. Methods

Smoking information was obtained by way of four LSS mail surveys (in 1965, 1969, 1978, and 1991) and three interview surveys (in 1963, 1965, and 1968) with the Adult Health Study cohort, an LSS subcohort. The average length of follow-up after the first provision by subjects of information on smoking status was 22.9 years. Age-adjusted death rates by smoking category and by calendar year of birth were calculated, resulting in the death rate ratio of current smokers or former smokers when compared with never smokers. Where smoking status that had been previously reported changed at a later occasion, such cases were reclassified in accordance with the newly reported smoking status. We also conducted analysis including radiation dose and lifestyle factors such as alcohol, confirming that there was no substantial change in the results.

2. Results of the study

A total of 67,973 subjects (27,311 men and 40,662 women) provided information on smoking status in at least one of the aforementioned surveys or interviews.

(1) Risk of smoking by calendar year of birth

Comparison of death rate by calendar year of birth revealed higher death rates for smokers in all of the birth-year groups than for never

smokers: death rate ratios of smokers to never smokers were 1.24 for men born before 1890 and 1.92 for men born in 1930–1945, revealing higher death rate ratios for smokers born in later decades than for those born earlier. A similar trend was observed for women.

(2) Impact of age at initiation of smoking

Death rate ratios of smokers were 1.48 and 2.21 for men born in 1920–1945 who did not start smoking until at least the age of 30 and for men who started smoking before the age of 20, respectively. For women, death rate ratios also increased with decrease in age at initiation of smoking.

(3) Reduction in life expectancy

Among men who smoked at age 35, 78% survived to the age of 70. In contrast, 78% of the never-smoker group survived to the age of 75. Similarly, among women who smoked at age 35, 88% survived to age 70, while the same percentage of never-smoker women survived to age 74. Consequently, it was found that smoking reduced life expectancy by about five years for both men and women in this group of smokers. Among men born in 1920–1945 who started smoking by 20 years of age and continued smoking, 72% survived to the age of 70 years, while the same percentage of men born in the same period who never smoked survived to the age of 78 years. For women, a similar comparison revealed that 79% of the smokers survived to the age of 70, with the same percentage of never smokers surviving until the age of 80. The latter comparison found that life expectancy among such smokers was reduced by eight years and 10 years for men and women, respectively.

(4) Impact of smoking cessation

Those who stopped smoking by 35 years of age could avoid almost all of the excess risk

found in those who continued smoking. Even those who stopped smoking by the age of 45 could avoid most of the excess risk.

Among those born before 1890, the mean ages at initiation of smoking were 23 years and 36 years for men and women, respectively; among those born in 1930–1945, however, the mean ages decreased to 19.8 years and 24.3 years for men and women, respectively. Among those born before 1890, the average numbers of cigarettes per day were 13 and seven for men and women, respectively; among those born in 1930–1945, the numbers increased to 24 and 13 for men and women, respectively. The present study observed similar levels of reduction

in life expectancy as those observed in studies in Europe and the U.S. among those born in 1920–1945 who started smoking before 20 years of age. The low risk observed in the past among Japanese may have been affected by the presence of people of previous generations whose ages at initiation of smoking were relatively high and numbers of cigarettes consumed were low. As is the case for Europe and the U.S., it is expected that Japanese people who started smoking in the early stages of adulthood and continued smoking will face a reduced life expectancy of about 10 years on average. However, most of such risk can be avoided if smoking is halted by the age of 35.

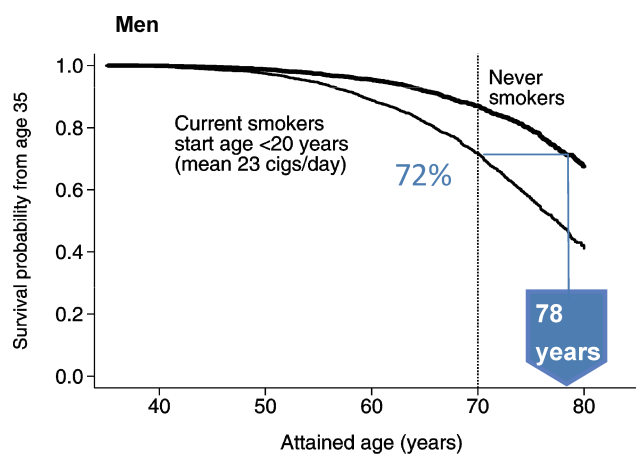


Figure. Survival probability from the age of 35 years for Japanese men born in 1920–1945 (comparison between non-smokers and smokers who started smoking by the age of 20)

Unrepairable DNA Double-strand Breaks That Are Generated by Ionizing Radiation Determine the Fate of Normal Human Cells*

Asao Noda

Department of Genetics, RERF

*This article is based on the following publication:

Noda A, Hirai Y, Hamasaki K, Mitani H, Nakamura N, Kodama Y. Unrepairable DNA double-strand breaks that are generated by ionising radiation determine the fate of normal human cells. *J Cell Sci* 2012; 125(22):5280–7 (doi: 10.1242/jcs.101006)

Study Findings

Our study confirmed that unrepairable chromosomal DNA double-strand breaks (DSBs) induced by radiation exposure were retained in cell nuclei over the long term as repair protein foci that are larger than repairable damages, and cells containing these DSBs exhibited a tendency to undergo premature senescence, with permanently arrested cell division observed. The numbers of unrepairable DSBs increased with increasing radiation dose (Figure 1) and built up in the cells with repeated irradiation, indicating the possibility that measurement of such DSBs could be used to estimate cumulative radiation dose received previously.

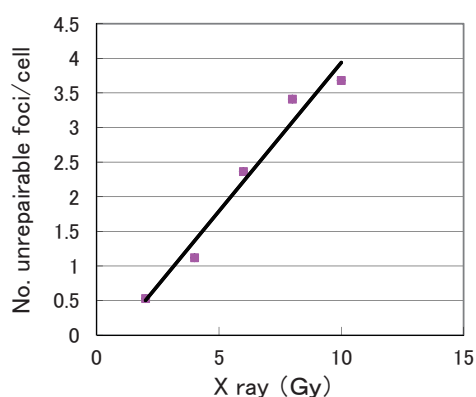


Figure 1. Formation of unrepairable DSBs according to radiation dose

Explanation

Among the long-term effects induced by ionizing radiation in biological organisms, unrepairable DSBs represent the most significant of the chromosomal DNA damages from radiation exposure. It was not fully understood, however, how the damages are generated and how they determine the fates of cells. Based on the idea that unrepairable damages caused by radiation exposure are retained in

the genome^{note)} and might eventually induce tissue malfunction leading to late radiation effects, we attempted to detect such damages. By considering the large repair protein foci retained in cell nuclei as a 'mark' of unrepairable DSBs, we examined the biological effects of radiation and analyzed the molecular mechanisms underlying such effects.

1. Purpose of study: Considering that unrepairable genome damages remain in cells and tissues previously irradiated, we aimed at inventing a method to detect such damages.
2. Study method: Normal human cells (cultured in the laboratory) and experimental mice were irradiated and DSBs remaining in the genome (chromosomal DNA) in cell nuclei over the long term were detected as large repair protein foci (Figure 2).
3. Results of the study: It has become clear that unrepairable damages accumulate in cell nuclei according to radiation dose. In the future, it is necessary to analyze how such damages could affect the long-term function of tissues and organs and how the results of this study tie in with what has been learned from the studies of atomic bomb survivors conducted thus far.

^{note)} The entirety of genetic information contained in DNA

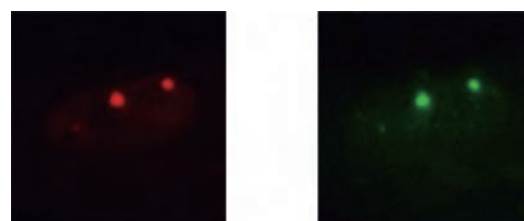


Figure 2. Unrepairable DSB repair protein foci observed in cell nucleus one month after irradiation with 6 Gy. Mostly existing in pairs: at left: 53BP1 antibody staining; at right: γ H2AX antibody staining

Translocations in Spleen Cells from Adult Mice Irradiated as Fetuses Are Infrequent, but Often Clonal^{note} in Nature*

Yoshiaki Kodama

Department of Genetics, RERF

*This article is based on the following publication:

Nakano M, Kodama Y, Ohtaki K, Nakamura N. Translocations in spleen cells from adult mice irradiated as fetuses are infrequent, but often clonal in nature. *Radiat Res* 2012; 178(6):600–3 (doi: 10.1667/RR3074.1)

Study Findings

We previously reported on the basis of studies of A-bomb survivors and mice that adults irradiated as fetuses do not record chromosome aberrations (translocations) in blood cells unlike irradiated adults. In the mouse studies, using a two-color fluorescent *in situ* hybridization (FISH) method to detect some of the translocations, the translocation frequencies occurring in all chromosomes were calculated. However, there is the possibility that such studies resulted in underestimated values. To overcome this problem, multi-color FISH (mFISH), a method that can detect translocations occurring in all chromosomes, was employed in this study. This re-examination showed that translocation frequency previously estimated on the basis of the two-color FISH method correctly represented the aberration frequency in all chromosomes. It also was indicated that among adult mice irradiated as fetuses or neonates, radiation damage was recorded in an extremely small population of hematopoietic stem cells as chromosome aberrations, and their progenitors proliferated as clonal cells bearing those chromosome aberrations.

Explanation

Irradiated mouse fetuses or neonates showed very few translocations when the mice were subsequently examined at 20 weeks of age. Reasons include that the two-color FISH method, which can detect only some translocations, may not have been able to correctly detect all chromosome aberrations including those of a clonal nature. For this reason, Dr. Mimako Nakano, Department of Genetics, RERF, and others used mFISH technology, which can detect translocations in all chromosomes, to verify the previous outcomes.

1. Purpose

The result by the two-color FISH method

showed potential bias due to the method's technical limitations (it can only detect some translocations). To look into these problems and to detect all translocations, mFISH was used for analysis in this study.

2. Methods

B6C3F1 fetal mice at 15.5 days (maternal age: 12 weeks old) and three- to four-day-old neonates were exposed to 2 Gy of X rays. When the offspring or neonates reached 18–21 weeks of age, chromosome specimens were prepared from their spleen T lymphocytes. For four and three mice irradiated as fetuses and neonates, respectively, as well as one exposed mother of an irradiated fetus, the mFISH analysis was conducted (Figure).

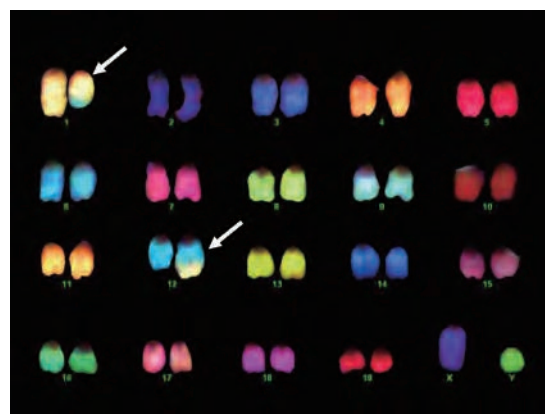


Figure. Translocation of chromosomes 1 and 12 detected by mFISH: t(1q-;12q+). Aberrant chromosomes (arrow) are of different colors, indicating a transfer took place between chromosomes 1 and 12 (translocation).

3. Results of the study

The present mFISH analysis of the same mice of the previous studies confirmed that translocation frequency in spleen cells was nearly zero, the same as was indicated in the previous studies when mice were irradiated as fetuses or neonates

and analyzed for translocations. Furthermore, translocations that were previously suggested to be clonal were indeed confirmed to be clones in the present analysis. New clonal chromosome aberrations previously not detected were also identified. At the same time, a number of translocations were detected in the mother exposed to X rays, consistent with the result from the previous studies, but no clonal chromosome aberrations were detected. The above results suggest that while a majority of hematopoietic stem cells in fetuses and neonates do not record radiation effects, a very small proportion not only record radiation-induced chromosome aberrations in the same way as hematopoietic lymphocytes of adults but also proliferate as a small number of surviving stem cells (detected as clonal chromosome aberrations). Since the previous studies indicated no record of chromosome aberrations in lymphocytes when fetuses were exposed to radi-

ation, we began to wonder about the results of studies conducted in England and other countries in the 1950s indicating that childhood leukemia increased with fetal exposure to diagnostic X rays (exposure to about 10 mGy). The present study showed that radiation effects were recorded in some of the fetal hematopoietic stem cells and furthermore that such cells clonally proliferated. Thus we now have some evidence in an animal model that chromosomal alterations induced by radiation *in utero* may be persistent enough to cause childhood leukemia.

^{note)} In chromosome studies, identical chromosome aberrations are sometimes detected in multiple cells. It is considered that a single stem cell with chromosome aberrations proliferated within the organism to give rise to such cells, resulting in what are called clonal chromosome aberrations.

Association between Chronic Kidney Disease and Cardiovascular Disease Risk Factors in Atomic Bomb Survivors*

Nobuko Sera

Department of Clinical Studies (Nagasaki), RERF

*This article is based on the following publication:

Sera N, Hida A, Imaizumi M, Nakashima E, Akahoshi M. The association between chronic kidney disease and cardiovascular disease risk factors in atomic bomb survivors. *Radiat Res* 2013; 179(1):46–52 (doi: 10.1667/RR2863.1)

Study Findings

We observed among the A-bomb survivors associations between chronic kidney disease (CKD) and the cardiovascular disease (CVD) risk factors of hypertension, diabetes mellitus (DM), hyperlipidemia, and metabolic syndrome (MetS). We also observed an association between CKD and radiation dose. The most severe category of CKD (severe renal dysfunction) in particular was significantly associated with radiation dose.

Explanation

Still much debated is whether the mechanism of CVD development is the same for high-dose exposure from cancer radiotherapy (50–60 Gy) and exposure in the A-bomb survivors (1–4 Gy). However, associations between A-bomb radiation dose and metabolic CVD risk factors including hypertension, abnormal lipid profiles, fatty liver, and high inflammatory marker values have been observed, suggesting the involvement of such factors in the increased CVD rates observed among the A-bomb survivors.

In recent years, CKD has become known as a risk factor for CVD. CKD is a new disease concept first advocated by the U.S. National Kidney Foundation in 2002. An association between renal failure mortality and radiation dose was recently reported in terms of kidney disease in the A-bomb survivors. Until now, however, there were no reports and little was known about the association between A-bomb radiation and CKD.

This study investigated among the Adult Health Study (AHS) participants in Nagasaki the associations between CKD and hypertension, DM, hyperlipidemia, and MetS, and between dose in air at the survivor's shielded location and CKD as well as renal dysfunction.

1. Purpose of the study

To examine the associations between CKD and the CVD risk factors of hypertension, DM, hyperlipidemia, and MetS, and the association between radiation dose and CKD.

2. Materials and methods

We classified renal dysfunction in 1,040 AHS participants in Nagasaki, who were examined in 2004–2007, as normal (121 persons; estimated glomerular filtration rate [eGFR] ≥ 90 ml/min/1.73 m²); mild (686 persons; eGFR 60–89 ml/min/1.73 m²); moderate (217 persons; eGFR 30–59 ml/min/1.73 m²); or severe (16 persons; eGFR < 30 ml/min/1.73 m²). We diagnosed subjects in the moderate and severe renal dysfunction groups as having CKD (233 persons; eGFR ≤ 59 ml/min/1.73 m²) based on accepted diagnostic standards.

After adjusting for age, gender, and smoking and drinking habits, we investigated the associations between CKD and hypertension, DM, hyperlipidemia, and MetS. Among the 1,040 participants, we analyzed the associations between CKD/renal dysfunction and radiation dose for 746 whose A-bomb radiation doses were known.

3. Results of the study

(1) Association between CKD and CVD risk factors

CKD was found to be associated with the CVD risk factors of hypertension (odds ratio [OR] 1.57, 95% confidence interval [CI] 1.12–2.20, $P = 0.009$), DM (OR 1.79, 95% CI 1.23–2.61, $P = 0.002$), hyperlipidemia (OR 1.55, 95% CI 1.12–2.14, $P = 0.008$), and MetS (OR 1.867, 95% CI 1.32–2.63, $P < 0.001$), with mild renal dysfunction in particular associated with hyperlipidemia and MetS (Table 1).

(2) Association between CKD and radiation dose

CKD was associated with radiation dose (OR/Gy 1.29, 95% CI 1.01–1.63, $P = 0.038$), and severe renal dysfunction was significantly

associated with radiation dose (OR/Gy 3.19, 95% CI 1.63–6.25, $P < 0.001$) (Table 2).

Our study was the first to indicate associations between radiation dose and CKD or severe renal dysfunction in the A-bomb survivors. Moreover, the study revealed that CKD was associated with the CVD risk factors of hypertension, DM, hyperlipidemia, and MetS.

The aforementioned findings suggest the pos-

sibility that CKD is associated with the increased CVD rates observed among the A-bomb survivors. Care should be taken when interpreting the results, however, since the study subjects were AHS participants in Nagasaki, and as a result, the number of those with severe renal dysfunction, 16 persons, was small. For that reason, we are planning a larger future study involving both Nagasaki and Hiroshima AHS participants.

Table 1. Odds ratio (95% confidence interval [CI]) of cardiovascular disease (CVD) risk factors for chronic kidney disease

CVD risk factor	Odds ratio (95% CI)	<i>P</i>
Hypertension	1.57 (1.12–2.20)	0.009
Diabetes mellitus	1.79 (1.23–2.61)	0.002
Hyperlipidemia	1.55 (1.12–2.14)	0.008
Metabolic syndrome	1.86 (1.32–2.63)	<0.001

P: Compared with combined normal and mild renal dysfunction groups ($n = 807$). CKD (moderate-severe) groups ($n = 233$) were adjusted for age, gender, and smoking and drinking habits.

Table 2. Odds ratio (95% confidence interval [CI]) of radiation dose for chronic kidney disease (CKD)

Renal dysfunction	<i>n</i>	Not adjusted OR/Gy (95% CI)	<i>P</i>	Adjusted OR/Gy (95% CI)	<i>P</i>
Normal-mild	584	1		1	
Moderate	149	1.13 (0.90–1.44)	0.295	1.15 (0.89–1.48)	0.293
Severe	13	2.25 (1.36–3.78)	0.002	3.19 (1.63–6.25)	<0.001
CKD (moderate+severe)	162	1.26 (1.01–1.57)	0.040*	1.29 (1.01–1.63)	0.038*

*Compared with combined normal and mild renal dysfunction groups ($n = 584$). Adjusted for age, gender, and smoking and drinking habits, hypertension, diabetes mellitus, hyperlipidemia, and metabolic syndrome. Radiation dose for CKD analyzed with ordinal logistic regression model.

A Farewell Note with Reflections on the Last Five Years

Evan B. Douple
Former Associate Chief of Research

It has been about six months since I retired from RERF and, as I reflect back on my five years in Japan, I feel very fortunate to have had the professional opportunity to work at RERF and to live in Hiroshima. That experience was far more enriching, meaningful, and enlightening to me than I had ever imagined. It also helped to bring a form of closure to my career in radiation science.

In graduate school at Kansas University the professors included early findings of ABCC in their lectures, my post-doctoral mentor at the University of Wisconsin—Dr. Kelly Clifton—became a director at RERF, and while serving as a professor in the Dartmouth Medical School I would use the findings published in RERF papers in my lectures. I would learn that over the years several Dartmouth-affiliated scientists supported RERF including such influential scientists as Dr. James Neel, Dr. Gilbert Beebe, Dr. James Crow, and Dr. Stuart Finch. It was very gratifying, therefore, that after supporting RERF through my responsibilities at the National Academies, I would have the opportunity to contribute to RERF as Associate Chief of Research.

It was an exciting and interesting time to be at RERF with some unique opportunities to try to help RERF face several interesting challenges. For example, RERF transitioned to a public interest incorporated foundation, explored how to improve its public relations activities and more effectively and proactively communicate its findings and enhance global visibility, as well as increased its educational activities including the inauguration of a series of public lectures. RERF scientists developed guidelines for the use of its precious biosamples and establishment of the Biosample Center. They also began developing a long-range future plan for RERF and sought advice and assistance in examining the future role of RERF's basic science departments in meeting RERF's research goals. Workshops were held that explored the potential for RERF collaborative studies to incorporate state-of-the-art technologies to examine a role for: (a) epigenetics as a mechanism for radiation-induced effects; (b) stem cells as targets for damage that ultimately leads to health effects; and (c) genomic sequencing to resolve the issue of radiation risk for heritable effects in humans. It was exciting to be involved in a large external five-year grant from the U.S. National Institute of Allergy and Infectious Diseases that enabled RERF scientists to explore the role of radi-

ation-induced immunosenescence in collaboration with approximately 26 scientists from laboratories in Japan and the U.S. And while it was professionally an especially interesting time to be living in Japan when the Fukushima accident occurred, the event posed a large number of challenges for RERF scientists to communicate RERF's results in a relevant manner to the exposed populations, the general public, and local and national governments.

I already miss many things about RERF, Hiroshima, and Japan, including the natural beauty, culture, and people. In reflecting back on the last five years, I am even more grateful for the many RERF *nakama* (colleagues and friends) who helped support me and made my experience at RERF so special. My fondest memories are of the “team” effort, the hard work of many loyal employees, and the spirit of dedication of the RERF leadership, scientists, and support staff. I will never forget the words of appreciation expressed by Mr. Hisashi Onishi as the representative of the Long Service Award recipients at the first RERF Long Service Award ceremony that I attended in 2008: “It would be self-indulgent of us to sentimentally dwell on RERF's past achievements and memories, for RERF faces many challenges to overcome in the future”; and “We pay our sincere respects to the major achievements reached by our many predecessors and to their dedicated work, and at the same time, we will continue to do our utmost to secure RERF's future. . .” I too hope to continue to help support RERF, and since I hope our paths will continue to cross, somehow “farewell” sounds better than “goodbye.”

Ganbatte kudasai!



Dr. Evan B. Douple in his office at RERF

Reflections on My Retirement

**Kazue Imai, Former Associate Senior Scientist
Department of Radiobiology/Molecular Epidemiology**

I have special feelings about Hiroshima. I was born on August 6, 1952, in Tokyo. By a curious coincidence, this is also the anniversary of the atomic bombing of Hiroshima. Perhaps because of this, my mother developed a strong interest in the atomic bombings. She read books on the bombings and in 1968 took my younger brother and me to the first A-bomb exhibition, which was held in the Matsuzakaya Department Store in Ginza, Tokyo. I was shocked by the exhibition and horrified by the cruelty of the atomic bombings. Despite my mother's intention, this experience had the effect of making me keep my distance from Hiroshima and Nagasaki. So when I received an offer to move from the Saitama Prefectural Cancer Center to the Radiation Effects Research Foundation (RERF) in Hiroshima, I was hesitant about it, even though I was already in my late forties. However, I considered the offer to be an opportunity, and I found the courage to move to Hiroshima.

If you walk around Hiroshima, you will see cenotaphs and memorial monuments for A-bomb victims everywhere in the city. In temples, you see that almost every *sotoba* (a tall, narrow wooden tablet set up behind a grave for the repose of the dead) is inscribed with the date August 6, 1945. People I have become acquainted with in Hiroshima, including taxi drivers, with almost no exception, had an A-bomb survivor in their family or among their relatives. Every year with the approach of August 6, the anniversary of the Hiroshima atomic bombing, many people come to Hiroshima from other parts of Japan, as well as from abroad, during the heat of the Hiroshima summer. While the city center is packed with visitors, in the part of Hiroshima where I lived, I could hear my neighbors chanting Buddhist sutras, granting a feeling of somber tension to the atmosphere.

Because Hiroshima is located along the Seto Inland Sea, the city is blessed with a temperate climate and natural beauty. Tasty fish and fruit are readily available. Hence, Hiroshima is a very easy city to live in, with a touch of urban style. While I was living in Hiroshima, breathing the air, I could imagine how actively people in this city must have gone about their own

lives before the atomic bombing. Before I came to live in Hiroshima, I learned about the city indirectly, through written documents and video images. But actually living in Hiroshima enabled me to understand more closely the grief of A-bomb survivors who lost their family members, friends, and other close associates through the atomic bombing, and who still suffer from radiation effects and fear them. I believe that this is the most significant experience I gained by working for RERF.

In terms of my life as a researcher, I moved from the Saitama Prefectural Cancer Center to RERF together with Dr. Hidetaka Eguchi in July of 2001. We were recruited by RERF when Dr. Kei Nakachi, also from the Saitama Center, assumed the position of Chief of RERF's Department of Epidemiology. I was assigned to the Department of Epidemiology in my first year with RERF. Because I was poor in English, I was very nervous, as there were a number of foreign research scientists working at the Departments of Epidemiology and Statistics. Contrary to my apprehensions, however, I was warmly welcomed and encountered no problems whatsoever.

In the second year, I was transferred to the Department of Radiobiology/Molecular Epidemiology (RME) together with Drs. Nakachi and Eguchi. The Immunology Laboratory was studying immune-related biomarkers in relation to radiation exposure, using blood samples donated by A-bomb survivors to elucidate the mechanisms that made it possible for health effects from radiation to persist for more than 60 years. When I was with the Saitama Prefectural Cancer Center, I was engaged



Dr. Kazue Imai (center) in meeting with her colleagues

in a study of individual variation in carcinogenic risk. We considered lifestyles and measured metabolism- and immune-related biomarkers and gene polymorphisms, using molecular epidemiological methods based on biological samples (such as blood) to study their associations with cancer development. For this reason, I had no trouble adapting to the research focus at RERF's RME. I believe that I was able to contribute to immunogenome and immunosenescence research projects, for

example, in cohort selection and preliminary analysis, through my experience in the area of molecular epidemiology of cancer.

I consider myself very lucky to have had the opportunity to participate in the RME studies. I was able to conduct useful research right up to the day of my retirement. I owe this accomplishment to my colleagues at RME as well as my other RERF coworkers. In conclusion, I would like to express my sincere appreciation to everyone at RERF.

LSS Survivors with Unknown Doses

**Harry M. Cullings, Chief
Department of Statistics**

Among the members of the Life Span Study (LSS), 7,070 of 93,741 survivors who were in Hiroshima or Nagasaki at the times of the bombings, or 7.5%, do not have doses calculated by the 2002 dosimetry system DS02—we commonly refer to such individuals as having “unknown doses.” All of these survivors have known distances and therefore the unshielded doses in air at their distances are known—it is their *shielding* that is unknown. A survivor's dose can almost always be estimated with an estimate of average shielding or similar method. In fact, some large groups of survivors who lack detailed shielding data, such as those who were inside Japanese wooden houses, have dose estimates that are calculated by using population-average shielding factors derived from survivors who do have the detailed shielding data. However, the quality of the estimate that can be obtained by such methods depends on the type of shielding and the available data, and even the best feasible estimate may not be acceptable for use in RERF studies. There are various reasons why an acceptable estimate of an average shielding factor might not be available. If the dosimetry system cannot calculate doses for a given type of structure, an accurate estimate of the shielding for survivors in a structure of that type cannot be made, even if detailed information about the structure is available. On the other hand, for a group of survivors who lack detailed shielding data, it may be that generically acceptable estimates of shielding factors are available from the dosimetry system for the shielding categories of at least some of the survivors in the group, but a statistically unbiased average shielding factor for the group cannot be reliably constructed.

The decisions whether or not to calculate doses

in particular situations have always been made in a systematic way as part of the implementation of each new dosimetry system. They have changed somewhat with the systems: most notably, the implementation of dosimetry system DS86, established in 1986, involved more rigorous criteria than were used for T65D, the tentative dosimetry system initiated in 1965. Whereas the implementation of T65D used *ad hoc* estimates of shielding in some cases, DS86 relied exclusively on shielding that could be calculated systematically using its models of buildings, terrain, and other factors, along with its Monte Carlo methods, and the most recent dosimetry system DS02 continued in the same vein.

Here, then, is a breakdown of the classification of survivors with unknown doses in the current implementation of DS02:

- A total of 3,729 of the survivors with unknown doses were in concrete buildings or underground air-raid shelters. Some of the physical and statistical issues affecting the decision not to calculate those doses are discussed in a report of an RERF workshop on heavy structural shielding in this issue of *Update* (see page 13).
- A related category of unknown doses, comprising 2,515 survivors, is for those with well-described but complex or unusual shielding that was not practical to model for calculation by DS86 or DS02. This category includes survivors who were inside of a streetcar, on a boat, behind a large tree, and so on.
- Another category, 415 survivors, includes those who were outside but lack detailed data on their shielding by nearby structures, if

any—such survivors do not receive dose estimates if they were at distances less than 2,000 m. This category also includes survivors who indicated they had been “in the open,” i.e., not near any building or terrain that would have provided shielding, but who did not have any thermal injury to exposed skin (“flash burns”), as a lack of this type of injury was considered to be implausible at distances <2 km if the person had been completely in the open. (At greater distances, overall population-average shielding factors, based on information from survivors with detailed shielding data who were outside buildings or in the open, are used.)

- Another 205 survivors with unknown doses were located in factory buildings that could not be modeled by DS86 and DS02 due to limited resources affecting the number of building models that could be made or unavailability of the details of building construction.
- Finally, there were 206 survivors with no shielding information whatsoever, and these

survivors do not receive calculated doses if they were at distances where the unshielded dose in air exceeds 10 mGy. (At greater distances, overall population-average shielding factors, including detailed shielding data for both those who were inside and those who were outside buildings, are used.)

These implementation decisions are subject to review by the RERF Dosimetry Committee and could change in the future with advances in the physics and statistics of the dosimetry. Additional details appear in the reports of dosimetry systems DS86 and DS02, which are available on the RERF website (www.rerf.jp), in Cullings *et al.*, *Radiation Research* 166(1): 219–54, 2006, and in Ozasa *et al.*, *American Journal of Epidemiology* 177(6): 569–73, 2013. The author would particularly like to acknowledge the extensive work that was done at RERF by Dr. George D. Kerr and Dr. Dale L. Preston, along with many others such as Dr. Shoi-chiro Fujita and Ms. Sachiyo Funamoto, in the implementations of DS86 and DS02.

RERF's Views on Residual Radiation

The article titled “RERF's Views on Residual Radiation” was posted on the RERF website on December 8, 2012.

Based on the results of analyses of radiation doses from the atomic bombings that have been conducted by the Radiation Effects Research Foundation (RERF) and many other researchers in this field, RERF has consistently explained that the involvement of residual radiation is not as significant as the effects from initial radiation (direct radiation). Nevertheless, criticism and doubts continue to arise that RERF has not given due consideration to data on residual radiation. The relevant website article maintains that such criticism and doubts are based on misunderstandings and aims to provide the public with accurate information about the issue of residual radiation.

Since the media's first coverage of the Yamada-Jones Report (Oak Ridge National Laboratory Report, ORNL-TM-4017, 1972) in 2011, the

“black rain” issue has again attracted the public's attention. As a result, the matter has been picked up by numerous media outlets, leading to some reports that are not entirely accurate. As an extreme example, one television program implied that RERF's risk data were useless because the radiation doses used in our radiation risk analysis work did not include doses from residual radiation. We are concerned that, if the present situation continues, RERF's research results, which provide the scientific basis for radiation risk assessment and radiation protection standards throughout the world, may be grossly misunderstood, leading to unnecessary worries among the public, including A-bomb survivors. We are therefore informing our readers in this latest *Update* about the website article (http://www.rerf.jp/news/pdf/residualrad_ps_e.pdf) in the hopes of explaining RERF's views and providing information on this important issue.

Research Protocol Approved in May 2012–April 2013

RP 2-12 A Study of Circulatory Diseases Using Animal Models Irradiated with Lower Doses (Addendum to RP 1-11)

Takahashi N, Niwa Y, Murakami H, Ohishi W, Misumi M, Hsu WL, Hayashi T, Kokubo T, Inaba T, Nagamachi A, Oghiso Y, Tanaka S, Kusunoki Y

The Life Span Study (LSS) data indicate that there are radiation-associated risks for hypertensive heart disease and stroke, and the Adult Health Study (AHS) data suggest there are radiation-associated risks for hypertension. We hypothesize that radiation may result in a higher risk for circulatory diseases (CD), and we started a study using stroke-prone spontaneous hypertensive rats (SHRSP) as a CD animal model. In the study of RP 1-11, radiation doses from a brief single exposure were given to the rats (1, 2, and 4 Gy, with non-exposed [0 Gy] rats used as controls). The results suggested that the life span of irradiated rats decreased with statistical significance compared to the control rats. We also evaluated radiation effects for morphological and pathological phenotypes in collaboration with the Institute for Environmental Sciences. The results showed that the phenotypic changes observed in the organs (brain, heart, and kidney) of irradiated rats were more severe than those observed in the organs of control rats. Thus, our results suggest that a separate study in which rats are irradiated with less than 1 Gy may be an opportunity for providing us with additional interesting data. The purpose of this addendum RP using SHRSP rats is that we will evaluate radiation effects on CD focusing on lower-dose radiation exposure (<1 Gy) in rats by examining morphological and pathological phenotypes and measuring the same blood biomarkers as used in the original RP. In addition to the above, we plan to examine the effects of lower-dose radiation exposure on the life span of SHRSP rats.

The second purpose of this addendum is to evaluate acceleration of the development of hypertension in spontaneous hypertensive rats (SHR) after radiation exposure (0 Gy to 4 Gy). In the previous study using SHRSP rats, we could not measure blood pressure after SHRSP rats showed the first stroke symptoms, since we were concerned that the measurement of blood pressure might cause the next stroke symptoms in the rats. We will also conduct the same examinations in the SHR rats as in the SHRSP study. The SHR rat study will be able to provide more information on the association between radiation exposure and development of CD.

Recent Publications

(Japanese): the original article is in Japanese.

Asakawa J, Kodaira M, Cullings HM, Katayama H, Nakamura N: The genetic risk in mice from radiation: An estimate of the mutation induction rate per genome. *Radiat Res* 2013 (March); 179(3):293-303. (RERF Report 9-12)

Asia Pacific Cohort Studies Collaboration (RERF: Nakachi K): Diabetes, body mass index and the excess risk of coronary heart disease, ischemic and hemorrhagic stroke in the Asia Pacific Cohort Studies Collaboration. *Prevent Med* 2012 (January); 54(1):38-41.

Boffetta P, Hazelton WD, Chen Y, Sinha R, Inoue M, Gao YT, Koh WP, Shu XO, Grant EJ, Tsuji I, Nishino Y, You SL, Yoo KY, Yuan JM, Kim J, Tsugane S, Yang G, Wang R, Xiang YB, Ozasa K, Nagai M, Kakizaki M, Chen CJ, Park SK, Shin A, Ahsan H, Qu CX, Lee JE, Thornquist M, Rolland B, Feng Z, Zheng W, Potter JD: Body mass, tobacco smoking, alcohol drinking and risk of cancer of the small intestine—a pooled analysis of over 500,000 subjects in the Asia Cohort Consortium. *Ann Oncol* 2011 (December); 23:1894-8. doi: 10.1093/annonc/mdr562 [Epub]

Hamasaki K: Radiation effects on the human body. *Sangyo Hoken* 21 [Occup Health 21] 2013 (January); 18(3):5-7. (Japanese)

Hamatani K, Mukai M, Takahashi K, Hayashi Y, Nakachi K, Kusunoki Y: Rearranged anaplastic lymphoma kinase (*ALK*) gene in adult-onset papillary thyroid cancer amongst atomic bomb survivors. *Thyroid* 2012 (November); 22(11):1153-9. (RERF Report 15-11)

Hayashi T, Morishita Y, Khattree R, Misumi M, Sasaki K, Hayashi I, Yoshida K, Kajimura J, Kyoizumi S, Imai K, Kusunoki Y, Nakachi K: Evaluation of systemic markers of inflammation in atomic-bomb survivors with special reference to radiation and age effects. *FASEB J* 2012 (November); 26(11):4765-73. (RERF Report 10-12)

Hsu WL, Preston DL, Soda M, Sugiyama H, Funamoto S, Kodama K, Kimura A, Kamada N, Dohy H, Tomonaga M, Iwanaga M, Miyazaki Y, Cullings HM, Suyama A, Ozasa K, Shore RE, Mabuchi K: The incidence of leukemia, lymphoma and multiple myeloma among atomic bomb survivors: 1950-2001. *Radiat Res* 2013

- (March); 179(3):361-82.
- Imaizumi M: Radiation and thyroid diseases— Knowledge of atomic-bomb survivors. *Saishin Igaku [Mod Med] Extra Issue 2012 (October)*; 235-41. (Japanese)
- Imaizumi M: Radiation effects on the thyroid: What has been learned from the atomic bomb radiation and Chernobyl accident. *Proceedings of the FY2011 Radiation Epidemiology Research Meeting*. Tokyo: Radiation Effects Association; 2012, pp 6-8. (Japanese)
- Imaizumi M, Yamashita S: Radiation exposure and thyroid function disorder. *Curr Ther 2013 (January)*; 31(1):92. (Japanese)
- Kodama K: Epidemiological studies on cardiovascular disease in Hiroshima and Nagasaki, NI-HON-SAN Study, and training of young cardiovascular epidemiologists by conducting teaching seminar. *Nihon Junkankibyō Yobogakkaishi [Jpn J Cardiovasc Dis Prev] 2013 (January)*; 48(1):42-50. (Japanese)
- Kodama K: Radiation health effects: radiation and cancer risk in atomic bomb survivors. *Medical Science Digest 2012 (November)*; 38(13):20-3. (Japanese)
- Kondo H, Soda M, Mine M, Yokota K: Comparison by bombing status and changes of cancer incidence among the A-bomb survivors in Nagasaki City (1970-2007). *Nagasaki Igakkai Zasshi [Nagasaki Med J] 2012 (September)*; 87(Special issue):191-4. (Proceedings of the 53rd Late A-bomb Effects Research Meeting, 2012) (Japanese)
- Kusunoki Y, Yoshida K, Kubo Y, Yamaoka M, Kajimura J, Hayashi T, Nakashima E, Ohishi W, Fujiwara S, Hakoda M, Akahoshi M: Effects of atomic-bomb radiation on human immune responses. Report 26: Dose-dependent increases in percentages of both Th1 and Th2 cells in the peripheral blood lymphocyte population. *Nagasaki Igakkai Zasshi [Nagasaki Med J] 2012 (September)*; 87(Special issue):265-8. (Proceedings of the 53rd Late A-bomb Effects Research Meeting, 2012) (Japanese)
- Lin Y, Fu R, Grant E, Chen Y, Lee JE, Gupta PC, Ramadas K, Inoue M, Tsugane S, Gao YT, Tamakoshi A, Shu XO, Ozasa K, Tsuji I, Kakizaki M, Tanaka H, Chen CJ, Yoo KY, Ahn YO, Ahsan H, Pednekar MS, Sauvaget C, Sasazuki S, Yang G, Xiang YB, Ohishi W, Watanabe T, Nishino Y, Matsuo K, You SL, Park SK, Kim DH, Parvez F, Rolland B, McLerran D, Sinha R, Boffetta P, Zheng W, Thornquist M, Feng Z, Kang D, Potter JD: Association of body mass index and risk of death from pancreas cancer in Asians: findings from the Asia Cohort Consortium. *Eur J Cancer Prevent 2012 (October 10)*:1-7. doi: 10.1097/CEJ.0b013e3283592cef [Epub ahead of print]
- Nakamura N: How to tell the public about issues that are under debate. *Kankyo to Kenko [Environ Health] 2013 (March)*; 26(1):38-42. (Japanese)
- Nakamura N, Nakano M, Hamasaki K, Ohtaki K, Sakata R, Sugiyama H, Noda A, Kodama Y: Is it true that radiation-associated risks are higher following irradiation of fetuses as compared with children? *Hoshasen Seibutsu Kenkyu [Radiat Biol Res Commun] 2012 (September)*; 47(3):272-86. (Japanese)
- Nakano M, Kodama Y, Ohtaki K, Nakamura N: Translocations in spleen cells from adult mice irradiated as fetuses are infrequent, but often clonal in nature. *Radiat Res 2012 (December)*; 178(6):600-3. (RERF Report 7-12)
- Noda A, Hirai Y, Hamasaki K, Mitani H, Nakamura N, Kodama Y: Unrepairable DNA double-strand breaks that are generated by ionising radiation determine the fate of normal human cells. *J Cell Sci 2012 (November)*; 125(22):5280-7. (RERF Report 10-11)
- Ozasa K: Association between radiation exposure and non-cancer disease death in the atomic-bomb survivors. *Hoshasen Bogo Bunkakaishi [Jpn Soc Radiol Technol] 2012 (October)*; No. 35:27-30. (Japanese)
- Ozasa K: Health effects of atomic-bomb radiation. *Nippon Eiseigaku Zasshi [Jpn J Hyg] 2013 (March)*; 68(Supplement):S78-9. (Abstracts of the 83rd Annual Meeting of the Japan Society for Hygiene, Kanazawa, 24-26 March 2013) (Japanese)
- Ozasa K: Late health effects of radiation among the atomic-bomb survivors. *Nagasaki Igakkai Zasshi [Nagasaki Med J] 2012 (September)*; 87(Special issue):157-60. (Proceedings of the 53rd Late A-bomb Effects Research Meeting, 2012) (Japanese)
- Ozasa K: Radiation effects at low-dose levels and effects of age at bombing among the atomic-bomb survivors. *Proceedings of the FY2011*

- Radiation Epidemiology Research Meeting. Tokyo: Radiation Effects Association; 2012, pp 4-5. (Japanese)
- Ozasa K, Grant EJ, Cullings HM, Shore RE: Invited commentary: Missing doses in the Life Span Study of Japanese atomic bomb survivors. *Am J Epidemiol* 2013 (February); 177(6):569-73. (RERF Report 15-12)
- Sakata R, McGale P, Grant EJ, Ozasa K, Peto R, Darby SC: Impact of smoking on mortality and life expectancy in Japanese smokers: A prospective cohort study. *BMJ* 2012;345:e7093. doi: 10.1136/bmj.e7093 [Epub] (RERF Report 6-11)
- Samartzis D, Nishi N, Cologne JB, Funamoto S, Hayashi M, Kodama K, Miles EF, Suyama A, Soda M, Kasagi F: Ionizing radiation exposure and the development of soft-tissue sarcomas in atomic-bomb survivors. *J Bone Joint Surg Am* 2013 (February); 95(3):222-9. (RERF Report 1-11)
- Semmens EO, Kopecky KJ, Grant EJ, Mathes RW, Nishi N, Sugiyama H, Moriwaki H, Sakata R, Soda M, Kasagi F, Yamada M, Fujiwara S, Akahoshi M, Davis S, Kodama K, Li CI: Relationship between anthropometric factors, radiation exposure, and colon cancer incidence in the Life Span Study cohort of atomic bomb survivors. *Cancer Causes Control* 2013 (January); 24(1):27-37. (RERF Report 27-11)
- Sera N, Hida A, Imaizumi M, Nakashima E, Akahoshi M: The association between chronic kidney disease and cardiovascular disease risk factors in atomic bomb survivors. *Radiat Res* 2013 (January); 179(1):46-52. (RERF Report 20-11)
- Sugiyama H, Ozasa K, Tanaka J, Kakehashi M, Tsunematsu M, Takeda N, Arita K, Kamada N: Childhood cancer incidence and circumstances regarding diagnosis and treatment in Hiroshima prefecture, 2004-2008. *Hiroshima Igaku [J Hiroshima Med Assoc]* 2012 (November); 65(11):685-95. (Japanese)
- Taga M, Eguchi H, Shinohara T, Takahashi K, Ito R, Yasui W, Nakachi K, Kusunoki Y, Hamatani K: Improved PCR amplification for molecular analysis using DNA from long-term preserved formalin-fixed, paraffin-embedded lung cancer tissue specimens. *Int J Clin Exp Pathol* 2013 (January); 6(1):76-9. (RERF Report 6-12)
- Taga M, Mechanic LE, Hagiwara N, Vahakangas KH, Bennett WP, Alavanja MCR, Welsh JA, Khan MA, Lee A, Diasio R, Edell E, Bungum A, Jang JS, Yang P, Jen J, Harris CC: *EGFR* somatic mutations in lung tumors: Radon exposure and passive smoking in former- and never-smoking U.S. women. *Cancer Epidemiol Biomarkers Prev* 2012 (June); 21(6):988-92.
- Takahashi I, Furukawa K, Ohishi W, Takahashi T, Matsumoto M, Fujiwara S: Comparison between oscillometric- and Doppler-ABI in elderly individuals. *Vasc Health Risk Manag* 2013 (March 8); 9:89-94. doi: 10.2147/VHRM.S39785 [Epub] (RERF Report 3-12)
- Tatsukawa Y, Cologne JB, Hsu WL, Yamada M, Ohishi W, Hida A, Furukawa K, Takahashi N, Nakamura N, Suyama A, Ozasa K, Akahoshi M, Fujiwara S: Radiation risk of individual multifactorial diseases in offspring of the atomic-bomb survivors: a clinical health study. *J Radiol Prot* 2013 (June); 33(2):281-93. (RERF Report 28-11)
- Wang C, Nakamura S, Oshima M, Mochizuki-Kashio M, Nakajima-Takagi Y, Osawa M, Kusunoki Y, Kyoizumi S, Imai K, Nakachi K, Iwama A: Compromised hematopoiesis and increased DNA damage following non-lethal ionizing irradiation of a human hematopoietic system reconstituted in immunodeficient mice. *Int J Radiat Biol* 2013 (February); 89(2):132-7.
- Yamada M, Shimizu M, Kasagi F, Sasaki H: Reaction time as a predictor of mortality: The Radiation Effects Research Foundation Adult Health Study. *Psychosom Med* 2013 (January 29); 75:154-60. doi: 10.1097/PSY.0b013e3182822b4a [Epub ahead of print] (RERF Report 25-11)
- Yasumura S, Hosoya M, Yamashita S, Kamiya K, Abe M, Akashi M, Kodama K, Ozasa K, for the Fukushima Health Management Survey Group: Study protocol for the Fukushima health management survey. *J Epidemiol* 2012 (September); 22(5):375-83.