放影研 RERF update

Summer
Volume 26, Issue 1, 2015
News and Views

Radiation Effects Research Foundation

Hiroshima and Nagasaki, Japan

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[LEFT] U.S. Ambassador to Japan Caroline Bouvier Kennedy (right) and Chairman Toshiteru Okubo (left) exchanging gifts in Chairman's Office, with Mr. Jeffrey Miller (Energy Attaché, U.S. Dept. of Energy; center); see page 8

[RIGHT] Dr. Norio Takahashi, Consultant, Associate Chief of Research Office, being interviewed for local BSS TV variety program by comic duo Daisuke and Hanako Miyagawa; see page 11

From the Editors

Welcome to the Summer issue of Update for 2015. The sakura have come and gone, and so has the Hiroshima Flower Festival, and despite our best intentions of going to press earlier, it appears that we will be getting this issue published in its English version in late June, much as we did last year.

We have had a mild spring again this year. The sakura were in full bloom for a tragically short time due to the rainy weather, and "if one blinked, one missed it" this year. Golden Week, however, was glorious. We are now nearing the start of rainy season, typically a full month or more of fairly constant precipitation, some of it quite heavy.

This year marks the 70th year since the atomic bombings and the 40th anniversary of the founding of RERF. With the passage of that much time, one might imagine that there would be some major changes on the horizon. And in fact, some important new developments are taking place at RERF. One of these is a big new initiative to deal with the space and energy demands of RERF's extremely valuable collection of biosamples, including a large robotic freezer system scheduled to go into operation later in the fall that will keep samples in ultracold storage in a large chamber to be accessed only by the mechanical sample-handling system.

Another is a new study of a different population from the atomic bomb survivors—the Fukushima nuclear accident emergency workers—which was recently awarded to RERF and will draw upon the accumulated expertise of our scientific staff. Although this cohort was exposed to ionizing radiation, it has important differences from the cohorts

of atomic bomb survivors, such as its smaller size, lower maximum doses, chronic vs. the survivors' acute exposure, clearly delineated occupational status, and less diversity of gender and age at exposure.

We have a full issue with the usual kinds of offerings: a full complement of science articles, news items including the 42nd meeting of the Scientific Advisory Committee, a report on a visit to RERF by the U.S. Ambassador to Japan, and five conference and workshop reports. We hope you enjoy this issue!

May 20, 2015

Harry M. Cullings
Editor-in-Chief

Technical Editors
Jeffrey L. Hart
Setsumi Harachi
Tomoe Matsumoto

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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.

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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.*

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Report on the 42nd Scientific Advisory Committee Meeting, 2015

The 42nd Scientific Advisory Committee (SAC) meeting to review RERF's research activities was held March 2–4, 2015, in Hiroshima. The SAC consists of 10 scientists, five each from Japan and the United States. The co-chairs this year were Dr. Michael Cornforth (University of Texas Medical Branch) and Dr. Yoichi Gondo (RIKEN BioResource Center). The SAC has a new member, Dr. Francesca Dominici (Harvard University School of Public Health), replacing Dr. Sally Amundson (Columbia University), to whom we owe gratitude for her outstanding, dedicated service to RERF. RERF requested to have more focused reviews this year of the departments of Genetics and Radiobiology/Molecular Epidemiology. To aid the focused reviews, two additional experts were appointed temporarily to the SAC—Dr. Ryo Kominami (Niigata University) and Dr. Ralf Kittler (University of Texas Southwestern). Their insights were very valuable, and it was a great pleasure for us to work with these excellent scientists.

RERF Chairman Dr. Toshiteru Okubo opened the meeting with a warm welcome to all, emphasizing the importance of SAC's work to the mission of RERF. He briefly summarized progress on several items, including the plans for a working-group research structure and purchase of a robotic biorepository to facilitate integrated biosample storage and use. Particularly noteworthy is a new long-term study of Fukushima nuclear emergency workers.

Next, Vice Chairman Dr. Roy E. Shore spoke on responses to SAC recommendations and on new research achievements. In response to the 2014 SAC recommendations, RERF has formed a high-level committee to assign priorities to studies based on relevance to RERF's mission and importance of the science; is introducing new technologies ("omics") to take advantage of the valuable resource of data and biosamples; is working to develop high-quality studies throughout their life cycle, from planning through strong data methodologies, analyses and manuscripts; and is facilitating public understanding through press conferences, media forums, and public forums.

Dr. Shore followed with highlights of RERF's research accomplishments during 2014. Among the research achievements were manuscripts on the associations of radiation with thyroid nodules,[3] liver cancer,[5] cognitive deficits, retinal macular degeneration, and chromosome aberrations.[4] Papers also were published on A-bomb neutron dosimetry[1] and fallout rain exposure,[6] and on assessing the joint effects of smoking and radiation on lung cancer risk.[2] Improvements in the DS02 dosimetry input data having to do with increasing the accuracy of A-bomb survivor locations and a more comprehensive application of the DS02 terrain shielding module were completed and have been implemented. New radiation research initiatives included to begin a third round of clinical examinations of the children of A-bomb survivors, to conduct echocardiographic screening of A-bomb survivors, and to explore radiation-associated metabolomic patterns. Significant progress was also made in conducting analyses and preparing reports on an 11-year update of cancer incidence data in the Life Span Study (LSS) of over 95,000 A-bomb survivors and an update of cancer and noncancer mortality among about 76,000 children of the survivors.

RERF scientists have continued their active involvement with international radiation-protection and risk-assessment organizations, such as the ICRP (International Commission on Radiological Protection) and UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation). They also gave a number of invited lectures abroad and have collaborations with investigators at over 40 different institutions in Europe, America, or Asia, and nearly 40 in Japan.

Dr. Robert L. Ullrich, Associate Chief of Research, presented plans for restructuring RERF research programs. The broad outline of research priorities includes the roles of radiation in cancer, genetic damage, and cardiovascular disease. The merger of the departments of Genetics and Radiobiology/Molecular Epidemiology into the Department of Molecular Biosciences is underway, with the current four laboratories of Cell Biology, Cytogenetics, Immunology, and Biochemical Genetics remaining the same for the present. An early task will be the development of a five-year plan of goals and directions for the new Department.

A second element of restructuring relates to the development of research clusters, initially in the areas of cancer, genetics, and cardiovascular and other non-neoplastic diseases. These are intended to enhance communication, collaboration, and mentoring, and to both develop and critically evaluate integrated, multidisciplinary research projects ("program projects"), with a focus on salient radiation research questions. These projects would have their own funding and budget management and would be held accountable for research innovation and productivity.

Dr. Kazunori Kodama, Chief Scientist, reported on the Biosample Center, which provides for integrated storage and management of various types of biosamples, including blood constituents, urine, pathology tissues, and teeth. RERF

has a rich repository of historical biosamples, for example, about 490,000 serum, 100,000 plasma, and 130,000 lymphocyte samples from A-bomb survivors and their offspring. To facilitate the storage of frozen samples, a robotic −80°C biorepository is being installed that will accommodate all existing frozen samples and those obtained over the next two decades. Work is ongoing to prepare and document samples for when the system begins operation in September 2015.

Dr. Okubo reported on the new RERF grant to conduct a long-term cohort study of Fukushima nuclear emergency workers. The cohort consists of about 20,000 workers who conducted emergency operations at the Fukushima Daiichi nuclear plant between March 14 and December 16, 2011, the period when the permissible dose limit was raised from 100 mSv to 250 mSv. RERF is serving as the lead institution and coordinating center, but since those workers are now scattered throughout Japan, a number of medical institutions are being enlisted to conduct yearly health examinations of the workers in a standardized fashion with informed consent. The examinations will include, among other things, biosample collection and screening for thyroid and other cancers, cataracts, and psychological effects. The data will be linked to information on estimated whole-body and thyroid doses, as well as to cancer-incidence and mortality data.

The SAC provided a written report of their recommendations; a brief statement of the key general recommendations is as follows:

- The SAC was pleased to see that RERF is in the course of merging the departments of Genetics and Radiobiology/Molecular Epidemiology, and of forming Working Groups to develop focused research initiatives. However, they cautioned that upper management needs to implement the changes thoughtfully to assure that the innovations increase research effectiveness.
- RERF must prioritize its development of "omics" research and give prime attention to the development of computational and statistical informatics capability. Hiring a computational biologist should be a priority.
- Regarding sample and data sharing, RERF needs to learn how to leverage its unique data and sample base for the purpose of forging research alliances that can help with its mission. RERF should anticipate overtures made on behalf of outside research entities for access to biological data and physical samples, and consider beforehand how to deal with and prioritize requests from potential collaborators.
- The collection and preservation of biosamples is among the most important responsibilities of RERF. A database for access to sample identification, location, and other information is underway and should include all samples with associated information from every department. Issues of intellectual rights and cross-platform databases also need to be addressed.
- New plans for the biosample repository are impressive. The SAC notes that researchers will need information about the quality of samples, particularly regarding their intended use for studies involving the newer technologies of metabolomics, proteomics, and transcriptomics.
- It is important for RERF to place a high priority on recruiting young researchers. Attracting top-notch talent in this environment will be challenging and requires a firm commitment on the part of RERF. RERF needs to project an image to prospective recruits that showcases its unique research opportunities and that reassures them that they can make a career at RERF.
- There is a need for further prioritization, at various levels. Among these was the way that research proposals were assessed as to overall quality and testable hypotheses connected to RERF's mission.
- RERF's recent commitment to the Fukushima accident is a positive development, especially in terms of public relations, but care needs to be taken that resources are not diverted away from RERF's primary mission.
- The public lecture forums that have been conducted in Hiroshima and Nagasaki are appreciated by the SAC.

Selected highlights of the recommendations to the departments with the primary focus this year include:

- Department of Genetics: The SAC considers the use of appropriate and rigorous computational analyses essential for gleaning useful information from genomic data, and this requires extensive bioinformatics expertise and computational infrastructure. To obtain sufficient expertise we recommend the recruitment of an investigator with a research and publication record in computational biology to establish a bioinformatics group at RERF.
- Department of Radiobiology/Molecular Epidemiology: Aging is probably related to impairment of the immune system, such as decreases in the number and function of T cells and other immune-related cells. However, these changes have not yet been related to chronic or persistent inflammation or to the development of cancer and other age-related common diseases. Further study of this issue in that context is encouraged.

In summary, the SAC highlighted the unique role RERF plays in determining radiation risks and the high continuing potential for studies that make important contributions. 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. Michael N. Cornforth, Co-chairperson, Professor and Director of Biology Division, Department of Radiation Oncology, University of Texas Medical Branch

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

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

Dr. Tomotaka Sobue, Professor, Department of Social and Environmental Medicine, Graduate School of Medicine, Osaka University

Dr. Shunichi Yamashita, Director, Vice President, Nagasaki University

Dr. Michiaki Kai, Member of the Board of Trustees, Professor, Environmental Health Science, Department of Health Sciences, Oita University of Nursing and Health Sciences

Dr. Marianne Berwick, Distinguished Professor, Department of Internal Medicine and Department of Dermatology, 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. Anatoly Dritschilo, Professor and Chairman, Department of Radiation Medicine, Georgetown University School of Medicine

Dr. Francesca Dominici, Professor of Biostatistics, Biostatistics Department, and Senior Associate Dean for Research, Harvard School of Public Health (Absent)

Special Scientific Advisors

Dr. Ryo Kominami, Professor Emeritus, Niigata University, and Part-time Research Staff, RIKEN Tsukuba Institute

Dr. Ralf Kittler, Assistant Professor of Pharmacology and Director of McDermott Next Generation Sequencing Core Laboratory, The University of Texas Southwestern Medical Center

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42nd Scientific Advisory Committee meeting participants, at Hiroshima RERF Hijiyama Hall

20th Meeting of the Hiroshima Local Liaison Council
Progress Status of Biosample Storage Reported

The 20th meeting of the Hiroshima Local Liaison Council (HLLC), a body composed of local advisors and established for incorporation of local community input in RERF's operations, was held at the Hiroshima RERF Auditorium on December 1, 2014. Of the 15 Council members, 13 including 2 proxies attended the meeting and expressed many valuable opinions.

The Council members were introduced by Mr. Eiji Akimoto, RERF Chief of Secretariat, following which RERF Chairman Toshiteru Okubo, in his opening remarks, explained the objectives of the establishment of the liaison council. After greetings by HLLC Chairman Dr. Toshimasa Asahara (President, Hiroshima University), the meeting's proceedings began, with Dr. Okubo reporting on RERF's present status. Dr. Okubo's explanation was followed by reports made by Vice Chairman and Executive Director Roy E. Shore on recent progress in research and the status of the Clinical Study of the F1 Offspring of A-bomb Survivors, by Chief Scientist Kazunori Kodama on the status of the RERF Biosample Center, by Dr. Okubo on progress made in the collaborative study with the U.S. National Institute of Allergy and Infectious Diseases (NIAID), and by Executive Director Takanobu Teramoto on RERF's public relations activities. Each of these reports was followed by a question-and-answer session.

It also was reported that a contract had been entered into in September 2014 for the purchase of a robotic biorepository for biosample storage to replace the deep freezers used previously, and that operation of the new equipment was scheduled to begin by the end of September 2015.

In an exchange in one of the question-and-answer sessions, a Council member requested that RERF enhance the approaches it employs to widely disseminate the foundation's research activities and results to the public.

After completion of the meeting's proceedings, Dr. Okubo expressed his appreciation to the participating Council members, thereby concluding the 20th HLLC meeting.

20th Local Liaison Council meeting held at Hiroshima RERF Auditorium

Hiroshima RERF Holds Fifth Public Lecture

At the end of last year, on November 22, 2014, RERF held a public lecture for citizens based on the theme "Considering Uses for RERF's Stored Samples—Part 2." The event was held in the International Culture Hall on the first basement floor of the main building of the International Culture Center, Hiroshima YMCA, located in downtown Hiroshima. A total of 184 persons attended the event to listen to three lectures and a panel discussion. This year's theme was the second in a two-part lecture series, beginning last year, which touched on the issue of uses for the biosamples stored at RERF. It was the fifth public lecture organized by Hiroshima RERF.

Sometime after studies were initiated in 1947, ABCC-RERF started the storing of biosamples such as blood and urine provided by the survivors of the atomic bombings and their children. Over the years, many such samples have been collected, particularly as a part of the medical examinations in which members of the RERF Adult Health Study participate on a biennial basis. To store such samples in a centralized location and introduce to RERF the latest and most appropriate methods for storage, the RERF Biosample Center was established on April 1, 2013, with preparations ongoing to construct a robotic biorepository system. At the same time, efforts are being made to create a framework for the storage process, such as improving organization of tissue samples not yet registered in a database, as well as enhancing and investigating quality-control and ethical issues, with the aim of appropriate use of the samples both inside and outside of RERF.

The biosamples stored at RERF have been collected with understanding and cooperation from

the A-bomb survivors, as well as from the local communities of Hiroshima and Nagasaki. It is therefore crucial that fundamental policies for the management and use into the future of such biosamples be determined on the basis of input RERF receives from study participants and the public. For these reasons, RERF decided to hold a public discussion, in continuation from last year, about the theme Considering Uses for RERF's Stored Samples—Part 2, based on the idea of having RERF researchers present lectures with local people serving as panelists in a panel discussion.

There were three talks at the event, with the first, titled "What we have learned about A-bomb radiation health effects," delivered by Dr. Atsuko Sadakane, Associate Research Scientist, RERF Department of Epidemiology. The next two talks were based on the topic "What we can learn from stored biosamples," with Dr. Yoichiro Kusunoki, Chief, Department of Radiobiology/Molecular Epidemiology, speaking on "The history of health and disease as told by genetic changes," and Dr. Waka Ohishi, Chief, Department of Clinical Studies, presenting a lecture titled "Seeking signs of impending disease."

Based on these three keynote lectures, a panel discussion was held, with Dr. Yasuyoshi Komizo, Chairman, Hiroshima Peace Culture Foundation, acting as panel chair. The discussion featured debate among the panelists, as well as a question-and-answer period with the audience. The panelists were Mr. Hiroshi Harada (A-bomb Witness, former Director, Hiroshima International Peace Office, Director, Hiroshima Peace Memorial Museum), Dr. Kenichi Arita (Respiratory Department Director, Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital), Ms. Yumi Kanezaki (Chugoku Shimbun Hiroshima Peace Media Center), and Ms. Akiko Furutani (President, Hiroshima Interpreter & Guide Association). Participating in the discussion on behalf of RERF were Dr. Kazunori Kodama (Chief Scientist/then Director of the RERF Biosample Center), Dr. Kusunoki, and Dr. Ohishi.

The panelists expressed a variety of opinions, with Mr. Harada emphasizing his view that the biosamples should be utilized not only for the A-bomb survivors but also for unexposed persons. He added his hope that opportunities for exchange can be expanded to ensure that information is communicated as effectively as possible and that the samples can be used for the cause of peace as an asset shared by all of humanity. Dr. Arita indicated his hospital's determination to diligently care for the samples received from the A-bomb survivors, explaining that such samples are closely tied to the concept of human dignity. With that in mind, he called the establishment of the RERF Biosample Center "significant," and requested that continued debate surrounding such issues take place in other open forums in the future. Ms. Kanezaki talked about how communication with the public about RERF's research results represents a major issue, relating her own experience in her job as a journalist of struggling to understand technical terminology used by scientists. She stressed the importance of communication of such issues as methods for clearly explaining RERF's research results, how to ensure good health, and other such information to the A-bomb survivors who have donated their samples to the organization for study. Ms. Furutani, from her perspective as an interpreter and guide, proposed that RERF do more to market its facility tours for those interested in learning about radiation effects on human health.

After Chairman Komizo emphasized the importance of listening to the opinions of the public regarding the limits and conditions placed on use of RERF's biosamples, Dr. Kodama remarked that RERF was prepared to embark on the creation of standards for collaborative sample use, but that collaborative research would be conducted at the beginning with the involvement of RERF researchers, rather than starting right away with only scientists unaffiliated with RERF. He said that RERF would later seek a way for such external researchers to use the samples in their own collaborative research.

Questions and comments from the audience included a statement that RERF should remain an organization able to continue its international contributions from Hiroshima. There were also questions about preservation of thyroid cancer samples in the radiation-contaminated areas of Belarus, and whether the samples of those who entered the cities soon after the A-bombings of Hiroshima and Nagasaki (early entrants) were included in the RERF stored samples.

Despite the fact that this fifth of the RERF series of public lectures featured the fairly technical theme 'uses for stored samples,' more people

Large crowd gathers for Hiroshima RERF's fifth Public Lecture

attended this year's public lecture in Hiroshima than last year's event, with college students also in evidence. Perhaps most importantly, the public lecture offered an opportunity to engage in a conversation with the public about the uses of RERF's biosamples, stored over so many years, given that the biosamples are the heritage of not only RERF, but also of Hiroshima, Nagasaki, and the entire world.

Nagasaki RERF Holds Fifth Public Lecture

Nagasaki RERF holds its fifth Public Lecture

Nagasaki RERF held its fifth public lecture event at the Nagasaki Atomic Bomb Museum Hall on January 31, 2015. The lecture series is designed to enhance communication by conveying information to the general public, including atomic bomb survivors and their offspring, about results from RERF's long-standing research on A-bomb radiation health effects.

This most recent public lecture event was the second in a series of two lectures, following the first held last year, having the theme "Considering Uses for RERF's Stored Samples—Part 2," with the aim of obtaining feedback from the Nagasaki public about possible uses for the biosamples stored at RERF, including in collaborative research. Offered in the format of a panel discussion, the event was attended by more than 100 people.

RERF Chairman Toshiteru Okubo opened the lecture event by remarking, "The samples in the custody of RERF have been collected with the understanding and cooperation of A-bomb survivors and local communities. I believe that it is important to create a basic policy toward future management and utilization of these samples by referring to opinions expressed by cooperating parties and the general public. We hope that all of you will provide us with your honest feedback."

The event's first speaker, Dr. Misa Imaizumi, Chief, Divisions of Radiology and Clinical Laboratories, Department of Clinical Studies, Nagasaki RERF, elaborated on the topic "What we have learned about A-bomb radiation health effects." Based on the idea of what we can learn from stored biosamples, Dr. Yoichiro Kusunoki, Chief, Department of Radiobiology/Molecular Epidemiology, spoke on "The history of health and disease as told by genetic changes," followed by a lecture by Dr. Ayumi Hida, Acting Chief, Department of Nagasaki Clinical Studies, titled "Seeking signs of impending disease."

In the panel discussion following the aforementioned keynote lectures, the panelists exchanged opinions under the guidance of the panel chair Dr. Takehiko Koji, Chief, Nagasaki University Graduate School of Biomedical Sciences. The panelists included Dr. Masahiro Nakashima, Professor, Department of Tumor and Diagnostic Pathology, Atomic Bomb Disease and Hibakusha Medicine Unit, Atomic Bomb Disease Institute, Nagasaki University; Ms. Miyako Jodai, Atomic Bomb Survivor Representative, The 69th Nagasaki Peace Ceremony "Pledge for Peace"; Mr. Tokusaburo Nagai, Director, Nagasaki City Nagai Takashi Memorial Museum; and from RERF, Chief Scientist Kazunori Kodama, Dr. Kusunoki, and Dr. Hida.

The panelists expressed the following opinions: Mr. Nagai commented that "the samples donated by A-bomb survivors are as valuable as precious jewels and represent a huge source of information." He added, "RERF is requested, however, to take special care in handling personal information." Ms. Jodai stated, "After undergoing health examinations at RERF, my image of the foundation completely changed. Data obtained in Nagasaki should be utilized in cases of radiation emergencies, including in the recent nuclear disaster in Fukushima." Dr. Nakashima mentioned, "It is important to obtain the understanding of A-bomb survivors who have donated samples, create a structure for the preservation of samples, build a framework to promote shared use of biosamples and related collaborative research, and develop rules concerning use of such samples."

In the question-and-answer session that followed, many audience members expressed their own ideas, including, "I think RERF is currently working on the development of rules concerning the use of stored biosamples, but will such rules cover outside investigators?" said one. "I feel as if communication between scientists and A-bomb survivors is lacking somehow. Releasing information about research results and carrying out related

PR activities is therefore crucial."

The event concluded with closing remarks by Executive Director Takanobu Teramoto, who expressed his gratitude for the participation in the public lecture and the valuable opinions expressed therein.

Panelists at Nagasaki RERF Public Lecture (please refer to article for names and affiliations of panelists)

US Ambassador to Japan Caroline Kennedy Pays Visit to Hiroshima RERF

On April 17, 2015, RERF had the pleasure of receiving a brief visit from Ms. Caroline Bouvier Kennedy, Ambassador Extraordinary and Plenipotentiary to Japan, a position to which Ambassador Kennedy was nominated by U.S. President Barack Obama on July 24, 2013, and officially confirmed by the U.S. Senate on October 16, 2013. She is the first female U.S. Ambassador to Japan. Ambassador Kennedy was accompanied on her visit to RERF by Ms. Roshni Nirody (Special Assistant to the Ambassador), Mr. Jeffrey Miller (Energy Attaché, U.S. Department of Energy), Mr. Allen Greenberg (U.S. Consul General Osaka-Kobe), and three officers/staff members from the U.S. Consulate Osaka-Kobe.

The group was hosted by RERF Chairman Toshiteru Okubo and other RERF Directors and senior staff in Dr. Okubo's office. After official greetings and introductions, Dr. Okubo provided the group with overviews on the history of RERF and the Atomic Bomb Casualty Commission (ABCC), RERF's predecessor organization, as well as with details about the various cohorts that ABCC-RERF has studied over the years. Ambassador Kennedy asked detailed questions about the research being undertaken at RERF, especially in terms of the offspring (F1) generation.

US Ambassador Caroline Kennedy on RERF facility tour with Chairman Toshiteru Okubo

Following the initial overview meeting, a facility tour was provided to the Embassy team, during which descriptions of the clinical examination areas were presented by Dr. Okubo together with Dr. Waka Ohishi, Chief, Department of Clinical Studies. Thereafter, Dr. Okubo guided the group to the recently established Biosample Center, where he and Dr. Yoshiaki Kodama, Director of the Biosample Center, explained the significance of centralized storage of RERF's more than 900,000 biosamples.

This was the second visit to RERF for Ambassador Kennedy. On January 11, 1978, her uncle, Senator Edward M. Kennedy, from the U.S. state of Massachusetts and the brother of President John Fitzgerald Kennedy (JFK), visited the RERF laboratory in Hiroshima. Accompanying him on his trip were his wife and three children, three of his sisters, as well as Caroline Kennedy, JFK's daughter, and Michael Kennedy, JFK's nephew (please refer to our March 14, 2013, Facebook article on the visit). Dr. Okubo presented Ambassador Kennedy

with a copy of a photograph of Senator Kennedy taken during his visit to RERF, as the group passed by the same framed photograph on their way to the Biosample Center.

We truly appreciated the opportunity to explain our organization and its scientific results to Ambassador Kennedy and her staff. We feel confident that the findings from our research can serve to remind all those who visit RERF of the importance of our scientific program.

Ambassador Caroline Kennedy and staff outside Hiroshima RERF with RERF Directors, senior staff

US Consul General, Consulate General Osaka-Kobe, Pays Visit to Hiroshima RERF

On December 8, 2014, RERF had the pleasure of receiving a visit from Mr. Allen Greenberg, Consul General, U.S. Consulate General Osaka-Kobe, Japan, a position to which Mr. Greenberg was appointed in August 2014. Mr. Greenberg was accompanied on his visit to RERF by Mr. Brian DaRin (Consul, Political and Economic Affairs), and Ms. Naomi Shibui (Economic Assistant).

The group was hosted by RERF Chairman Toshiteru Okubo and other RERF Directors and senior staff in Dr. Okubo's office and given overviews on the history of RERF and the Atomic Bomb Casualty Commission (ABCC), RERF's predecessor organization, as well as on RERF's past, present, and expected future research and other activities. Mr. Greenberg and his staff exhibited keen interest in the research being undertaken by RERF.

Following the initial overview meeting, an extensive facility tour was provided to the Consulate team, where more detailed descriptions of the responsibilities and activities of the various research departments of RERF were presented. Each of the group members asked relevant questions of the RERF staff and showed interest in understanding the basic knowledge that ABCC-RERF has collected about radiation health effects based on the organization's long-term studies of A-bomb survivors in Hiroshima and Nagasaki since the founding of ABCC in 1947.

We truly appreciated the opportunity to explain our organization and its scientific results to senior officials of the U.S. government's diplomatic ranks. We feel confident that the findings from our research can serve to remind all those who visit RERF of the importance of continuing our scientific program, which involves the long-term study of the health effects in the A-bomb survivors and their children of radiation from the atomic bombings of Hiroshima and Nagasaki in 1945.

Mr. Allen Greenberg, Consul General (left), US Consulate General Osaka-Kobe, with RERF Chairman Toshiteru Okubo

Media Explanatory Session about Thyroid Findings Held

The Great East Japan Earthquake, on March 11, 2011, and the subsequent radiation release from the Tokyo Electric Power (TEPCO)'s Fukushima Daiichi nuclear power plant have heightened the consciousness of Japan's public regarding radiation exposure and development of thyroid nodules/cancer, particularly in children. Given that situation, on February 2, 2015, RERF held a simultaneous explanatory session, "Recent papers related to thyroid cancer and nodules in A-bomb survivors," at both the Hiroshima and Nagasaki laboratories.

The aim of such explanatory sessions is the communication of complex scientific concepts in language that is accessible to the media. Nine journalists in Hiroshima and six in Nagasaki attended the event, representing both local and national news outlets; the laboratories in the two cities were connected by teleconferencing.

The journalists in attendance expressed keen interest in learning from the RERF researchers experienced in investigating thyroid diseases, which have been shown to be linked to radiation exposure in the case of the Hiroshima and Nagasaki atomic bombings. Increased incidences of these diseases have been reported in the children living in Fukushima prefecture at the time of the radiation accident, although whether the increase is due to radiation exposure or the result of increased testing remains an open question.

First, Dr. Kyoji Furukawa, Associate Senior Scientist, RERF Department of Statistics, provided background information from the Hiroshima Laboratory on radiation and thyroid cancer risk in the A-bomb survivors, based on his March 2013 paper titled "Long-term trend of thyroid cancer risk among Japanese atomic-bomb survivors: 60 years after exposure." Following Dr. Furukawa's talk, members of the media in both Hiroshima and Nagasaki asked questions of a fairly technical nature, such as about the difference in definition between excess relative risk and relative risk in thyroid cancer.

Next, Dr. Misa Imaizumi, Chief, Division of Radiology, Chief, Division of Clinical Laboratories, Department of Clinical Studies, Nagasaki RERF, spoke from the Nagasaki Laboratory on her paper "Association of Radiation Dose With Prevalence of Thyroid Nodules Among Atomic Bomb Survivors Exposed in Childhood (2007–2011)" (see page 25), which was published online at the end of December 2014 and announced publicly for the first time at the media event.

When questioned by journalists in both Hiroshima and Nagasaki about whether the results from her study could be used to explain the apparent increase in thyroid nodules in Fukushima, Dr. Imaizumi responded by saying that the results could not be applied directly, since her study was based on A-bomb survivors who were exposed to radiation at ages of less than 10 years and examined when they were aged 60. She did emphasize, however, that her data could be used as reference information in terms of protecting the health of the Fukushima children many years into the future.

The detailed questions and interest the media members exhibited at the explanatory event suggest that RERF's efforts to broaden journalists' understanding of health effects caused by radiation exposure have been effective as an educational tool. The media can use the information to better inform the public not only about RERF's atomic bomb-related health information, but also about information related to other instances of radiation exposure throughout the world, including the case of Fukushima.

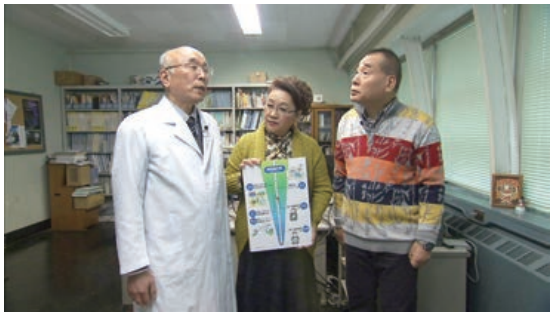
Media explanatory session about thyroid findings held at Hiroshima and Nagasaki RERF, with Dr. Kyoji Furukawa, Associate Senior Scientist, Statistics Dept., at podium, and Dr. Misa Imaizumi, Chief, Radiology Division, Chief, Clinical Laboratories Division, Nagasaki Clinical Studies Dept., on screen from Nagasaki

Regional Television Crew Visits RERF to Film Educational Story about Radiation

Two episodes of a popular educational television program hosted by comic duo Daisuke and Hanako Miyagawa, titled "Let's See…," were filmed at the Hiroshima RERF Laboratory on December 16, 2014. The short program is produced by the regional Broadcasting System of San-in, or BSS, and explores somewhat knotty environmental, energy, and other issues that seem simple but in reality are not. In these episodes, two questions were posed to RERF: Where does radiation exist? And, what effects does radiation have on people?

Dr. Norio Takahashi, a consultant for the RERF Associate Chief of Research's Office, demonstrated to the film crew how to measure radiation in various places using a dosimeter. He also instructed the crew that radiation exists in nature, is used in medicine in X-ray imaging and other technologies, and has health effects depending on the radiation doses to which an individual is exposed.

The two separate episodes were broadcast on February 8 and 15, 2015, but only in Japan's San-in region (on the Japan Sea side of the main island of Honshu) not Hiroshima. Nevertheless, appearing on the program provided RERF with a good platform from which to inform the public, albeit within a limited framework, about the organization. It was also useful for us as an institute engaged in scientific issues, because we were able to ascertain that such basic questions attracted great interest from the general public.



Dr. Norio Takahashi, Consultant, Associate Chief of Research Office, explaining differences in radiation exposures to Daisuke (right) and Hanako (center) Miyagawa for BSS program "Let's See…"

PR Professional Speaks to Hiroshima and Nagasaki RERF

Public relations dates back to around the turn of the 20th century, with Britain or America thought to be the starting point of the profession in its modern form. Public relations tools are used by RERF for communicating research results to the public and obtaining understanding of our objectives and operations as a research organization. Despite RERF's surrounding environment, which has long demanded nuanced yet open communication with stakeholders, we are relative newcomers to the field: RERF's Public Relations and Publications Office was only established on January 1, 2006.

On February 20, 2015, to foster deeper understanding among staff regarding the field and practice of public relations, RERF invited a specialist from Hakuhodo, Inc., in Tokyo, to address the theme of public relations in a lecture to all staff, and about specific ideas related to strategy in a workshop to staff involved in communicating with the public. Hakuhodo is the oldest advertising firm in Japan and has a significant public relations arm. The company's footprint is global, with offices located throughout the world.

The lecturer, Mr. Masahiko Haga, was accompanied by two other Hakuhodo staff, bringing the total to three. Mr. Haga holds the titles of Consultant and Senior Director at Hakuhodo. He has been involved in the field of public relations with the company for several decades, most notably, at the beginning of his career, in work on the 1985 Japan Airlines Flight 123 accident in Japan's Gunma prefecture that resulted in more than 500 deaths, then during 1992–1995 in efforts to help establish J-League professional soccer in Japan.

The lecture was attended by about 70 staff members in Hiroshima, and in Nagasaki by teleconferencing. Mr. Haga touched on the basics of public relations, including the fundamental workings of the media and social media, as well as the importance of working with, as well as utilizing, the media for communicating RERF's message. He explained, using past examples of Hakuhodo-led projects, how RERF can market its accomplishments by emphasizing the importance of RERF's research to global considerations, such as the establishment of worldwide radiation protection standards.

The training session that followed was attended by around 30 employees in Nagasaki and Hiroshima

engaged directly in public relations work. Mr. Haga spoke on a wide range of issues, including the history of public relations, and noted that the start of public relations in Japan probably began after the end of World War II, with the arrival of U.S. General Douglas MacArthur. MacArthur's headquarters aimed to persuade Japan to accept an open democratic government by, in part, setting up public relations offices in each of Japan's prefectures.

After Mr. Haga's talk, staff directly involved in public relations work broke up into small groups and discussed methods that could help inform the public about RERF. Each of the groups then presented the best of its ideas. One recurrent theme in the group presentations was the idea that the research results RERF has reported over the years need to be conveyed to younger generations by, for example, conducting small public lectures in locations apart from the cities of Hiroshima and Nagasaki or having RERF researchers travel to schools to teach children about the basics of radiation health effects.

The three Hakuhodo staffers, using the same format, announced their unique proposals for RERF's future public relations activities, including the idea of holding a picnic in the Hijiyama area and inviting the public to join in, which sounded like an appropriate plan as the weather started to turn to spring with a hint of warmth in the air following a cold winter.

PR specialist from Hakuhodo, Inc. Mr. Masahiko Haga speaks about effective communications to PR staff at Hiroshima RERF

Fourth ABCC–RERF History Forum Held

Hiroaki Katayama, Chief
Department of Information Technology

The fourth ABCC-RERF History Forum, organized by the Historical Materials Management Committee, was held at the Hiroshima RERF Auditorium on April 9, 2015. The series of History Forums, which began in April 2013 at the Nagasaki Laboratory, are designed to offer current RERF employees the opportunity to hear first-person accounts by individuals employed during the days of the Atomic Bomb Casualty Commission (ABCC). These vivid, detailed presentations help sharpen and deepen the understanding among current employees about the history of studies of A-bomb survivors conducted at ABCC-RERF.

The featured speakers at the fourth History Forum were Ms. Kiyoko Minato and Ms. Hisae Tanaka, both of whom served as nurses at ABCC. Ms Minato, who retired in 1966, joined ABCC in 1949 as it prepared to open temporary facilities in Ujina. Thoroughly trained by American nurses, she conducted health examinations of job candidates and made home visits for examinations associated with genetics studies. Ms. Tanaka, who retired from RERF in 1987, joined ABCC in 1951 and was engaged in nursing activities in various areas, including outpatient clinics in internal medicine and pediatrics.

Both Ms. Minato and Ms. Tanaka remembered countless details of their work in those early days, and gave interesting, straightforward descriptions, such as how a nurse would stay with each examinee during his or her tests and examinations to offer support. They described how medicines were prescribed at the clinics when necessary, and

Fourth ABCC-RERF history forum held at Hiroshima RERF; Ms. Kiyoko Minato (center) and Ms. Hisae Tanaka (right) with Executive Director Takanobu Teramoto

recalled how rooms were established in the 1950s to accommodate 10 inpatient beds for people who needed to be hospitalized, information that was sure to be news to many in the audience. Examinees wore gowns, rare in those days, not only because they made examination easier but also out of consideration for examinees who did not want to be viewed by others. Ms. Minato and Ms. Tanaka used actual examination instruments as they explained these matters. Executive Director Teramoto proved a hearty moderator for the forum, and both former nurses, who appeared somewhat nervous at the outset, gradually began to relax and smile, creating a friendly atmosphere among the attendees.

The History Materials Management Committee hopes to continue to provide such opportunities for former employees to talk about their experiences at ABCC. Such information is valuable in promoting accurate recognition and understanding of ABCC activities. Please visit the official RERF website for details, in Japanese, of the History Forums (http://www.rerf.or.jp/history/histforum.html). An English version will be available shortly.

RERF Receives Award from Latvia for Chernobyl Assistance

RERF has for many years provided training for medical workers and researchers from Latvia and lent its cooperation to the health management of the military veterans and other emergency personnel who worked at the Chernobyl nuclear accident site. On October 13, 2014, for those contributions, RERF was presented with an honorary award by the Latvian Republican Union Chernobyl, a social organization of such workers, at Pauls Stradins Clinical University Hospital in Riga, Latvia. President Arnolds Vērzemnieks, the leader of the Latvian Republican Union Chernobyl, honored Dr. Tomonori Hayashi, Assistant Chief, RERF Department of Radiobiology/Molecular Epidemiology, with a certificate of merit and medals.

Dr. Tomonori Hayashi, Assistant Chief, Radiobiology/Molecular Epidemiology Dept., holding certificate of merit and medals awarded to RERF

Media Forums Held at Nagasaki and Hiroshima RERF

RERF in Nagasaki and Hiroshima conducted the fourth round of media forums in April 2015 to expand knowledge among members of the media about studies into the health effects of A-bomb radiation conducted at RERF. The Nagasaki forum, held on April 22 in the conference room on the 3rd floor of the Nagasaki Laboratory, included seven media representatives from seven companies. The Hiroshima forum, which took place at the Hiroshima Laboratory on April 24, hosted 10 representatives from 7 media outlets.

The purpose of the forums is to present new research achievements and increase understanding among media representatives about studies that have been conducted for nearly 70 years at ABCC-RERF to provide them with knowledge they can use to inform the public in an easy-to-comprehend manner. At this year's forums, the media participants were encouraged to ask questions at any point during the explanations provided by RERF directors.

At the Nagasaki forum, RERF Chairman Toshiteru Okubo first outlined the "Epidemiological Study of Health Effects in Fukushima Emergency Workers," which will be initiated on a full scale this fiscal year. Participants asked numerous questions including how ABCC-RERF data could be used to help people exposed to radiation in the Fukushima nuclear accident. Then, Executive Director Takanobu Teramoto explained the RERF "FY2015 event and activity plans."

Two days later, at the Hiroshima forum, media

participants raised questions with regard to the Epidemiological Study of Health Effects in Fukushima Emergency Workers, asking how many people's addresses were known among the about 20,000 emergency workers who were potential study participants. Those attending the forum also inquired about the number of people whose consent had been obtained among these candidates and about the future prospects for relevant studies. In response to the presentation of the RERF FY2015 event and activity plans, questions arose about whether more detailed examinations than in prior studies would be conducted in the upcoming third cycle of the ongoing Clinical Study of the F1 Offspring of A-bomb Survivors.

Questions were posed vigorously in both Nagasaki and Hiroshima, evidence that the forums are accomplishing their original goal of helping the media convey complex scientific information to the public in a readily understandable manner. RERF hopes to continue these forums to maintain positive working relations with the media.

Media forum held at Hiroshima RERF, with Chairman Toshiteru Okubo (left) and Executive Director Takanobu Teramoto as speakers

US Journalism Students Visit RERF

Two journalism students from Indiana University (IU), located in Bloomington, Indiana, visited Hiroshima RERF on March 17 and 18, 2015. Mary Shown and Kami Mackin belonged to a student group from an IU international reporting class that had traveled to Japan. The group of 16 students, led by an IU professor, visited Hiroshima to study such topics as the atomic bombings and ABCC-RERF's research into the bombings' radiation health effects. All of the students were tasked with writing stories about Hiroshima given that 2015 is the 70th year since the atomic bombings of Hiroshima and Nagasaki.

At RERF, Mss. Shown and Mackin interviewed Dr. Eric J. Grant, Assistant Chief, RERF Department of Epidemiology, to familiarize themselves with RERF's findings. The two also spoke with Mr. Jeffrey L. Hart, Chief, Public Relations and Publications Office, about RERF's history and communications efforts with regard to the public and the media.

Ms. Shown is a senior working toward a degree in journalism and biology, with a concentration in scientific and international reporting. Ms. Mackin is a junior in the same journalism program, with a focus on international reporting and war correspondence for print. The students showed particular interest in the methods ABCC used in the early stages of research to encourage A-bomb survivors to participate in the organization's studies, in addition to RERF's research.

For most of the week they spent in Japan, the IU students were in Hiroshima reporting on the current anti-nuclear weapons movement and visiting with a group of survivors in a nursing home specifically designed for *hibakusha*. After Hiroshima, the students traveled to Tokyo, where they covered an anti-nuclear protest and made a trip to the Yasukuni Shrine (for a more detailed account, access their Japan trip blog at: http://mediaschool.indiana.edu/japan-2015/).

RERF strives to accommodate requests for cooperation in educational activities. We wish Mary and Kami 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 other students to contact RERF for information related to radiation's health effects.

Indiana University students Ms. Mary Shown (center) and Ms. Kami Mackin (left) after interview with Dr. Eric Grant, Assistant Chief, Epidemiology Dept.

Staff News

Yoshiaki Kodama, Senior Scientist (fixed-term research scientist), completed his term as Chief of the Department of Genetics as of December 31, 2014, and assumed the position of Director of the Biosample Center, effective January 1, 2015. **John B. Cologne**, Senior Scientist of the Department of Statistics, retired under the mandatory age limit as of March 31. He was reappointed as Senior Scientist (fixed-term research scientist) of the same department effective April 1, in order to continue research. On the other hand, **Keiko Ueda**, Fixed-term Research Scientist of the Division of Clinical Laboratories, Department of Clinical Studies, **Masayuki Hidaka**, Postdoctoral Scientist of the Department of Genetics, and **Yiqun Hu**, Postdoctoral Scientist of the Laboratory of Immunology, Department of Radiobiology/Molecular Epidemiology, resigned upon term expiration as of March 31. **Kazumasa Sekihara**, research scientist of the Laboratory of Cytogenetics, Department of Genetics, resigned upon term expiration as of April 30. Also, **Kiyohiro Hamatani**'s term as Adjunct Specialist (research scientist) of the Laboratory of Cell Biology, Department of Radiobiology/Molecular Epidemiology expired on March 31. He was reappointed as Consultant to the same department, effective April 1, to continue research at RERF.

RERF presents awards to employees for their long-term service in April every year. This year, eight employees—five employees for 30 years of service, two employees for 20 years, and one employee for 10 years—were awarded in Hiroshima. Among them were research scientists **Tomonori Hayashi**, Assistant Department Chief of the Department of Radiobiology/Molecular Epidemiology, and **Kyoji Furukawa**, Associate Senior Scientist of the Department of Statistics, awarded for 20 years and 10 years, respectively. In Nagasaki, one general employee was awarded for 20 years of service.

Visiting Research Fellow

Caitlin M. Milder, Visiting Student Fellow of the Department of Epidemiology from October 24, 2013 to October 10, 2014, rejoined RERF to conduct research as Visiting Research Fellow of the same department for one year (February 23, 2015–February 22, 2016). She introduces herself below.

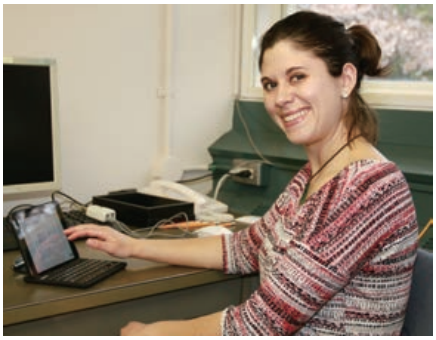
I am a returning Visiting Research Fellow training under Dr. Eric J. Grant in the Department of Epidemiology. I am the recipient of a fellowship through the National Academy of Sciences (NAS) with U.S. Department of Energy funding that will allow me to continue my work here for one more year. I am delighted to be back at RERF, continuing the projects I worked on during my first year at RERF, from October 2013 to October 2014, and broadening my research at the institution.

I have long been interested in Japan. As an undergraduate student at the University of Arizona, I majored in both physiology and East Asian studies, with a focus on Japanese. By the end of my time at the university, I had studied abroad for six months in Tokyo and completed a Japanese-to-English medical translation for a journal article concerning nephrotic syndrome.

I am therefore very excited for the opportunity to see more of Japan. Last year, I took trips to a number of cities in Honshu and Kyushu, where I expanded my ideas about Japan and Japanese culture. This year, I hope to take weekend trips to continue to gain insights into regional Japanese religion, art, and language. As I did last year, I will take language classes to improve my Japanese abilities. I look forward to speaking with everyone at RERF in both English and Japanese.

This past year, I graduated with a master of science in public health from the Johns Hopkins Bloomberg School of Public Health. My former year at RERF enabled me to achieve this goal: I am grateful to RERF and its employees for having helped me to complete my practical requirements.

During my last year at RERF, I contributed to multiple projects being conducted at the institu-



Ms. Caitlin Milder, visiting research fellow, returns to RERF

tion. I participated in the National Cancer Institute (NCI) collaborative LSS cancer incidence studies, and I contributed to the F1 cohort studies. I also helped publish the material from the Low-Dose Symposium held in 2013 which should shortly be available for public review.

This year, I have a number of aims I want to realize at RERF. First, I want to contribute more to the NCI collaborative LSS cancer incidence studies. I believe that the results from these studies will be important to how exposures are handled in the future, and I want to play a bigger role in that process. I aim to finish what remains of my projects from the previous year. I will also strive to improve my presentation abilities as well as my skills in statistical software, particularly Epicure, to allow me to make this opportunity a productive educational experience.

I look forward to working with everyone here at RERF again, to contributing to its research, and to expanding my knowledge of radiation and radiation epidemiology.

RERF International Training Course: An Update on Advanced Technologies in Radiotherapy (HICARE/IAEA)

A group of 27 physicians and researchers from 15 countries—including Bangladesh, China, Mongolia, Nepal, Thailand, and the United States—visited Hiroshima for the training program "HICARE/IAEA International Training Course: An Update on Advanced Technologies in Radiotherapy," sponsored by the Hiroshima International Council for the Radiation-exposed (HICARE) and the International Atomic Energy Agency (IAEA). The training was designed to provide instruction involving "effective and safe radiotherapy to cancer patients through the optimal utilization of modern radiotherapy technologies."

HICARE was designated a "Collaborating Centre for: Capacity Building in Radiation Effects and Human Health" by the IAEA on May 26, 2014, a designation that will last at least four years. As an IAEA Collaborating Centre, HICARE conducts training programs for physicians and researchers. The designation is considered to be international recognition of HICARE's technical expertise and advanced level of research. HICARE is a collection of 10 entities, including RERF, Hiroshima Prefecture, Hiroshima City, and Hiroshima University. HICARE is the second IAEA Collaborating Centre in Japan.

The recent training course was the third HICARE/IAEA course held jointly since 2013, and the first to be conducted since HICARE was designated an IAEA Collaborating Centre. In the first joint training session, nine overseas trainees participated, with 12 participants at the second session. The total of 27 trainees at the recent training course thus represents a significant increase.

On the first day of the training course, January 19, 2015, RERF Chairman Toshiteru Okubo, who also serves as HICARE President, gave the opening address. The initial day of the event took place at the Oriental Hotel Hiroshima and covered novel radiation treatment technologies, clinical applications, and the basic physics of such treatments.

Dr. Kazunori Kodama (foreground), Chief Scientist, speaks to HICARE/IAEA International Training Course group at Hiroshima RERF

Dr. Kodama (left) explains ABCC-RERF history to HICARE/IAEA International Training Course group

After gathering at the same hotel the next day, January 20, to attend talks on cancer treatments worldwide, the group of 27 trainees moved to the Hiroshima University Hospital on January 21 to listen to an overview of the hospital and witness demonstrations of target and organs-at-risk (OAR) delineations within the framework of radiation medical therapy.

The next day, January 22, the group visited RERF, where Dr. Kazunori Kodama, Chief Scientist, introduced the organization in a presentation. Dr. Kodama, along with Dr. Toshiya Inaba, Director of the Hiroshima University Research Institute for Radiation Biology and Medicine, serve as the liaison officers between the HICARE and IAEA organizations. At the RERF Auditorium, each of the trainees was awarded a certificate for completion of the training course. The group then spent the afternoon touring the Hiroshima Peace Memorial Museum and the Atomic Bomb Dome, a building that stands as a monument to the destruction caused by the A-bombing and serves as a designated UNESCO World Heritage Site.

About the importance of the meeting, Dr. Kodama remarked that in 10 or 20 years, there will be a "big jump" in the number of cancer patients who survive radiation treatment, because certain cancers can now be cured. But, according to Dr. Kodama, those same people may be at increased risk of development of secondary cancers due to the radiation used to often successfully treat the initial cancer. In radiotherapy, radiation is used to expose cancer tissue, but at the same time, the treatment "gives radiation to normal tissues and

they [patients] suffer risks of other diseases," he said.

Dr. Kodama went on to say that the research results from RERF can go a long way toward making people understand the long-term health effects from radiation exposure. He added about the trainees, "They have to also learn about radiation risks," rather than study only the beneficial effects.

Several of the trainees remarked how the visit to Japan gave them a chance to learn about advanced radiotherapy technologies not currently available in their own countries, testimony to the importance of the training course.

RERF International Training Course: Training for Cambodian Breast Cancer Specialists Held at Hiroshima RERF

Three Cambodian physicians and two medical officers from the Cambodia Ministry of Health visited the Hiroshima RERF Laboratory for several hours on April 15, 2015, to study the health effects of A-bomb radiation exposure as part of their training in breast cancer examination. The Cambodian group was accompanied by Honorary Professor Koki Inai of Hiroshima University.

Following an introductory video about RERF and its scientific mission, Dr. Atsuko Sadakane, RERF Associate Senior Scientist and Acting Chief, Laboratory of Pathology, Department of Epidemiology, addressed the visitors by outlining the RERF Life Span Study (LSS) and its results. She described the LSS research methodology and summarized research results concerning risks of mortality and cancer incidence, with a focus on breast cancer incidence, due to A-bomb radiation exposure. The trainees were especially interested in the remarkably long duration of the LSS—the study was initiated in 1950—and asked many questions regarding ways to interpret research results and the significance of certain numerical values.

Dr. Mai Utada, Research Scientist, Department of Epidemiology, talked to the visitors about Hiroshima's cancer registry system. She explained that accurate information on cancer cases has been obtained in Hiroshima based on three cancer registries: the Hiroshima City Cancer Registry, Hiroshima Prefectural Cancer Registry, and Hiroshima Prefectural Tumor Registry. These cancer registries have been operated jointly with cooperation among local governments, medical institutes, medical associations, and RERF, which has been entrusted to perform the actual work of the registries. The trainees were especially interested in items included on a notification form for the Hiroshima Prefectural Cancer Registry.

Next, RERF's Dr. Tomonori Hayashi, Assistant Chief, Department of Radiobiology/Molecular Epidemiology, presented an explanation of radiation effects on immunological functions in A-bomb survivors. He explained individual differences in stomach cancer susceptibility to radiation exposure, especially the relationship between radiation exposure and stomach cancer risks by genotype of immunosuppressive gene IL10, a subject that has been reported in international scientific journals. Dr. Hayashi also described the relationship between radiation exposure and developmental mechanisms of thyroid cancer among A-bomb survivors. In response to a question about whether thyroid cancer cases that developed early after A-bomb radiation exposure were considered to be a direct effect of radiation on DNA, Dr. Hayashi noted the likelihood that some thyroid cancer cases developing early after exposure were related to radiation. He added that, because numerous leukemia cases were observed among A-bomb survivors within about 10 years after exposure, some of them were likely to have been caused by the direct effects of radiation on DNA.

Based on their many questions and comments, the Cambodian visitors appeared to find their RERF visit both interesting and fruitful.

Group of Cambodian breast cancer specialists receiving training at Hiroshima RERF

RERF International Symposium: Application of "Omics" to Radiation Research

Robert L. Ullrich
Associate Chief of Research

An international symposium was held at Hiroshima RERF on December 2 and 3, 2014, titled "Application of 'Omics' to Radiation Research." This symposium was made possible through funding from the Japan Ministry of Health, Labour and Welfare (MHLW) international exchange program. Many of the participants were from overseas and the working language of the symposium was English, with all presentations, including those of Japanese scientists, made in that language.

The purposes of this symposium were twofold: first, to provide the opportunity for RERF scientists to become familiar with the latest cutting-edge "omics" technologies, including proteomics, proteogenomics, and metabolomics, and how they could be applied to identify biomarkers and molecular changes associated with mechanisms of radiation-induced disease in the survivors of the atomic bombings; second, to familiarize the outside participants with the opportunities through collaborative research programs to better understand radiation risks, develop new tools to facilitate the early diagnosis of disease processes important to the survivors, and improve treatment approaches.

Such collaborative studies using these new technologies have the potential to make a major impact on understanding of disease processes such as cancer and cardiovascular disease that is likely to result in improvement of the lives of people throughout the world.

Topics in the symposium included presentations from RERF scientific staff on the current status of the Adult Health Study (AHS), transcriptomic and proteomic analysis, lipidomics and integrated "omics" approaches, and metabolomics. Four internationally known Japanese scientists and three leading scientists from the United States were invited speakers. The symposium was attended by the RERF scientific staff, who also acted as discussants or moderators, by a number of scientists from academic and research institutions in Japan, as well as by international observers from Europe and the United States. Session I, involving the current status of RERF AHS studies, was chaired by Dr. Yoshiaki Kodama, then Chief, RERF Department of Genetics. The session was opened by Dr. Kazunori Kodama, Chief Scientist, then Director, Biosample Center, who introduced RERF's Life Span Study (LSS) and AHS biosamples and their significance to radiation research. Dr. Waka Ohishi, Chief, Department of Clinical Studies, went into further details about AHS studies, as a follow-up to Dr. Kodama's presentation. Dr. Tomonori Hayashi, Assistant Chief, Department of Radiobiology/Molecular Epidemiology, gave a general summary of RERF AHS immunology and National Institute of Allergy and Infectious Diseases (NIAID) immunosenescence studies. A discussion ensued, followed by a group photo session and lunch at Hijiyama Hall.

Session II, with the theme transcriptomics (study of all RNA molecules and their functions) and proteomics (study of all proteins produced by an organism), began in the afternoon, and Dr. Yoichiro Kusunoki, Chief, Department of Radiobiology/Molecular Epidemiology, chaired the session. Dr. Sumio Sugano, Professor, Division of Biosciences, Department of Medical Genome Sciences, Graduate School of Frontier Sciences, University of Tokyo, spoke about single cell transcriptome analysis using next generation sequencers, followed by Dr. David R. Goodlett, Professor and Isaac E. Emerson Chair of Pharmaceutical Sciences, University of Maryland School of Pharmacy, who spoke on label free proteomics for clinical analysis.

After a short break, Session III, relating to the fields of lipidomics (study of pathways and networks of cellular lipids in biological systems) and integrated "omics," was chaired by Dr. Ohishi, with Dr. Kazutaka Ikeda, Senior Researcher, Laboratory for Metabolomics, Center for Integrative Medical Sciences, Riken, giving a presentation on the topic of multi-lipidomics platforms for focusing globally on lipo-quality. Dr. Mark R. Emmett, Professor, Department of Biochemistry and Molecular Biology, Sealy Center for Molecular Medicine, University of Texas Medical Branch, then spoke on uses of integrated "omics" in cancer research. The day's events concluded with a reception hosted by RERF that was held at Andersen, a popular European-style bakery/restaurant in downtown Hiroshima.

Session IV, held the next day, December 3, was chaired by Dr. Hayashi under the theme metabolomics (study of metabolites present within an organism, cell, or tissue). Dr. Albert J. Fornace, Professor, Molecular Cancer Research Chair at Lombardi Comprehensive Cancer Center, and Professor, Department of Biochemistry and Molecular & Cellular Biology and Department of Oncology, Georgetown University, opened the session with his description of ongoing developments in

radiation metabolomics. Dr. Mitsuhiro Yanagida, Professor, G0 Cell Unit, Okinawa Institute of Science and Technology Graduate University (OIST), spoke on the issue of the science of blood metabolomics in humans. After a short break, Dr. Daisuke Miura, Associate Professor, Metabolic Profiling Research Group, Innovation Center for Medical Redox Navigation, Kyushu University, discussed a matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS: a soft ionization technique used in mass spectrometry for analysis of biomolecules)-based imaging technique and its application to pathological analysis.

Session V, which was time set aside for general discussion, marked the conclusion of the meeting and was finished with closing remarks by Dr. Robert L. Ullrich, Associate Chief of Research and the organizer of the event. Japanese *o-bento* lunches for the speakers rounded out the itinerary.

This "omics" symposium focused on a new research field for RERF and has already led to new research projects being developed by RERF scientists. In addition, the symposium has stimulated important scientific discussions between RERF scientists and leading scientists in Japan, as well as enhanced overseas researchers' interest in RERF as a laboratory in which they can become involved in collaborative research into radiation effects.

Participants in the RERF International Workshop "Application of 'Omics' to Radiation Research" outside Hiroshima RERF

RERF International Workshop: Meeting on Dosimetry Issues

Harry M. Cullings, Chief
Department of Statistics

On March 25–26, 2015, an international workshop was held at Hiroshima RERF on dosimetry issues related to calculation of doses for the atomic bomb survivors. This workshop was the third in an annual series of meetings. The plan for this workshop was to begin by summarizing the recently completed work on dosimetry at RERF, followed by discussions related to a new plan for improved organ dosimetry. Following these topics was a discussion of particular categories of survivors with "unknown doses," which made up the majority of the agenda.

After a brief greeting, Dr. Harry M. Cullings, Chief, RERF Department of Statistics, began the meeting with a summary of recent changes to survivors' DS02 dose estimates, as a result of the various projects included in the recent work at RERF during 2010–2014. This work included cross-checking, prioritization, and selection of the best U.S. Army map coordinates for each survivor

based on all available original source documents, as well as restoration of digits (tens of yards) that had been truncated for many survivors due to limitations in early data processing systems. In addition, geometrically corrected pre-bombing aerial photographs were prepared and assembled into photographic maps of Hiroshima and Nagasaki called "orthophotographic mosaics," and these were used to correct distortions in the U.S. Army maps, resulting in more accurate location information for survivors.

A major improvement in terrain shielding input data was achieved by using high-resolution digital terrain elevation data. Finally, the upgrade included a number of miscellaneous improvements such as a "fix" to the DS02 code for combining the shielding of houses and terrain features, and a change in the way that neutron and gamma-ray components of dose are handled when total shielded kerma exceeds 4 Gy.

Dr. Cullings showed various histograms of the new dose estimates, scatter plots of new vs. old doses, and tables related to changes in dose estimates. There were no major changes in the frequency distributions of dose estimates for the LSS. The overall effect of the changes on risk estimates is expected to be small, although some relatively subtle matters such as curvature in the dose-response may be affected. The effects on major risk estimates for the LSS are currently being evaluated. A manuscript combining three previous manuscripts on the new dose estimates is being prepared and is expected to be submitted to an appropriate journal.

In the next presentation, Dr. Cullings described a new plan for a binational working group on organ dosimetry to be created and funded by RERF. The plan is to combine the existing DS02 shielded fluences with newly created computational phantoms (models of the human body) to derive new calculations of doses to tissues and organs. The new phantoms would replace simple models of the human body developed in the 1980s, based on geometrical shapes such as cones and cylinders, and would have more anatomical detail and body sizes. These would include a pediatric series, male- and female-specific adolescent and adult phantoms, and trimester-specific fetal phantoms. In addition to the 15 organs originally included in DS86, additional organs including the esophagus, heart, kidney, major blood vessels, prostate, thymus, and various teeth would be calculated. Finally, there would be new combined "body + workbench" and "body + machine tool" phantoms for factory workers that were behind a workbench or free-standing machine tool to allow correct calculation of partial-body shielding. The binational working group held its first meeting May 20–21, 2015, at Hiroshima RERF (a report on this meeting is expected to appear in the next Update).

In the next presentation, Dr. Stephen D. Egbert discussed a number of factors that the organ dose working group would need to consider in its work, particularly in regard to how the radiation transport calculations would be performed. He began with a history of organ dose calculation, noting that modifications of the T65D dosimetry system were the first calculations of organ doses by use of transmission factors (ratio of organ dose to dose in air at the same location) that were not assumed to depend on any other factors such as distance or house shielding. Then in 1985 the DS86 leakage tables were created for 15 organs in 3 sizes of phantoms. These tables could be used with any shielded fluence calculated by DS86 (and later, DS02) and have been used for 30 years.

Next, Dr. Egbert discussed basic possible parameters for the new effort, and in particular he recommended several target values of statistical precision for the new tables, starting with 1% standard error due to sampling statistics, for total organ dose. He compared the advantages and disadvantages of a forward Monte Carlo transport code (Monte Carlo N-Particle, or MCNP) and an adjoint (backwards calculation in time) code (Monte Carlo Adjoint Shielding, or MASH). Key points were that MCNP was more modern and up-to-date than MASH in its inputs such as scattering probabilities ("cross sections") but is extremely inefficient for this problem, and leakage tables would have to be developed by *post hoc* processing of the results. Another important point was that conversion factors for converting fluence to dose would have to be developed in some cases and should be improved in others, particularly for heterogeneous organs and tissues involving an interface between two media, such as red bone marrow (soft tissue interface with bone), skin and lens of eye (soft tissue interface with air), and tooth enamel (small, sharply defined inclusions of enamel interfacing with dentin/pulp, soft tissue of the mouth, and bone in the jaw).

Following Dr. Egbert's presentation, the focus shifted to a discussion of survivors in two DS02 categories of shielding, namely categories "10" and "11," for which there is no DS02 module to calculate survivors shielding. The purposes of this discussion were to illuminate the detailed shielding situations of a large fraction of the survivors who currently have "unknown" doses and to suggest possible situations that might be amenable to dose calculation with modest effort, as well as to examine the assumptions under which survivors at long enough distances have their doses calculated in the current implementation of DS02 using averaged transmission factors (TF).

Several members of the Master File Section

Table: Details of DS02 categories 10 and 11

City	ds02cat	Outside				Inside					Other	Total
		In open	Behind Wall	Behind tree	Terrain	Factory	Barrack	Tram or Train	Concrete building	Earth covered shelter		
H	10	58	6	6	0	20	18	1	1	3	6	119
	11	50	87	7	19	65	31	192	56	17	42	566
N	10	15	0	132	57	30	47	1	2	1	11	296
	11	37	21	16	111	109	13	3	11	254	49	624
Total		160	114	161	187	224	109	197	70	275	108	1,605

Note: H: Hiroshima; N: Nagasaki

provided details on what is known about the shielding of survivors in these categories. Mr. Tadaaki Watanabe, Master File Section, Department of Epidemiology, began by presenting some detailed information and tables. Of 7,070 survivors with "unknown" doses, DS02 categories 10 and 11 comprise 5,863 (about 83%), of whom 5,448 are in category 11. Only about 27% of the survivors in these categories have shielding histories, but virtually all of them have some substantial information about their shielding on other early forms. Although DS02 category 10 is commonly referred to as "average outside," only about 69% of the survivors involved were outside, and the other 31% were actually inside at the time of the bombing. Similarly, although DS02 category 11 is commonly referred to as "average inside," only about 68% of the survivors involved were inside, and the other 32% were actually outside at the time of the bombing. Mr. Watanabe showed a detailed table, reproduced above, of the types of shielding for all survivors in DS02 categories 10 and 11.

Next, Mr. Takashi Oda, Master File Section, Department of Epidemiology, reviewed detailed information about three of the categories for persons who were outside: "in open," "behind a wall," and "behind a tree." Although the DS86 and DS02 implementation manuals and associated materials suggest that DS02 category 10 includes a number of survivors who were "in open" but did not have flash burns, and persons who were "in open with flash burns" are supposed to be categorized as DS02 category 0 ("in open"), there were 108 survivors in both DS02 categories 10 and 11 who were actually "in open" and more than half had flash burns, suggesting it might be feasible to reclassify them as DS02 category 0 with calculated doses. Persons who were classified as being "behind a wall" appeared similar to those who were found to be behind more massive earthen barriers in other recent work at RERF. That is to say, it might be possible to perform dose calculations for them based on their drawings in the cases where drawings exist.

Mr. Hiroshi Fuchi, Master File Section, Department of Epidemiology, then reviewed the details of persons in DS02 categories 10 and 11 who were inside of a building, i.e., in either factories or "barracks" type buildings. Some of the survivors who were in factories appeared to have actually been in the modeled parts of modeled buildings in Nagasaki, making reclassification possible for them. Others were clearly in other types of factory buildings or in sheds on the sides of larger buildings. Of the barracks type buildings, many cases shown were small buildings such as sheds, toilet buildings, and guard shacks. It is not clear whether the materials and construction of these barracks type buildings, especially the small ones in light of their small size compared to "9P" houses, would allow the use of the 9P house model for them with suitable adjustments.

Next, Dr. Cullings gave a talk that reviewed aspects of the history of the DS02 categories 10 and 11, the rules for when they are calculated with averaged transmission factors (TFs) as opposed to being classified as "unknown dose," and how the averaged transmission factors are calculated. A point that emerged from these detailed presentations is that the "average outdoor" and "average any" TFs are based on assumptions that are not completely consistent with the actual makeup of the shielding situations to which they are being applied, and may not be accurate estimates of the true mean TFs of the survivors to whom they are being applied. Furthermore, it may be possible to estimate better averaged TFs, and if it is, it may be reasonable to apply them at proximal as well as distal distances.

Dr. Cullings closed by reviewing criteria for possible calculation of currently "unknown" dose estimates, including cost and feasibility, and the precision and potential bias of feasible estimates. Finally, he pointed out that computational methods and resources have changed dramatically since the time 30 years ago when DS86 was created.

Dr. Eric J. Grant, Assistant Chief, Department of Epidemiology, gave a closing talk that provided

an illustration of the power of modern computational methods. He considered survivors who were classified as "in open," but may have had nontrivial shielding from nearby buildings and other structures, or tree canopy. He pointed out that technologies exist to create three-dimensional imagery or mathematical models from sources such as aerial photographs and/or survivors' shielding history diagrams. After showing some examples gleaned from the Geographical Information System (GIS) used for map work at RERF, he picked an example neighborhood and showed panoramic views from a three-dimensional model that he created in Google Sketchup™. He pointed out some advantages for survivors in DS02 categories 10 and 11 that are categorized as "in open":

- Most were interviewed and have shielding histories.
- Many were located at close ranges and have high doses.
- They could add to the statistical power of RERF studies.
- They would alleviate concerns regarding biases due to "unknown doses" and help us maximize the use of our data.

He pointed out, however, that implementing his idea might require developing some new models or methods for situations not well represented by RERF's current GLOBE models (e.g., the model house cluster of DS86) and methods.

With that the meeting ended on a positive note, with tangible ideas for possible future improvements to the dosimetry of survivors without shielding histories and ways to reduce the number of survivors with "unknown" doses, as well as a preview of upgrades being considered for organ dose calculation.

Participants in the RERF International Workshop on dosimetry issues in Hiroshima RERF's Auditorium

Seminar Held at RERF: Hiroshima Statistical Study Group — High-Dimensional Data Methods for Proteomics

Harry M. Cullings, Chief
Department of Statistics

For a number of years, RERF has been hosting the Hiroshima Statistical Study Group, which meets about once a month to hear a talk about some aspect of statistics. Members of the group come from RERF and local universities such as Hiroshima University. On January 23, 2015, the group was treated to a talk by Dr. Inge Koch, Associate Professor at the School of Mathematical Sciences of the University of Adelaide, Australia, who was visiting Hiroshima University. Dr. Koch is an expert in high-dimensional data and has written a book on the topic, "Analysis of Multivariate and High-Dimensional Data," published by Cambridge University Press. The title of Dr. Koch's talk was "Analysis of Spatial Data from Proteomics Imaging Mass Spectrometry."

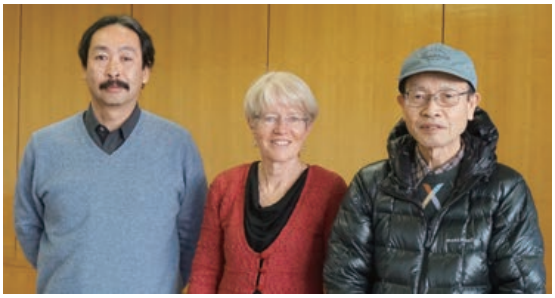
Mass spectrometry (MS) has become a versatile and powerful tool in proteomics for the analysis of complex biological systems. It works by separating proteins into peptides, ionizing them and electromagnetically accelerating them, then counting the ions as they reach a detector. In the instrument of

interest to Dr. Koch's work, the masses of these peptides are measured by the "time of flight" that elapses between the ionization and arrival at the detector, which generates a spectrum with thousands of very sharp peaks at different mass values.

Unlike the common MS techniques, the more recent imaging mass spectrometry (IMS) preserves the spatial distribution inherent in tissue samples by measuring analyte masses at thousands of individual locations across a specially prepared tissue sample. IMS data consist of tens of thousands of spectra measured over at the tissue locations, and each spectrum or profile consists of ion counts or ion intensities at a large range of masses, which are the variables. Each spectrum arises from a grid point on the surface of a tissue section, from which we obtain knowledge about the spatial distribution of the spectra.

Motivated by the requirements in cancer research to differentiate cell populations and tissue types of such data accurately and efficiently, Dr. Koch's group developed a combined cluster analysis and feature extraction approach to identify subsets of the spectral masses that distinguish cancerous tissue from adjacent normal tissue. She illustrated this approach using IMS data obtained from tissue sections of patients with ovarian cancer. To overcome problems with signal gain that depends on location in the tissue section, peaks are converted to binary data (present or absent) and a "differences in proportion of occurrence statistic" (DIPPS) is developed. In this way, the spectrum for a point on a tissue sample, which exhibits the ion intensities of masses of peptides, can be used without any particular knowledge of the spectrum that is generated by any particular protein or peptide.

These ideas were applied to the cancerous and non-cancerous regions of patient tissue sections to summarize the variables which best characterize cancer tissue in a single image that has a natural interpretation. Comparisons of DIPPS maps and their associated "cancer" variables for tissue samples from different cancer patients demonstrate the similarity or diversity of cancer tissue from different patients.



Dr. Inge Koch (center), Associate Professor at the School of Mathematical Sciences of the University of Adelaide, Australia, after talk to Hiroshima Statistical Study Group, with two group members, Dr. Hirofumi Wakaki (left), Professor, Hiroshima University, and Dr. Yasunori Fujikoshi (right), Professor Emeritus, Hiroshima University

Association of Radiation Dose with Prevalence of Thyroid Nodules among Atomic Bomb Survivors Exposed in Childhood (2007–2011)*

Misa Imaizumi

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*This article is based on the following publication:

Misa Imaizumi, Waka Ohishi, Eiji Nakashima, Nobuko Sera, Kazuo Neriishi, Michiko Yamada, Yoshimi Tatsukawa, Ikuno Takahashi, Saeko Fujiwara, Takao Ando, Toshiro Usa, Atsushi Kawakami, Masazumi Akahoshi, and Ayumi Hida: Association of Radiation Dose with Prevalence of Thyroid Nodules among Atomic Bomb Survivors Exposed in Childhood (2007–2011). *JAMA Intern Med* 2015 (February); 175(2):228–236 (doi: 10.1001/jamainternmed.2014.6692)

Study Findings

A thyroid study conducted among A-bomb survivors 62–66 years after exposure to radiation in childhood (at less than 10 years of age) revealed a significant association between the prevalence* of larger thyroid nodules (those with a diameter of 10 mm or more, or those with past surgery for a nodule) and A-bomb radiation dose to the thyroid; however, no association was observed for small nodules of less than 10 mm in diameter.

*The term "prevalence" here refers to the percentage of the population with a disease at the time of examination, regardless of whether or not they had been previously diagnosed.

Explanation

Adult Health Study (AHS) participants were examined to investigate the association between thyroid nodules and A-bomb radiation in survivors exposed in childhood (at less than 10 years of age). The AHS has examined the health status of A-bomb survivors in Hiroshima and Nagasaki since 1958 through biennial medical assessments.

[Note]

The term thyroid nodule refers to a benign or malignant growth in the thyroid gland. Thyroid ultrasound-based observation classifies such nodules into two major types: cysts or solid nodules. Nearly all cysts are benign, while solid nodules are further classified into malignant tumors (mostly cancers) and benign nodules. Benign nodules include benign tumors, hyperplasia, and thyroiditis-related nodules. Thyroid nodules that are not malignant usually do not require treatment; however, in the case of large nodules with pressure symptoms or when the possibility of malignancy cannot be ruled out, treatment may be necessary. This study focused on relatively large thyroid nodules (diameter of 10 mm or more, or post-surgical cases), which are likely to emerge as a clinical problem. The study also reviewed small nodules less than 10 mm in diameter, which are unlikely to be a clinical problem.

1. Objectives

It is known that the risk of thyroid cancer is higher after radiation exposure in childhood compared with exposure in adulthood. Determining whether or not the effects of radiation exposure on the thyroid appear among adults many years after exposure in childhood is an important public health issue. On the other hand, thyroid ultrasonography can detect thyroid nodules in 17–67% of the general population who have had little exposure to radiation. This study aims to elucidate the association between thyroid nodules and A-bomb radiation among A-bomb survivors more than 60 years after exposure in childhood.

2. Methods

Thyroid examinations, including thyroid ultrasonography, were conducted on 3,087 A-bomb survivors participating in the AHS between 2007 and 2011 who were less than 10 years old at the time of exposure. The study investigated the association of thyroid dose with the prevalence of larger thyroid nodules (diameter of 10 mm or more, or post-surgical cases), as well as small thyroid nodules (diameter of less than 10 mm) among 2,688 survivors for whom A-bomb radiation dose to the thyroid had been estimated. The mean age of participants was

68.2 years; 1,213 were males and 1,455 females; the median dose was 0.182 Gy (182 mGy); and the dose range was 0–4.040 Gy.

3. Results

(1) The prevalence (17.6% of those examined) of larger thyroid nodules (diameter of 10 mm or more, or post-surgical cases) was significantly associated with thyroid radiation dose; the estimated excess odds ratio** per gray (Gy) of thyroid dose was 1.65 (95% confidence interval (CI): 0.89, 2.64). We conducted the analyses by classifying the thyroid nodules into solid nodules and cysts, and then further classifying the solid nodules as malignant tumors or benign nodules. Respective analyses detected a significant association between nodule prevalence and thyroid dose.

**In this study, we considered the odds ratio to be nearly equivalent to relative risk; The odds ratio represents how many times higher the risk is for the radiation-exposed group than for the control group (i.e., those with a radiation dose of zero Gy). The excess odds ratio is represented by the odds ratio minus one and shows the portion of relative risk that can be attributed to radiation exposure.

(2) The study revealed that age at exposure significantly affected the association between the prevalence of larger thyroid nodules (diameter of 10 mm or more, or post-surgical cases) and radiation, and that the effects of radiation were greater with earlier childhood exposure. On the other hand, the radiation risk did not vary substantially by sex, family history of thyroid disease, presence of antithyroid antibodies, or intake of seaweed.

[Note]

Generally speaking, thyroid nodules occur with greater frequency in females and in those with a family history of thyroid disease and are also frequently observed in chronic thyroiditis patients (those with positive blood tests for antithyroid antibodies). It is also known that the nodules are affected by intake of iodine, and seaweed is rich in iodine. Consequently, we examined whether or not these factors affected the degree of radiation risk for thyroid nodules.

(3) No significant association was observed between small thyroid nodules (diameter of less than 10 mm) and radiation dose to the thyroid.

More than 60 years after exposure to radiation in childhood, instances of larger thyroid nodules (diameter of 10 mm or more, or post-surgical cases) were associated with radiation dose; however, such an association was not observed for small thyroid nodules (diameter of less than 10 mm). The term thyroid nodule refers to a variety of clinical states, including cancers, benign tumors, hyperplasia, and thyroiditis-related changes. The difference in effects of radiation in relation to the size of nodules may provide clues to the mechanisms through which radiation exposure affects the clinical state of thyroid nodules.

Skin Cancer Incidence among Atomic Bomb Survivors from 1958 to 1996*

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*This article is based on the following publication:

Hiromi Sugiyama, Munechika Misumi, Masao Kishikawa, Masachika Iseki, Shuji Yonehara, Tomayoshi Hayashi, Midori Soda, Yukiko Shimizu, Ritsu Sakata, Eric J. Grant, Fumiyoshi Kasagi, Kiyohiko Mabuchi, Akihiko Suyama, Kotaro Ozasa: Skin Cancer Incidence among Atomic Bomb Survivors from 1958 to 1996. *Radiat Res* 2014 (May); 181(5):531–9 (doi: 10.1667/RR13494.1)

Study Findings

Researchers observed that exposure to radiation is associated with a significant risk of developing basal cell skin cancer, with a dose-response threshold of 0.63 Gy and risk increasing as the age at exposure decreases.

Commentary

1. Objective

Researchers have reported a clearly increased risk of skin cancer, especially basal cell cancer, in association with exposure to ionizing radiation, based on studies of A-bomb survivors, workers in the field of radiation medicine, and individuals with a history of radiation treatment. The Radiation Effects Research Foundation (RERF) previously reported radiation risks for skin cancer based on cases diagnosed during the period from 1958 to 1987 in the Life Span Study (LSS) population. In the present study, the observation period was extended for nine years, and radiation risks for skin cancer according to histological type as well as the effects of ultraviolet radiation on radiation risks were investigated.

2. Methods

The subjects of this study were 80,158 of the 120,321 individuals in the LSS population who were alive in 1958, when both local cancer registries in Hiroshima and Nagasaki began operations, and whose radiation dose was estimated by the latest dosimetry system (DS02). Pathological review was conducted on potential skin tumors diagnosed from 1958 to 1996 to estimate radiation risks for first primary cancers by histological type. A Poisson regression model was used for the analysis.

3. Results

(1) Radiation risks for basal cell cancer

With regard to basal cell cancer (123 cases), the best fit was a linear-threshold model with a threshold dose of 0.63 Gy (95% confidence interval [CI]: 0.32, 0.89); the excess relative risk at 1 Gy of exposure (ERR_{1Gy}) was estimated to be 0.74 (95% CI: 0.26, 1.6) for those age 30 at exposure. The risk was estimated to increase by 11% with each one-year decrease in age at exposure; thus the ERR_{1Gy} was estimated to be about 7 after exposure at age 10. On the other hand, attained age did not significantly affect radiation risks.

(2) Relationship between ultraviolet radiation and radiation risks for basal cell cancer

The ERR_{1Gy} of basal cell cancer on skin areas likely to be exposed to ultraviolet radiation, such as the face and hands, was estimated at 0.6 (95% CI: <0, 2.1), and the ERR_{1Gy} of areas unlikely to be exposed to ultraviolet radiation, such as the trunk and extremities except for hands, was estimated as 2.3 (95% CI: 0.61, 6.7). Although there was no statistically significant difference between the two ($P = 0.15$), the results suggest that radiation risks were higher for the areas unlikely to be exposed to ultraviolet radiation.

(3) Radiation risks for squamous cell cancer *in situ* (Bowen's disease)

When a linear model was used, the ERR_{1Gy} of squamous cell cancer *in situ* (64 cases) was 0.71 (95% CI: 0.063, 1.9). However, by city, the ERR_{1Gy} of squamous cell cancer *in situ* (Bowen's disease) in Hiroshima (56 cases) was not significant, at 0.28 (95% CI: <0, 1.9), whereas that in Nagasaki (8 cases) was extremely high, at 17.6 (95% CI: 3.0, 149); and a statistically significant difference existed between the two ($P < 0.001$). However, the number of cases in Nagasaki was small, and there may have been a difference between Hiroshima and Nagasaki in the diagnosis of squamous cell cancer *in situ* and in the rate of reporting to local

cancer registries. Therefore, it was difficult to draw a conclusion about whether any significant dose-response relationship existed.

(4) Radiation risks for other histological types

There was no significant dose response relationship for malignant melanoma (10 cases), squamous cell cancer (114 cases), Paget disease (10 cases), or other skin cancers (15 cases). The null result for malignant melanoma with regard to radiation dose is especially notable since that is the most serious form of skin cancer.

The results of this study show that a linear dose-response relationship with a threshold dose of 0.63 Gy exists between basal cell cancer and A-bomb radiation, and that the lower the age is at exposure, the higher the radiation risk. There was no significant relationship between radiation exposure and malignant melanoma, squamous cell cancer, or Paget disease.

Handling Incomplete Smoking History Data in Survival Analysis*

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*This article is based on the following publication:

Kyoji Furukawa, Dale L. Preston, Munechika Misumi, and Harry M. Cullings: Handling Incomplete Smoking History Data in Survival Analysis. *Stat Methods in Med Res* 2014 (October 26) (electronic version prior to print publication) (doi: 10.1177/0962280214556794)

Study Findings

This study proposes a new method based on multiple imputation* for analysis involving incomplete smoking history data, a situation that could be problematic when analyzing cancer incidence data in the Life Span Study (LSS) of atomic bomb survivors. Applying the proposed approach to the LSS lung cancer incidence analysis, we observed the radiation-associated lung cancer risk to be larger among moderate smokers than heavy smokers. The smoking-radiation interaction, which had been estimated to be unusually strong in the previous analysis using a naive approach (relatively simple methodology to analyze missing data) with missing data indicators, was slightly weaker in the current analysis, which seems to be more interpretable. The proposed approach is expected to reduce estimation bias that might be unavoidable in naive analyses while preserving efficiency by using all available information, which should lead to radiation risk estimation with improved precision.

*A method to analyze data involving missing observations by averaging the estimation results across multiple imputed data sets.

Explanation

In studying the radiation effects on, for example, cancer incidence among atomic bomb survivors, it is important to account for effects of other important risk factors, such as smoking habit. However, data for such risk factors are frequently missing or only available incompletely. Generally, the choice of a method to analyze data involving missing data may have large impacts on the results of risk estimation. In particular, it is well known that a naive approach, such as the simple deletion of subjects with missing data, can lead to substantial bias in estimation. This study proposed a new approach using multiple imputation for analysis involving missing or incompletely observed smoking history data, applied it to analysis of the LSS lung cancer incidence, and compared the estimation results with those based on the simpler missing-data approaches.

1. Study purpose

To develop a new multiple imputation method to analyze data involving missing or incompletely observed time-dependent smoking history data and apply it to the LSS lung cancer incidence analysis.

2. Study methods

In analyzing the LSS lung cancer incidence during the period 1958–1999, about 40% of the 105,401 eligible subjects had no smoking data, and many of the others had smoking history known for only part of the time period. As a new approach of multiple imputation for incompletely observed smoking history data, prediction models for the age of smoking initiation and, given initiation, smoking intensity and cessation age, were estimated; based on which missing smoking data were predicted and imputed. Complete data sets including the imputed data were analyzed by multiple imputation.

3. Study results

In an analysis of the LSS lung cancer incidence, we confirmed that when one had both radiation exposure and smoking habit, the radiation-associated excess relative risk of lung cancer would be higher if he/she were a moderate smoker than a heavy smoker. The smoking-radiation interaction, which had been found to be unusually strong by a naive approach using indicators for missing data, was slightly weaker with the new approach, which seems to be more interpretable for the joint effect of radiation exposure and smoking habit. The proposed approach is particularly appealing in a large-scale cohort study such as the LSS, since it can reduce estimation bias that might be unavoidable in naive analyses while maintaining efficiency by retaining known information, which is expected to lead to radiation risk estimation with improved precision.

Participating in the Health Examination/Consultation Project for A-bomb Survivors Living in South Korea

Daisuke Haruta, Research Scientist
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The Health Examination/Consultation Project for A-bomb Survivors Living in South Korea has been conducted biannually since 2004 by the Nagasaki prefectural and city governments as part of an assistance program for the survivors currently residing in that country. The latest trip marks the 22nd of this project, and it was my third time to participate, following the first trip to Gwangju and Daejeon and the second to Seoul. This project aims at dispelling concerns about late effects of A-bomb radiation exposure and contributing to the good health of the A-bomb survivors in South Korea, through health examinations and consultations provided by medical teams dispatched from Japan.

Since A-bomb survivors reside throughout South Korea, the project targets cities and regions where a relatively large number of A-bomb survivors are concentrated, such as Seoul, Daegu, Hapcheon, Busan, Masan, Gwangju, Pyeongtaek, Daejeon, Ulsan, Jeju, and Gyeongsangnam-do. Our six-day schedule covered the Daegu region during the period February 1–6, 2015 (essentially four days, with the first and last days spent for travel). The project work was carried out by an eight-member team consisting of five internal medicine specialists from Nagasaki City, one public health nurse from the Nagasaki municipal government, and two staff members from the Nagasaki prefectural government.

On the first day of the project, we flew from Fukuoka Airport to Gimhae International Airport in Busan and from there traveled about two hours by bus to Daegu. After arriving in the city, we took a facility tour of the Daegu Red Cross Blood Center, where the health examinations/consultations were scheduled, and also visited a market. We were told that Daegu did not have many sightseeing spots, and our visit to the market was our only tourist activity during our stay.

During the four-day period from the second through the fifth days of the project, we studied the results of examinations conducted at local hospitals prior to our visit, and via interpreters, provided the A-bomb survivors with explanations on the examination results as well as health consultation and advice. Participating in the project for the third time, I had a somewhat better understanding of how to handle my work and could carry it out relatively smoothly.

Daegu has more project participants than other regions, with our five physicians having had consultations with 289 A-bomb survivors in total. In terms of the latest project in Daegu, the prevalence of lifestyle diseases was high, as in other areas, but it was noteworthy for me that the prevalence of diseases in the orthopedic area (osteoarthritis, rheumatoid arthritis, and disc herniation) was high compared with past times. On the last day of the project, we left our hotel at 5:30 a.m. for Gimhae International Airport for a 9:00 flight back to Japan.

Having participated in this project on multiple occasions, I keenly felt that, like the A-bomb survivors in Japan, those living in South Korea still suffer from the effects of A-bomb radiation exposure and that they need continued psychological and economic support. What otherwise impressed me were that many A-bomb survivors in South Korea desire friendly relations with Japan; winter in South Korea can be very cold; kimchi made in Japan better suits my taste; and my family told me that I smelled of garlic even some time after I returned to Japan. I hope that I can continue to be of some help in dispelling concerns among the A-bomb survivors in South Korea through this project.

I would like to express my appreciation to the research scientists and staff members at the RERF Nagasaki Laboratory who supported my participa-

Health Examination/Consultation Project for A-bomb Survivors Living in South Korea visits South Korea (Dr. Daisuke Haruta, author, at bottom left)

tion in this 22nd Health Examination/Consultation Project for A-bomb Survivors Living in South Korea, as well as to the employees and volunteer staff members from the Korean Red Cross and to our interpreters for their support during our stay in South Korea.

In Memoriam: Arthur Canfield Upton, MD

(February 27, 1923–February 14, 2015)

Arthur Canfield Upton, M.D., former director of the U.S. National Cancer Institute (NCI) (1977–1980) and president of the American Association for Cancer Research (AACR) (1963–1964), died on February 14, 2015, at the age of 92. Dr. Upton served on RERF's Scientific Council (present-day Scientific Advisory Committee, or SAC) as an independent scientific advisor for seven years during the 1970s and 1980s. In that role, he provided RERF with advice on RERF's research activities from a specialist's perspective.

Dr. Upton was internationally recognized for his research on the health effects of ionizing radiation and other hazardous environmental agents. He was also emeritus professor of environmental medicine and clinical professor of environmental and community medicine at the University of Medicine and Dentistry–Robert Wood Johnson Medical School in Newark, New Jersey.

Dr. Upton was appointed director of the NCI by President Jimmy Carter in 1977. He used his extensive knowledge of environmental carcinogenesis to make environmental issues one of his first initiatives. In 1980, he became director of the Institute of Environmental Medicine at New York University, whose members were instrumental in establishing the Environmental Protection Agency (EPA) and other environmental protection organizations.

Born on February 27, 1923, Upton received his medical degree in 1946 from the University of Michigan in Ann Arbor. In the course of his career, Dr. Upton published nearly 400 articles, books, and technical reports on the health effects of ionizing radiation and other hazardous environmental agents, and he held leadership positions on the principal national and international professional organizations concerned with the prevention and medical management of such effects, serving as president of the AACR, the American Society for Experimental Pathology, the Radiation Research Society, and the International Association for Radiation Research.

In recognition of his contributions, he was elected as a member to the Institute of Medicine of the United States National Academies, Honorary Membership in the Peruvian Oncology Society, the Japanese Cancer Association, the New York Academy of Sciences, as well as the American Registry of Pathology, and received many other honors, including the E.O. Lawrence Award, the Lovelace Medical Foundation Award for Excellence in Environmental Research, and the Distinguished Achievement Award of the Society for Risk Analysis.

Dr. Upton is survived by his wife Elizabeth (the former Elizabeth Perry), three children—Rebecca Tobey, Melissa P. Upton, and Bradley Upton—nine grandchildren, and seven great grandchildren.

RERF would like to offer its condolences to Dr. Upton's family and express our heartfelt appreciation for Dr. Upton's significant contributions to the field of radiation research over so many years, including to the research conducted at RERF.

In memoriam: Arthur Canfield Upton, MD, Scientific Councillor (1984)

Preservation of RERF's Biosamples

Yoshiaki Kodama, Director
Biosample Center

The Atomic Bomb Casualty Commission (ABCC) and the Radiation Effects Research Foundation (RERF) have for many years collected various biosamples from A-bomb survivors and their offspring (including blood, urine, tissue, tooth samples, as well as microscope slide and autopsy samples), a portion of which are preserved for future research.

For example, we have preserved blood samples such as serum, plasma, and lymphocytes donated by Adult Health Study (AHS) participants through biennial (every two years) health examinations since 1969, and by participants of the Clinical Study of the F1 Offspring of A-bomb Survivors (FOCS) through 2002–2006 health examinations and during subsequent quadrennial (every four years) examinations starting in 2010. In each case, consent was obtained from study participants. We also began preserving urine samples from AHS and FOCS participants in 2002.

As a result of these efforts, approximately 900,000 tubes of blood and urine samples from about 20,000 AHS and 10,000 FOCS participants are currently preserved, most in a frozen state; other biosamples, including about 700,000 paraffin-embedded samples and 1,400,000 microscope slide samples are stored separately (refer to the table below for sample numbers). Since all these materials are extremely valuable for clarification of the health effects of A-bomb radiation, we plan to continue such biosample collection and preservation into the future.

RERF's biosamples had been collected and preserved by individual research departments or individual research scientists in accordance with their respective research protocols. As a result, various problems emerged in preparing for the centralized utilization of the biosamples, including the absence of standardized methods for sample preparation and difficulty in creation of biosample databases. In addition, we encountered a number of hardware issues: preservation of samples in both Hiroshima

Table. Approximate breakdown of RERF's biosamples (as of the end of November 2013)

Biosamples	Total quantity (approximate)
1. Serum	490,000 tubes
2. Plasma	180,000 tubes
3. Lymphocytes	120,000 tubes
4. Urine	110,000 tubes
5. Paraffin embedded blocks	700,000 blocks
6. Microscope slide samples	1,400,000 slide samples

Serum, plasma, urine and other samples are stored in deep freezers (Hiroshima RERF).

Lymphocytes and other materials are stored in liquid nitrogen tanks (Hiroshima RERF).

Figure 1. Deep freezer room (left) and liquid nitrogen tank room

and Nagasaki locations, an important countermeasure against disasters such as fire and earthquake, is limited to a very small portion of the biosamples; and current countermeasures to protect the large number of deep freezers in the event of power outage are not necessarily sufficient.

To address such issues, we established the RERF Biosample Center in April 2013. Employing specialist staff to prepare samples using standardized methods, creating centralized management of biosamples and standardization of biosample quality, and compiling a biosample information database, the Biosample Center serves as a centralized, functional biosample "bank" for this valuable material. These efforts are expected to promote effective use of RERF's biosamples for a wide range of studies.

The biggest problem in the creation of the Biosample Center was a shortage of space for preserving the samples. As previously mentioned, nearly 900,000 tubes of biosamples are preserved in deep freezers or liquid nitrogen tanks, and already both Hiroshima and Nagasaki laboratories lack adequate space to accept any more (Figure 1). Because it has been difficult to secure more storage space, we were confronted with the task of how to store the ever-increasing numbers of biosamples. To address this challenge, we explored the introduction of a robotic biorepository system (automated biosample storage) and decided to launch the system (Figure 2) at the Hiroshima Laboratory in FY2015. The robotic biorepository will employ a supersized deep freezer system with a computer-automated sample-selection function and liquid nitrogen backup cooling function in the event of an extended power outage. The storage capacity of this system will depend on the size of biosample storage tubes; for example, it will be able to accommodate more than three million small-sized tubes. The introduction of the new equipment is expected to bring about various advantages, including conservation of space, energy, and workload, improved operation efficiency, and enhanced risk management. We project that the robotic biorepository system will provide enough storage space for the coming 20 years in Hiroshima. Introduction of a robotic biorepository at the Nagasaki Laboratory is also planned for some time in the future.

As of now, full-fledged operation of the robotic biorepository at the Hiroshima Laboratory is scheduled to begin in October 2015.

Figure 2. Robotic biorepository (–80°C BioStore II: Operation is scheduled to start in October 2015)

Full-scale Research Protocol Approved in November 2014–April 2015

RP 1-15 Effects of ionizing radiation on impairments of glucose and lipid metabolism and impact on risks of arteriosclerotic diseases and cancers

Yoshimi Tatsukawa, Ayumi Hida, Michiko Yamada, Young Min Kim, Harry M. Cullings, Nobuko Sera, Ritsu Sakata, Waka Ohishi, Shuhei Nakanishi, Masayasu Yoneda

Impairment of glucose metabolism and lipid metabolism are major risk factors for arteriosclerotic diseases, but the effects of atomic bomb radiation on those conditions are unclear. The Adult Health Study (AHS) cohort of atomic bomb survivors, which has been followed by biennial health examinations since 1958 and has obtained medical information at each examination cycle, is comprised of suitable subjects for assessing the effects of radiation on conditions such as diabetes and dyslipidemia. Furthermore, the AHS cohort was expanded in 2008 to include about 1,900 younger survivors (<10 years old at the time of bombing [ATB]), and various biomarkers for glucose and lipid metabolism have been measured in them as well as in the original cohort. Since the expansion group includes a large number of lightly exposed individuals relative to the original cohort, it will provide more precise information on dose response. In this proposed research protocol (RP), we will use a longitudinal study format to examine whether radiation exposure is associated with the development of diabetes and whether any such association is influenced by the city of exposure and age ATB.

It is well known that radiation exposure is associated with increased risk for many cancers. Recent studies have also suggested an association between radiation exposure and the risk of arteriosclerotic diseases; however, the underlying mechanism remains elusive. Diabetes and dyslipidemia are major risk factors for arteriosclerotic diseases. Recent epidemiological studies have also shown that diabetes is associated with risk for not only arteriosclerotic diseases but some cancers as well. This RP will also investigate whether radiation exposure is associated with increased risks of arteriosclerotic disease and cancer through impaired glucose and/or lipid metabolism, using 'causal modeling' to evaluate intermediate variables. We will use a cross-sectional study design, to investigate an association between radiation exposure and HbA1c, insulin resistance, lipid levels (such as HDL cholesterol), and biomarkers involving glucose and lipid metabolism (such as adiponectin).

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(Japanese): the original article is in Japanese.

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