放影研 RERF update

Summer
Volume 27, Issue 1, 2016
News and Views

Radiation Effects Research Foundation

Hiroshima and Nagasaki, Japan

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From the Editors

Welcome to the Summer issue of Update for 2016. This will be the last issue with the current Editor-in-Chief, Dr. Harry M. Cullings, at the helm. Starting with the next Update, the Winter 2016 issue, Dr. Eric J. Grant, the Radiation Effects Research Foundation (RERF)'s new Associate Chief of Research (ACOR), will take over the editorship duties. Mr. Jun Kitamura, Mr. Yutaka Ogasawara, and Ms. Sayaka Green, all staff in the Public Relations and Publications Office, joined the team earlier in the year as Technical Editors to replace previous editors who were transferred elsewhere within RERF or moved from Hiroshima due to family considerations. In addition to the news that Dr. Grant has left his longtime post in the Epidemiology Department to become the ACOR, other news is that Mr. Douglas C. Solvie, another long-time employee at RERF, was appointed to serve as RERF's first U.S. Chief of Secretariat.

Right now, as we finish up our final bit of editing, is the most beautiful time of year in Hiroshima, spanning Golden Week at the beginning of May and the onset of rainy season in early June. We have had a typical spring this year in terms of weather, although the gentle climate was punctuated by a violent series of earthquakes in the Kumamoto region of Kyushu, the southernmost major island of the Japanese archipelago, with the major quakes occurring on April 14 and 16. Although a disaster in Kumamoto, the tremors were only mildly perceptible here in Hiroshima and did not affect in any substantial way our laboratory in Nagasaki, which is located relatively close to Kumamoto.

Harry Cullings, Editor-in-Chief

The seismic-reinforcement and electrical-system overhaul and construction projects are being completed at the Hiroshima laboratory, and we are back to our usual state of affairs with the removal of most of the temporary structures. The major piece of news this spring so far has been that U.S. President Barack Obama came to visit Hiroshima, the first sitting American president to do so. He did not visit us here at RERF, undoubtedly for a number of reasons, but his coming to this A-bombed city has gone a long way to increasing our visibility in the U.S. and other media (please see a PBS video at http://www.pbs.org/video/2365764140/ and a Los Angeles Times article at http://www.latimes.com/world/asia/la-fg-hiroshima-researchers-20160519-snap-story.html;

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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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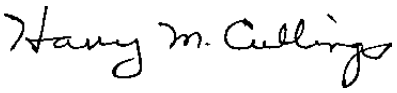
these links have also been posted on RERF's Facebook page). We have a full issue as usual, including greetings from Dr. Grant and Mr. Solvie, a review of the 43rd Scientific Advisory Committee meeting held in March, accounts of a number of public relations activities, a report on a Biosample Workshop in which we obtained expert advice and discussion related to our new Biorepository and Research Resource Center, and the usual complement of science articles.

We hope you enjoy this, my final, issue!

June 1, 2016



Harry M. Cullings
Editor-in-Chief

Report on the 43rd Scientific Advisory Committee Meeting March 2–4, 2016

The 43rd meeting of the Radiation Effects Research Foundation (RERF) Scientific Advisory Committee (SAC) was held March 2–4, 2016, at Hiroshima RERF, Japan. The 10 SAC members were joined by two Special Scientific Advisors, Dr. Hirotsugu Ueshima and Dr. Marjan Boerma, added for their expertise in epidemiological research and radiation cardiac toxicity, respectively. This year's in-depth review focused on the Department of Clinical Studies.

43rd Scientific Advisory Committee meeting, at Hiroshima RERF

Dr. Ohtsura Niwa, RERF Chairman, opened the meeting on Wednesday March 2, with a high-level overview of RERF as a public interest incorporated foundation and of its organizational structure focused on clinical studies and support services. He addressed the changing environment and the outside pressures that RERF faces and stressed the importance of transparency and accountability for the foundation. Consistent with RERF's objective to conduct research studies, he provided a leader's view of the Foundation's future plans.

Recently, RERF initiated a major restructuring that has involved the merging of the Radiobiology/Molecular Epidemiology and Genetics departments into the new Molecular Biosciences Department and the formation of a scientific structure comprised of "research clusters." This year, 2016, marks the first year this change has been fully implemented. While it may be premature to judge the impact of restructuring, the SAC indicated that it appreciates the substantial effort this change represents, viewing it as a positive response to some of the shortcomings the committee had previously identified.

Dr. Robert L. Ullrich, Vice Chairman and Chief of Research, reported next on RERF research developments following the initial restructuring by departmental merger (Molecular Biosciences Department) and the use of multidisciplinary meetings, interactions, and collaborations for performing research within the new "research cluster" system. The prioritization of research projects due to resource limitations was described next. Dr. Ullrich's vision for establishing a stronger computational biology emphasis includes strategic collaborations. The plans for maximizing the study of novel biospecimens include exploration of collaborations with Japanese companies and institutions as well as selected external collaborators, such as the U.S. National Institutes of Health (NIH) and the National Cancer Institute (NCI), but clearly within guidelines for sample-sharing that respect A-bomb survivor sensitivities. The efforts to strengthen the Research Resource Center were also described. In his presentation, Dr. Ullrich addressed all of the 2015 SAC comments and summarized RERF research achievements during the course of 2015. These achievements included the following:

- A comprehensive analysis to update radiation risk estimates for cancer incidence through 2009 was completed using updated individual doses and information on lifestyle factors such as smoking in collaboration with the U.S. NCI.
- A detailed analysis of mortality risk and dose

responses of heart-disease subtypes in separate observation periods from 1950 to 2008 was conducted in collaboration with the Cardiovascular Disease Research Cluster and Department of Clinical Studies.
- A first-author paper on the association of radiation dose with the prevalence of thyroid nodules among Adult Health Study (AHS) subjects exposed at younger ages was published.
- Two first-author papers on the effects of demographic factors and radiation on the age trend of cognitive function between 1992 and 2011 among subjects exposed at ≥13 years of age were published.
- A paper on cancer and non-cancer mortality risks among the children of the atomic bomb survivors during 1946–2009 was published.
- The RERF Statistics and Epidemiology departments revised location estimates for individual survivors resulting from recent map work by the Master File Section, as well as revised and improved input data on terrain shielding at those new locations resulting in changes in survivors' DS02 dose estimates.

An overview presentation by Dr. Waka Ohishi, Chief, Department of Clinical Studies, followed. The responses to SAC comments were provided and later fortified by examples in subsequent individual presentations. Dr. Ikuno Takahashi, Research Scientist, Department of Clinical Studies, presented on radiation and cardiovascular disease, and Dr. Daisuke Haruta, Research Scientist, Department of Clinical Studies (Nagasaki), focused on chronic renal disease in exposed individuals. Dr. Shunichi Yamashita, Dean/Professor, Graduate School of Biomedical Sciences, Nagasaki University, of the SAC provided comments for improving the working hypothesis slides to eliminate ambiguity. Dr. Ayumi Hida, Chief, Division of Medicine, Senior Scientist, Department of Clinical Studies (Nagasaki), summarized the ophthalmology studies, and Dr. Kazunori Kodama, Chief Scientist, provided information on the Fukushima nuclear emergency workers health study (known as the NEW Study, or NEWS) and the many difficulties encountered in locating subjects and obtaining their agreement to participate.

Dr. Kotaro Ozasa, Chief, Department of Epidemiology, presented that department's overview and addressed all of the prior SAC comments and concerns. Dr. Harry M. Cullings, Chief, Department of Statistics, provided that department's overview and focused on the aging research staff and needs for recruitment of researchers. Dr. Hiroaki Katayama, Chief, Department of Information Technology, provided his department's overview, which also was marked by an aging staff and resource limitations. Dr. Yoichiro Kusunoki, Chief, Department of Molecular Biosciences, completed the departmental presentations with an overview of the new department.

On Thursday, March 3, Dr. Yoshiaki Kodama presented a Biosample Center update and Dr. Niwa addressed RERF's future plans. A discussion with the SAC provided some of the issues to be addressed. The SAC members visited the departments Thursday morning and the Resource Center in the afternoon, followed by in-depth reviews, in preparation for discussions and report preparation.

After this thorough review the SAC provided overall recommendations for RERF as well as more specific recommendations for each department. The key written recommendations for RERF are given below:

1. The SAC recognized and expressed its appreciation for the organized meeting materials provided to SAC members. It also appreciated the enormous amount of work and resources involved in managing this RERF annual meeting and raised the question as to whether this large commitment of resources and investigator time might be better spent on research activities. Several SAC members have suggested that a biennial review cycle be considered. In alternate years, a written progress report, reviewed administratively, may suffice to monitor progress. Several others considered these annual reviews to be appropriate in their current format. RERF administration was encouraged to discuss these options with the U.S.-Japan official representatives.
2. Several presentations expressed concerns that the RERF investigators are aging, the facilities need investment, and the future of the foundation is in flux. The SAC discussed these concerns and recognized the need for RERF leadership to initiate the processes needed to develop a strategic plan for RERF's future.
3. RERF's primary directive was to perform epidemiological studies of subjects exposed to atomic bomb radiation. To this end, the carcinogenesis studies have provided outstanding data to advance the understanding of radiation effects in humans. Furthermore, the F1 generation studies will provide answers to critical questions about the potential trans-generational effects of human radiation exposures. Much of the recent research has focused on non-cancer studies of low-level radiation. The findings have been less convincing and more difficult to support, since the rationale for performing studies has been based on high-dose, clinical exposures (published literature),

and RERF observations of non-cancer diseases may be confounded by the aging process of subjects.

4. More involvement of the Department of Statistics at the early stage of research proposal design was recommended. The Statistics Department has been contributing to "after-the-fact" data analyses for many RERF studies in the other departments. The SAC strongly recommended that at least one Statistics Department member participates in the design stage of each research proposal. All new and continued Research Protocol (RP)'s should have a clear working hypothesis with the indication of expected statistical power and feasibility for the experimental design.
5. Similarly, the SAC urged the involvement of at least one member from the Epidemiology Department in the discussions, design, and analyses of these studies to ensure that the cohort data will be utilized appropriately.
6. The SAC recognized the increase in collaborations and communication that have been led by young scientists within RERF. The SAC recommended increasing the visibility of such activities within RERF as well as to the public. This may serve to attract more highly qualified candidates for recruitment to RERF. Academic positions for young scientists are limited in Japan so it is not clear why there are not more applications for positions at RERF.

An important recommendation for the Clinical Studies Department, which was the primary focus of review this year, is shown below:

- The equipment and resources have been purchased and are in place for completing the cataract study. It was somewhat disconcerting that only four participants can be evaluated per week per city for data collection due to a shortage of ophthalmologist time availability. This allocation of resources should be reviewed and the data collection accelerated, to complete this study in a timely fashion.

In summary, the SAC recognized the important and unique contributions that RERF makes to science as well as to the determination of radiation risks. Recognizing these important roles that RERF currently plays on the world stage, the SAC made the key suggestion to develop a strategic plan for the future of RERF covering the next 20–30 years.

Participants of 43rd Scientific Advisory Committee meeting, at Hiroshima RERF

Scientific Advisors

Dr. Anatoly Dritschilo, Professor and Chairman, Department of Radiation Medicine, Georgetown University School of Medicine, *Co-chairperson*
Dr. Shunichi Yamashita, Trustee, Vice President, Nagasaki University, *Co-chairperson*
Dr. Yoichi Gondo, Team Leader, Mutagenesis and Genomics Team, RIKEN BioResource Center
Dr. Michiaki Kai, Professor, Environmental Health Science, Department of Health Sciences, Oita University of Nursing and Health Sciences
Dr. Kazuo Sakai, Professor, Faculty of Nursing, Tokyo Healthcare University
Dr. Tomotaka Sobue, Professor, Department of Social and Environmental Medicine, Graduate School of Medicine, Osaka University
Dr. David G. Hoel, Distinguished University Professor, Department of Medicine, Medical University of South Carolina, and Principal Scientist, Exponent Inc.
Dr. Michael N. Cornforth, Professor and Director of Biology Division, Department of Radiation Oncology, The University of Texas Medical Branch
Dr. Francesca Dominici, Professor of Biostatistics, Department of Biostatistics; Senior Associate Dean for Research, Office of the Dean, Harvard School of Public Health
Dr. Jonine Bernstein, Attending Epidemiologist, Co-Program Leader, Survivorship, Outcomes and Risk Program, Memorial Sloan Kettering Cancer Center

Special Scientific Advisors

Dr. Hirotsugu Ueshima, Professor Emeritus, Shiga University of Medical Science and Special Contract Professor, Center for Epidemiologic Research in Asia, Shiga University of Medical Science
Dr. Marjan Boerma, Associate Professor, University of Arkansas for Medical Sciences, Department of Pharmaceutical Sciences, Division of Radiation Health

Sixth Public Lectures Held in Nagasaki and Hiroshima

Giving their presentation, Ms. Saki Anzai (right), Ms. Minori Saito, Fukushima High School

RERF held its sixth public lecture event in Nagasaki at the Nagasaki Atomic Bomb Museum Hall, on November 28, 2015. The lecture series is designed to enhance communication by conveying information to the general public, including atomic bomb survivors and their children, about results from RERF's long-standing research on A-bomb radiation health effects.

This most recent public lecture event was designed to introduce to Nagasaki citizens RERF's research results, involvement with Fukushima, future outlook, and how its scientific findings are utilized throughout the world, as well as details about a radiation study conducted by high school students. The event was attended by more than 100 people.

In his opening greetings, RERF Chairman Ohtsura Niwa remarked, "This year [2015], the 70th since the atomic bombings, is a milestone for passing down our knowledge gained from the experience of the atomic bombings to future generations. For this, we need debate from multiple perspectives. On this occasion of our public lecture event, I look forward to receiving candid opinions from people with different backgrounds, especially young people."

The event's first speaker, Mr. Malcolm Crick, Secretary, United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), presented a lecture titled "The World and RERF." He explained how RERF studies are crucially important to UNSCEAR and the international scientific community because data obtained from A-bomb survivors and their children serve as the "gold standard" for establishing radiation protection standards. He added that while the radiation exposures from the atomic bombings of Hiroshima and Nagasaki and the nuclear accident in Fukushima differ significantly in terms of physics, there are some similarities in terms of societal and psychological impacts as well as effects on the human body. He also emphasized the importance of not losing objectivity and maintaining a holistic perspective.

Mr. Malcolm Crick, Secretary, United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) (left), Dr. Kazunori Kodama, Chief Scientist, RERF

The second talk, titled "RERF Research Results, Involvement with Fukushima, and Future Outlook," was presented by Dr. Kazunori Kodama, RERF Chief Scientist. He outlined what has been learned from RERF studies on radiation health effects and what needs to be investigated further. He also introduced the activities in which RERF has engaged since the Fukushima nuclear plant accident, with special focus on a study involving about 20,000 Fukushima Daiichi nuclear plant emergency workers that RERF initiated approximately one year ago in collaboration with other organizations. Lastly, he explained the future outlook regarding remaining questions and issues.

The last presentation, titled "Project for Individual Dose Measurement of High School Students Inside and Outside of Fukushima," was made by Miss Minori Saito and Miss Saki Anzai, students from Fukushima Prefectural High School, and their teacher, Mr. Takashi Hara. They presented their research project, which looked into when, where, and how much radiation individuals were exposed

A choir of Nagasaki Junshin Girls High School students perform with wishes for peace

to on the basis of the collation of information on their daily activities along with a record of hourly radiation dose readings using a dosimeter called "D-Shuttle." Time and date information at the time of each reading was additionally provided. They also described the hardships Fukushima now faces and called for broad understanding of the actual situation in Fukushima based on scientific facts. This project was carried out in collaboration with high school students inside and outside of Fukushima as well as overseas. The results were published in the Journal of Radiological Protection (http://iopscience.iop.org/article/10.1088/0952-4746/36/1/49) and have been presented in not only Japan but also France and Italy.

Following the lecture and presentations, there was a question-and-answer session with the audience chaired by Mr. Takanobu Teramoto, RERF Executive Director.

As 2015 marked the 70th year since the atomic bombings and the 40th anniversary of the founding of RERF, remarks of gratitude to A-bomb survivors and their children for their participation in RERF's studies were read aloud by an RERF staff member. In addition, a choir comprised of Nagasaki Junshin Girls High School students performed songs to express heartfelt condolences to those who perished in the atomic bombings and their desire for the realization of a world free of nuclear weapons.

The event concluded with closing remarks by Vice Chairman Robert L. Ullrich, who expressed his gratitude in Japanese to the audience for their participation in the Nagasaki public lecture and the valuable opinions expressed therein.

In Hiroshima, RERF held its sixth public lecture event at the International Culture Hall on the first basement floor of the main building of the Hiroshima YMCA International Culture Center on November 29, 2015. Despite the cold weather, the event was attended by 143 people.

Following opening greetings by Chairman Niwa, guest greetings were provided by Mr. Sunao Tsuboi, Chairman, Hiroshima Prefectural Confederation of A-bomb Sufferers Organizations. Once again, remarks of gratitude to A-bomb survivors and their children for their participation in RERF's studies were read aloud by a Hiroshima RERF staff member. Three presentations were then provided by RERF's Dr. Kodama, Fukushima Prefectural High School's Super Science Club, and UNSCEAR's Mr. Crick. Between the presentations, students from Hiroshima Municipal Funairi High School performed a musical interlude to express their sincere condolences to those who died as a result of the atomic bombings.

Prior to the public lecture event in Hiroshima, a gathering that featured an A-bomb survivor's testimony was held at a different venue in the same building. At the gathering, Mr. Tsuboi—who was exposed to the atomic bombing in Hiroshima at the age of 20 and has long engaged in peace activities while struggling with numerous health issues—talked about his extraordinary experiences to those in attendance, including the Fukushima High School students, their teacher Mr. Hara, and Mr. Crick from UNSCEAR.

Mr. Teramoto chaired a question-and-answer period, which followed the final and third presentation. Vice Chairman Ullrich once again closed the lecture with his closing remarks in Japanese.

Media Forums Held in Nagasaki and Hiroshima

RERF held media forums on April 13, 2016, at Nagasaki RERF and on April 18 in Hiroshima. The Nagasaki forum, convened in the conference room on the 3rd floor of the Nagasaki Laboratory, gathered 11 media representatives from eight organizations. The Hiroshima forum, which took place in the Auditorium of the Hiroshima Laboratory, hosted 13 reporters from seven media outlets.

The purpose of the annual media gathering is to present new research achievements and increase understanding among media representatives about the studies conducted over a period of nearly 70 years at ABCC-RERF. In this way, the forums provide knowledge the media can use to better inform the public about the health effects from A-bomb radiation.

At both the Nagasaki and Hiroshima forums, Dr. Ohtsura Niwa, Chairman, opened this event

Media Forum at Nagasaki RERF, with Hiroshima RERF researchers attending via TV conferencing (at rear)

—his first, as he was appointed to the post in June 2015—by providing greetings and his impressions of RERF's operations in a general sense. Dr. Kazunori Kodama, Chief Scientist, followed by

giving an extensive presentation titled "Overview of RERF research," including the topics of RERF research issues and policies.

Mr. Takanobu Teramoto, in charge of public relations as the Executive Director, closed the presentations by speaking on the topic "FY2016 plans for events/projects." Mr. Teramoto described the major events scheduled for both Nagasaki and Hiroshima in the upcoming fiscal year, including the Open House events in August, the Local Liaison Council meetings in both cities in September, and the public lectures scheduled for some time in the fall.

At the forums, media participants raised questions regarding the Epidemiological Study of Health Effects in Fukushima Emergency Workers (NEWS) and its progress, about the new RERF "research cluster" concept, and for further clarification of RERF epidemiological findings.

Compared with the same event last year, the number of media representatives in 2016 was almost double (11 vs. seven in 2015 in Nagasaki; 13 vs. six in Hiroshima), perhaps indicating their heightened interest in listening to Chairman Niwa for the first time in such a setting, or perhaps signaling increased interest among the media in this informal gathering.

Media Forum held in Hiroshima, with Dr. Ohtsura Niwa, Chairman, giving opening greetings (at rear)

Filmmakers Study A-bombing Health Effects for Documentary of Nuclear Testing on Australia's Aboriginal Lands

John Mandelberg, an award-winning documentary filmmaker from Australia who has produced and directed film and television for 25 years and is a founder/producer at Blue Water Productions, visited Hiroshima RERF on April 11, 2016, together with his crew. His film team hoped to obtain background information on RERF's findings for production of a documentary covering British nuclear testing on Aboriginal lands in Australia in the 1950s and early 1960s.

To inform their filmmaking, the group interviewed Dr. Harry Cullings, Chief, Statistics Department, about RERF findings regarding health effects from radiation and the aftermaths of the Hiroshima and Nagasaki A-bombings. The interview included questions about the size of the atomic weapon that was exploded over Hiroshima in terms of TNT equivalency, prevalent types of cancers in atomic bomb survivors in Japan, and health effects found by ABCC-RERF in the offspring of survivors.

According to Mandelberg, who also teaches at the Waikato Institute of Technology (Win-

Mr. John Mandelberg of Australia media team interviewing Dr. Harry Cullings, Chief, Statistics Department (Photo source: Nicholas Sherman, ACS)

tec) School of Media Arts & Moving Image in New Zealand, the group visited RERF because "Filming in Hiroshima will give us context for the start of the nuclear age and the effects of this tragedy," in reference to the atomic bombings. The film will conclude with a description of the situation in Fukushima and a discussion of the future of nuclear energy and nuclear weapons, Mandelberg said.

Blue Water Production's documentary, "Totem & Ore," is set to be released some time in 2018.

Sixth ABCC-RERF History Forum Held at Hiroshima—with Dr. Hideya Tamagaki, former ABCC physician, as speaker

Hiroaki Katayama, Chief
Department of Information Technology

The sixth ABCC-RERF History Forum was held at the Hiroshima RERF Auditorium on April 21, 2016, and featured former ABCC physician Dr. Hideya Tamagaki as speaker. Born in 1922, Dr. Tamagaki is now 93 years old. In 1949, he started his career at a branch office of the Japanese National Institute of Health (located within ABCC at that time), and conducted genetics and other studies. Over a period of 16 years until 1965, he was involved in both clinical work and research at ABCC.

Like Ms. Kiyoko Minato and Ms. Hisae Tanaka, both of whom served as nurses at ABCC and spoke at a previous History Forum, Dr. Tamagaki conveyed a vivid and detailed account of his memories of his work in the early days of ABCC. He administered new medicines to leukemia patients which came from the U.S. and were not yet available in Japan, and treated seriously ill patients at the ABCC inpatient facilities, some of whom went home after remission of their conditions. When

Dr. Hideya Tamagaki (right), talking about his past experiences at ABCC

Dr. Hideya Tamagaki (first row right); Mr. Takanobu Teramoto (left), Executive Director; (from second row left) Ms. Nozomi Tamagaki, daughter of Dr. Tamagaki; Mr. Toraji Miyagawa, Historical Material Management Committee member and former Chief of General Affairs Section; Ms. Hisae Tanaka and Ms. Kiyoko Minato, former ABCC nurses; Dr. Hiroaki Katayama, Chief of Information Technology Department; Dr. Kazunori Kodama, Chief Scientist; Dr. Ohtsura Niwa, Chairman

he examined newborns for the genetic study, the examinee families were delighted with the soap and towels given by ABCC for their cooperation. At the inception of the Adult Health Study, he had experienced being admonished when visiting houses to request A-bomb survivors for cooperation for participation in the A-bomb survivor study. He could not speak English when he joined the department of internal medicine, but one year later, he was able to communicate in English without difficulty.

What was the most impressive was Dr. Tamagaki's repeated emphasis that ABCC had taught him the importance of sticking to the basics when performing medical examinations, even though he had learned the basics of the examinations at medical school. His statement shows his sincerity when he did such examinations. I would like to add, on a slightly off-topic note, that after the forum he told us with laughter that he still exercises twice a week, which made me deeply conscious of carelessness about my own health.

To widely promote recognition of RERF's activities, this forum included media representatives in the audience. RERF will continue to actively publicize such activities to the extent possible.

RERF still maintains a high participation rate of nearly 80% in the AHS. As Dr. Tamagaki mentioned in his talk, the foundation owes a debt of gratitude to the hard work of employees who visited people's homes to request their participation in RERF's health examinations. It is not hard to imagine the hardship they endured in such jobs. We hope to feature former employees who were assigned to this duty to talk about their experiences in the next forum. For details about this most recent and previous forums, visit RERF's website (http://www.rerf.or.jp/history/histforum.html).

Staff News

Benjamin French was appointed as Associate Senior Scientist (fixed-term research scientist), Department of Statistics, on February 1, 2016. **Caitlin M. Milder**, Visiting Research Fellow, Department of Epidemiology, finished her term of appointment on February 22. **Ayako Takamori**, Visiting Student Fellow, Department of Epidemiology, finished her training at RERF on March 31. **Eiji Akimoto**, RERF Chief of Secretariat, resigned on March 31, and **Douglas C. Solvie**, Associate Chief of Secretariat, was appointed to the post of Chief of Secretariat on April 1. **Eric J. Grant**, Assistant Department Chief (Senior Scientist), Department of Epidemiology, was newly appointed as Associate Chief of Research on April 1. **Takahiko Ogawa**, Visiting Research Fellow, Department of Molecular Biosciences, **Yasuharu Niwa**, Associate Senior Scientist (fixed-term research scientist), Laboratory of Cell Biology, and **Midori Soda**, Adjunct Specialist (research scientist), Department of Epidemiology (Nagasaki), all resigned upon expiration of their terms on March 31. **Young Min Kim**, research scientist, Department of Statistics, resigned effective April 20.

The following are a greetings message from **Eric J. Grant**, the new Associate Chief of Research, and a farewell message from **Eiji Akimoto**, former Chief of Secretariat, and greetings from **Douglas C. Solvie**, newly appointed Chief of Secretariat, and **Benjamin French**, Associate Senior Scientist, with a farewell message from **Young Min Kim**, former research scientist.

Greetings and Farewells

Greetings from New Associate Chief of Research

Eric J. Grant

Many RERF staff will know me from my long-term service in the Department of Epidemiology, but for those readers who do not, please let me introduce myself.

I was originally hired by Dr. Kiyohiko Mabuchi, then Chief, Department of Epidemiology, in 1998 and rose to the rank of Assistant Chief of the Department in 2012, under the direction of Dr. Kotaro Ozasa, Chief of the same department. I have enjoyed working for the many talented researchers at RERF over these years. After Dr. Robert L. Ullrich was promoted to the post of Chief of

New Associate Chief of Research, Dr. Eric Grant

Research, in June 2015, he encouraged me to apply for the Associate Chief of Research position, to which I was promoted on April 1, 2016. I therefore had to say farewell to my colleagues in the Epidemiology Department and move to a different wing of the building within the RERF Secretariat.

Dr. Ohtsura Niwa, who was appointed as Chairman also in June 2015, Dr. Ullrich, and Mr. Takanobu Teramoto, Executive Director and the longest tenured director among the three, are together leading RERF during a time of transition. Upon starting my new post, I was assigned to spearhead the Cancer Research Cluster, part of a new "research cluster" initiative that aims to promote multidisciplinary research within the institute by organizing research work according to theme rather than department. It is my hope that I can assist them during this exciting time.

I have also been asked to pilot an effort to update our data-sharing policies to foster simpler and more comprehensive collaborations with outside institutes interested in using our data and samples in collaborative research. Another task of mine is to work together with Dr. Kazunori Kodama, Chief Scientist, and Dr. Hiroaki Katayama, Chief, Department of Information Technology, to develop the new RERF "Research Resource Center," which is designed to simplify access to RERF data for research scientists within the institute.

I realize I have much to learn and continue to be grateful for the support I receive from my coworkers at RERF. I am hopeful that I will be able to fulfill my responsibilities and reward the confidence my superiors have shown in me by selecting me for this challenging position. I ask everyone for continued support and patience as I grow into my new job and role. I look forward to continuing to work with everyone here at RERF and interacting with the public and other scientists outside of the foundation.

Greetings from New Chief of Secretariat

Douglas C. Solvie

I begin by extending my greetings to all readers of the RERF *Update* newsletter.

On April 1 this year, 2016, I assumed the position of Chief of Secretariat at RERF. For a number of years previous to that, I had been Associate Chief of Secretariat. I am grateful to RERF for this new opportunity and have found the position to be interesting and invigorating.

RERF faces many obstacles as we move towards the future. One of great concern to me is the aging of our management and general staff. To secure our future human resource needs, RERF must continue to look both inside and out to prepare a younger generation to take over management duties. I believe that people of talent and aspiration, regardless of their age, should be given the opportunity to hold leadership positions. This philosophy breaks somewhat with RERF and Japanese tradition, but I believe it is essential if we are to reinvigorate RERF and assure our future.

Another issue we face is that of bureaucracy. Since RERF became a Public Interest Incorporated Foundation (PIIF), keeping up with the related paperwork and rules and regulations has been a handful for staff, especially those in the Secretariat. RERF also has many outdated practices and regulations that need to be refined to the extent possible. We need to uncover inefficiencies and unproductive practices so that we can concentrate on areas of work that directly contribute to RERF's future.

New Chief of Secretariat, Mr. Douglas Solvie

As Chief of Secretariat, I plan to implement, with the help of the directors and all other staff, the changes I feel necessary to make RERF a more efficient and productive organization. It is important to find a balance between moving too slowly and moving too fast. To use a baseball analogy, I feel it is better in the initial innings to hit singles and doubles, one after another, than to swing for the fences. Staff will accept changes more easily if they are carried out in an orderly fashion with a clear path and vision to follow.

In closing, I realize my new responsibilities at RERF are great. I hope for your support and input to help me successfully repay the confidence placed in me in this way.

Farewell Message from the Former Chief of Secretariat

Eiji Akimoto

Former Chief of Secretariat, Mr. Eiji Akimoto

On March 31, 2016, I retired from my position as Chief of Secretariat at RERF and take this opportunity now to convey my heartfelt message of farewell.

I would like to express my sincere appreciation to all those who provided me with such tremendous support during my tenure at RERF, a period spanning 11 years and nine months since my initial appointment in July 2004.

Looking back on the time when I first was appointed to the post, great efforts were made to reach out to various stakeholders to notify them of the importance of continuing the research conducted at RERF, which had celebrated its 30th anniversary. Those efforts included our working on the first draft of RERF's future plans.

Amid such circumstances, I helped reform the personnel system through raising employee awareness and developing regulations based on a theory which holds that organizations reach their peak after 30 years but then decline if they fail to adapt to the latest business environment by focusing too much on only one facet of business.

After that, RERF was thrown into an unprecedented situation in which we needed to considerably shift the way we manage and operate RERF's budget, given that the yen rose to more than 80 yen per U.S. dollar. I am not fully confident that our suggestions and methods of handling the situation as the Secretariat were appropriate, but I did my best to fulfill my duties.

For RERF's April 2012 transition to a public interest incorporated foundation, an unprecedented project team was formed to work on this matter, as it was thought that the change could greatly affect the continued existence of the foundation. Transition to a public interest incorporated foundation was a major systemic reform for RERF, which at that time was approaching its 40th anniversary.

While at my post, I was fortunate to have had opportunities to engage in such work as taking care of the budget, personnel management including staff training, and reform of various systems in accordance with socioeconomic trends. I would like to extend my heartfelt gratitude to everyone at RERF for their heartfelt support. I acknowledge that a good number of issues remain at RERF, but I ask everyone's forgiveness for passing them on to the new Chief of Secretariat (see the article on previous page for Mr. Douglas C. Solvie's message).

In closing, I sincerely hope RERF can continue to shine as a research foundation that produces and conveys to the rest of the world its research findings from the field of radiation science.

Greetings

Benjamin French

On February 1, 2016, I joined RERF as Associate Senior Scientist in the Department of Statistics.

My undergraduate degree in mathematics and the Norwegian language was awarded in 2001 from St. Olaf College in Northfield, Minnesota. (Northfield is approximately 120 km from my hometown of Chatfield, Minnesota.) I earned a doctorate in biostatistics from the University of Washington in Seattle in 2008. After that, I served as an Assistant and then Associate Professor of Biostatistics at the University of Pennsylvania in Philadelphia. At RERF, I hope to share my expertise and experience in a prominent, multidisciplinary research environment, while contributing to this important binational endeavor.

My research until now has focused on statistical methods for analyzing longitudinal data, joint modeling of longitudinal and survival outcomes, and evaluating the accuracy of risk-prediction models. At RERF, I hope to contribute to epidemiological studies of mortality and cancer incidence, as well as to clinical studies regarding the effects of radiation exposure, particularly with respect to cardiovascular disease. I also hope to join efforts to use state-of-the-art scientific tools that make it possible to understand the mechanisms involved in disease development. I look forward to learning from my new collaborators here at RERF in Hiroshima.

Dr. Benjamin French, Associate Senior Scientist, Department of Statistics

Statisticians play an important role in the design of research studies and the analysis of research data. They also help to ensure that a research study is conducted properly and with scientific rigor. This is particularly important at RERF, where we owe so much to the dedication of the atomic bomb survivors. It is only through their sacrifices that our work can contribute new knowledge regarding the health effects of radiation exposure.

I am excited to experience life in Japan and to learn more about Japanese language and culture. In my free time, I enjoy cooking, reading, and hiking. If you have any favorite recipes, books, or hiking trails, please let me know!

Farewell

Young Min Kim

I do not want to say "Good-bye (さよなら), Hiroshima," but rather "See you later (またね), Hiroshima." After three years at RERF, I have decided to return to my home of Korea.

Hiroshima was the first city I experienced in Japan. Before the on-site interview at RERF, I had not been to any cities in Japan. My first impression of Hiroshima was that its people were so kind and helpful, enabling me to adapt to life in Hiroshima, even though I had problems adjusting to the new climate with its high temperatures and humidity in my first year.

Since arriving in Hiroshima, I fell in love with many kinds of Japanese food, such as sushi, the various types of noodles, and the Japanese version of Western food. I do not think I will be able to eat such nice sushi, especially considering its price and quality, anywhere outside of Japan. When I return to Korea and eat sushi there (Korean people also love the Japanese specialty), I know I will miss Hiroshima. Moreover, even though I did not like noodles before I came to Hiroshima, wondering why I would eat noodles instead of rice as a meal, I now love their taste. I worry because it is not easy to find such noodles outside Japan. Finally, even though I have always loved Japanese Western food like *tonkatsu* (deep fried breaded pork cutlet on rice), *omuraisu* (omelet filled with rice), hamburger steak, *hayashi* rice (hashed beef on rice), and so on, I have reconfirmed my love of such food.

From the perspective of work, I learned many things at RERF. I wanted to study long-term radiation effects on humans and nature. However, since I did not study biology the last 30 years and was unfamiliar with medical terms, it was not easy to follow RERF research. But RERF researchers, especially Statistics Department members, helped me understand such concepts and follow current

Dr. Young Min Kim, former research scientist, Department of Statistics

RERF research. Only with their help was I able to make it to the present time. In addition, I was able to learn the psychology of scientists and researchers during my time at RERF, an understanding that will enable me to continue conducting research as a scientist and statistician. I will thus persist in conducting long-term radiation-associated research when I return to my home of Korea.

I succeeded in getting a job in Daegu, which is the third biggest city in Korea and has a sister-city affiliation with Hiroshima. I learned of this relationship last year, 2015, when I visited the Hiroshima Memorial Museum and saw members of a team from that city participating in Hiroshima's Flower Festival. After RERF, I will start work in Daegu, a place I have never visited even though many of my friends are from there. I cannot adequately introduce anything about the city now, but at some point in the future I will likely discover such information and be able to report on it.

I offer my best wishes for the good health and happiness of all RERF staff, in both private and professional lives. I hope to see all my Japanese

friends and colleagues again. I truly appreciate everyone's kindness and help during my time here at RERF. I will remember Japan and RERF with fondness wherever I happen to be.

First Group of Trainees for RERF Training Recruited through Homepage

In late November last year, 2015, for about one month, RERF enjoyed the presence of four overseas trainees. The four were unique for RERF in one aspect: they were recruited as a result of RERF's first use of its homepage to contact heads of international research organizations asking for their trainee recommendations.

The four trainees were: Mr. William Mueller, formerly, Oversight Analyst, Waste Diversion Ontario, Canada; Dr. Hyeon Woo Lim, Physician and Research Scientist, Department of Radiation Oncology, Korea National Cancer Center, South Korea; Ms. Min Kyeong Kim, Research Scientist, Translation Epidemiology Branch, Research Institute, Korea National Cancer Center, South Korea; and Dr. Gulsym Koshpessova, Senior Scientific Associate, Scientific Research Laboratory, Scientific Research Institute of Radiation Medicine and Ecology (SRIRME), Kazakhstan.

The following is an account by Mr. Mueller, acting as the representative for the group of four trainees.

William Mueller (Training period: November 13–December 11, 2015)

As part of RERF's international exchange program, I spent four weeks working under the auspices of Dr. Eric J. Grant, then Assistant Chief, Department of Epidemiology. My research during that time involved modeling the incidence of prostate cancer in atomic bomb survivors in RERF's Life Span Study (LSS), which started in 1958 as a 120,000-person cohort study and is among the longest and largest epidemiological studies in the world. This work provided me with a valuable appreciation of the myriad factors that contribute to cancer incidence, as well as the challenges inherent in quantifying the contribution of exposure to ionizing radiation from the atomic bombings of Hiroshima and Nagasaki.

Mr. William Mueller

Prior to visiting RERF in Hiroshima, I was employed in the environmental field in Toronto, Canada; however, I decided to pursue my interest in environmental health and enrolled in a Master's program in epidemiology at the University of London. Upon completion of my degree, I spent two months at the Caribbean Public Health Agency in Trinidad & Tobago assisting with work on violence and injury prevention before my visit to RERF in Japan.

I benefitted greatly from working with Dr. Grant, as well as from receiving guidance from the other members of the Epidemiology and Statistics departments, and felt privileged to gain practical experience working with such a rich, longstanding dataset. In addition, while staying in Japan, I was fortunate enough to visit other areas of the country, including parts of Hokkaido and Kyushu, to learn more about fascinating Japanese culture.

During my training at RERF, I was offered a position with Imperial College in London, England, as a research assistant for an environmental epidemiology study examining the effects of mobile phone use on cognitive function. Having the chance to conduct analysis on such a well-established study at RERF will certainly help me with this next endeavor in London. I am thankful to the Japanese government for funding my exchange and appreciative of the support I received from RERF colleagues during my stay. I will miss them all, but look forward to future visits to Japan and hopefully collaboration with RERF.

Looking Back

Revisiting ABCC-RERF Memories

"God gave us memory so that we might have roses in December"–J.M. Barrie

On the afternoon of March 4, the final day of 43rd RERF's Scientific Advisory Council (SAC) meeting (please see the article about the SAC on page 2), several veterans familiar with the ways, workings, and history of the Atomic Bomb Casualty Commission (ABCC)-RERF reunited at Hijiyama Hall over lunch and reminisced over times past.

The organizer of the lunch, Mr. Richard D. Sperry, was back in Hiroshima for his annual few months here; he spends the rest of his time in Fairfax County, outside Washington, D.C. Mr. Sperry worked for 30 years on and off at ABCC and RERF as the Assistant Chief of Secretariat, retiring from RERF in 2003. He had arranged to meet Mr. David Williams, an auditor member of the RERF Board of Directors (BOD), which also met on the final day of the SAC meeting.

Mr. Sperry worked for Mr. Williams for several years at the National Academy of Sciences (NAS) in Washington, D.C., from 1975 to 1988, at which time he returned to RERF (formed as ABCC's succeeding organization in 1975). Mr. Sperry and Mr. Williams meet frequently in the U.S., but it was the first time in several years for them to have met in Japan.

Also on the guest list was Mr. Michael E. Rappaport, who helped to direct construction of the ABCC buildings on Hijiyama beginning in 1946 and later held the position of Business Administrator until his retirement in 1988. Mr. Rappaport was responsible for the hiring of Mr. Sperry at ABCC in 1958. Mr. Rappaport is now 95 and typically helped in daily activities for part of each month by his son Mark, who was a guest at the lunch and now lives and works as a music producer and critic in Tokyo.

Mr. Shizuo Inoue also attended the meeting. Mr. Inoue was recruited as an ABCC Motor Pool Dispatcher in 1949 and later assisted Dr. Itsuzo Shigematsu, who served as RERF Chairman for 16 years, from 1981 to 1997. Mr. Inoue, who also held the post of Assistant Chief of Secretariat, retired from RERF under the mandatory age limit in 1994, was rehired as an Advisor, and ultimately called it a career in 1997. Mr. Inoue holds the distinction of being the longest serving employee of ABCC-RERF, working at the two organizations over a period of 48 years.

Mr. Mark E. Rappaport recalled his time as a youngster living in Hijiyama Hall. He said they had lived in the separated living unit in the southeast corner of the Hijiyama Hall compound for the first two years of his life. He remembered the yard and playing there more clearly than he did the living quarters. Some of his later memories include labor

(From left) Mr. Shizuo Inoue, Mr. David Williams, Mr. Michael Rappaport, Mr. Mark Rappaport (son of Mr. Rappaport), Mr. Richard Sperry

union strikes with placards denigrating his father as a representative of ABCC management. According to the elder Rappaport, who smiled as he said, "Mark wanted to go beat those guys up." Mark was quick to add, however, that whenever he walked by the strikers they all smiled, waved, and called him "*botchan*," a Japanese term of affection for a young boy.

The younger Rappaport also remarked that the RERF buildings have not changed much since the days when he would visit his dad's workplace. He was impressed by the longevity of the buildings, which went up in 1949 and 1950; the older Quonset-hut structures never required refurbishing to protect against earthquakes. But as mentioned in the previous Update (please see the From the Editors section, page 1, of the Winter 2015 issue), the newer rectangular buildings on the RERF 'campus' recently had to undergo earthquake protection renovations.

During lunch, the reunited group talked about old times and mutual friends and friendships. Upon conclusion of the confab, Mr. Sperry remarked as he looked around Hijiyama Hall, "This room has many nostalgic memories for us."

In a later email sent to the PR office at RERF, Mr. Sperry wrote, "Looking back and seeing the people in this photo (see related photos) in the place that to each of us is now historic Hijiyama Hall (built under the direction of Mr. Rappaport and with the name bestowed by former director Dr. George Darling who instituted so many fundamental changes in the operation of the scientific program at ABCC), I am fully conscious of the debt I owe to each of them. Working directly under Mr. Rappaport and Mr. Williams for many years and with Mr. Inoue who has been such a critical help to me for even more years…I realize what a heavy burden of debt I owe to each of them for all their help and forbearance during these past times."

At the conclusion of the lunch, the group disbanded and the members went their own way, with promises to meet again.

Enjoying lunch and old times

Dr. Michael D. Danzig, Janice Danzig—April 8, 2016

Dr. Michael D. Danzig, who worked at ABCC around the time it transitioned to RERF, visited Hiroshima RERF with Janice Danzig, his wife, on April 8, 2016. Dr. Danzig worked at ABCC for about three years (July 1972–June 1975) as a Research Associate in the clinical department before returning to the U.S. Before coming to Japan he worked as an internist and U.S. Public Health Service Officer.

(From left) Mrs. Janice Danzig, Dr. Kazunori Kodama, Chief Scientist, Dr. Michael Danzig

The main purpose for his visit to RERF was to meet Dr. Kazunori Kodama, Chief Scientist, with whom he worked at the time, and to try to find the house in Itsukaichi, now a bedroom community to the southwest of Hiroshima but at the time a separate town, where he and his family used to live. His medical specialty is cardiology and he presently works as an invasive cardiologist in the U.S. state of Florida.

Dr. Thomas T. Aoki and Family—May 18, 2016

Dr. Thomas T. Aoki, a U.S. Public Health Service Officer at ABCC for two years from July 1966 to July 1968, visited Hiroshima RERF on May 18, 2016, together with his family. Dr. Aoki is now Emeritus Professor at the University of California, Davis, where he taught at the medical school.

On his return trip to Japan, Dr. Aoki was accompanied by his wife, Susan, also a physician, his first daughter, Betsy Aoki, and her husband Jason McCullough. Betsy and Jason live and work in Seattle.

Dr. Aoki became a specialist in treatment of diabetes based on his experience at ABCC, where he says his interest was sparked by differences in the disease experienced by Japanese patients and his U.S. patients back home. Dr. Aoki developed and published a treatment for slowing and stopping the progression of diabetic complications and now holds over 17 patents, including two in Japan, for this procedure. He still works five mornings a week at his private Aoki Diabetes Research Institute in Sacramento.

Dr. Aoki recalled how his family enjoyed their stay in Japan, living in a spacious home in Ushita, a neighborhood a couple miles north of the downtown area. He would be taken out by his Japanese colleagues for sushi and beer, because he was "unusual," in his words, being a second-generation Japanese physician. According to the husband and wife, in those days, Hiroshima was a sleepy town, different from the modern appearance today with many high-rises dotting the city's skyline.

(From left) Mr. Jason McCullough (married to Betsy), Ms. Betsy Aoki (daughter), Dr. Thomas Aoki, and Mrs. Susan Aoki

Report on RERF Workshop (Niwa Study Group sponsored by MHLW): Storage and Use of Biosamples

Atsuko Sadakane
Research Scientist, Biosample Center
Acting Chief, Pathology Laboratory
Department of Epidemiology
Hiroshima Laboratory

As part of the activities of the Niwa Study Group, which is developing methods for long-term preservation and utilization of biosamples, an RERF workshop addressing the storage and use of such biosamples was held on February 3, 2016, at the Auditorium of the Hiroshima Laboratory. With the goal of ensuring appropriate preservation and use of biosamples at the Biosample Center, which was established at RERF in April 2013, the workshop presented the experiences and knowledge of lead-

ing investigators currently engaged in "biobank" operations in Japan who have expertise in international trends in biobanking. The workshop was also designed to obtain advice regarding RERF's future direction.

Opening the workshop was Dr. Yoshiaki Kodama, Director, RERF Biosample Center, who provided background information: the basic outlines of the research activities at RERF, the objectives for establishing the Biosample Center and its organization, and tasks in which the Biosample Center is currently engaged. Dr. Y. Kodama mentioned that a new robotic biorepository had been introduced to the Hiroshima Laboratory for securing additional biosample space as well as for safeguarding and efficiently managing biosamples. He emphasized the importance of ethical considerations in the use of biosamples, stating that renewed efforts were required to obtain the understanding of study participants and local communities.

Dr. Yohei Miyagi, General Manager, Kanagawa Cancer Center Research Institute (hereinafter: Kanagawa Cancer Center), concurrently assigned as Chief, Molecular Pathology and Genetics Division, described his experiences of, under the initiative of the Kanagawa Cancer Center, creating a structure to organize academic institutions and corporations hoping to use biosamples collected by the cancer center and other organizations, as well as providing samples and information to these academic institutions and corporations. Through this project, samples were collected and used on the basis of comprehensive consent obtained from research participants and provided to public- and private-sector users at no charge.

The Tohoku University Tohoku Medical Megabank Organization (ToMMo) was established after the Great East Japan Earthquake in 2011, with the aim of providing health support to the affected people, reconstructing medical systems, and developing next-generation human resources. ToMMo embarked on cohort studies of the Tohoku area's residents and established a biobank for samples to be collected through the relevant cohort studies. Dr. Naoko Minegishi, ToMMo Professor, who provided useful information at a similar workshop last year, reported on current progress being made in the Tohoku Medical Megabank Project. Dr. Minegishi explained that enrollment of cohort members was mostly completed; that biosamples had been collected from about 120,000 cohort members; and that automated processing procedures and the Laboratory Information Management System (LIMS) had been introduced for quality assurance and quality assessment of biosamples, respectively. She also reported that ToMMo was aiming at becoming a biobank open to outside researchers, using numerous examples such as that ToMMo had released the results of its 'omics' analyses and called for applications relating to sample provision and/or collaborative projects.

As biobanking has improved, the importance of biosample quality has gained recognition, and investigators have become more focused on securing quality rather than simply quantities of samples. Dr. Koh Furuta, Director, Division of Clinical Technology, Kanagawa Cancer Center, delivered a presentation focused on quality control and utilization of biosamples at biobanks. He noted that the international community is currently proceeding with standardization of data, samples, and human work required to secure quality of such biosamples. He also explained a new idea—that of the "active biobank," which is expected to serve as a venue for research and development.

Subsequently, Dr. Eisaburo Sueoka, Professor, Laboratory Medicine, Faculty of Medicine, Saga University, concurrently assigned as Chief, Clinical Research Division, Clinical Research Center, Saga University Hospital, explained an initiative to create a biobank at Saga University. He reported that the intended purposes of samples and information to be collected by the proposed biobank had already been specified; that other projects addressing effective management of patient information and collection of side-effect information were involved; and that, using the project's status as a university hospital-affiliated biobank to full advantage, the biobank's plans call for the establishment of a workable link via electronic health record systems with clinical information accumulated thus far.

Dr. Tohru Masui, Professor, Center for Medical Genetics, Keio University School of Medicine, made recommendations about how to utilize biosamples in a socially acceptable manner by clarifying the characteristics inherent in biobanking and medical research. He stated that biobanks

Workshop "Storage and Use of Biosamples" held at Hiroshima RERF

should collect samples for comprehensive purposes because the value of the biosamples might not be recognized immediately, and their actual use might occur only in the future. Dr. Masui also presented several examples showing that although genome information belonged to individuals, such information could also be considered as belonging to all of humanity, and that biosamples obtained through clinical practice might be used for ongoing or future studies conducted remotely from patients. Based on these statements, he concluded that we all should sincerely consider what is required in our current work from different scientific, legal, and ethical perspectives for future generations.

The workshop generated practical opinions from investigators with experience and expertise in biobanking, those now collecting information and samples via biobanks, and those working on biobank creation. Discussions about the latest trends in biobanking and related ethical issues were also held. Each investigator showed deep interest in RERF's biosamples and spoke about his or her experiences, discussed cases he or she had encountered, and presented the gathering with useful knowledge. In closing, we would like to express our heartfelt appreciation to all the workshop participants for their suggestions regarding the potential of RERF's biosamples.

Participants of "Storage and Use of Biosamples" workshop

Association of Acute Radiation Syndromes and Rain after the Bombings in the Atomic-bomb Survivors*

Kotaro Ozasa

Department of Epidemiology, Hiroshima, RERF

*This article is based on the following publication:

Kotaro Ozasa, Ritsu Sakata, Harry M. Cullings, Eric J. Grant: Association of Acute Radiation Syndromes and Rain after the Bombings in the Atomic-bomb Survivors. *Radiat Res* 2016 (June); 185(6):604-15 (doi: 10.1667/RR14038.1)

Study Findings

Association between exposure to rain that fell soon after the atomic bombings and development of acute symptoms was examined based on responses to interview surveys of Life Span Study (LSS) members conducted during the 1950s. Although the frequency of development of such acute symptoms was slightly higher in those who reported exposure to rain, the association was not thought to be caused by uniform radioactivity in the rain with potential effects equivalent to a level of several hundred milligray (mGy); rather, recall bias, and other factors, were thought to be more plausible explanations. Nevertheless, such issues as insufficient data available for use in the study limited the effectiveness of the study analysis.

Explanation

1. Study purpose

Based on various experiences of atomic bomb (A-bomb) survivors, it has been thought that acute radiation syndrome, which includes symptoms such as epilation and bleeding that appeared after the bombings, was associated with exposure to radiation from rain that fell soon thereafter. However, an epidemiological analysis had not been conducted. The association was examined by comparison of information involving exposure to rain soon after the bombings and development of acute symptoms. This information was obtained in interviews of Life Span Study (LSS) members in the 1950s, with direct radiation effects from the A-bombings taken into consideration.

2. Study methods

Several interviews of LSS members were conducted in the late 1940s to collect information regarding their situation at the time of the bombings, and in the 1950s the interviews included questions about exposure to rain that fell soon after the bombings and development of acute radiation symptoms. The responses obtained consisted of: "was exposed" (in this case, information on location at exposure was requested), "not exposed," and "unknown." This study analyzed typical acute radiation symptoms such as epilation, bleeding, and oropharyngeal lesions in relation with responses to questions regarding exposure to rain.

3. Study results

The frequency of the development of acute symptoms differed significantly among levels of direct radiation from the A-bombings: 30–80% at the level of 3 Gy or higher, 1–6% at around 100 mGy, and 0.04–2% at less than 5 mGy, for a variety of symptoms. At the same level of direct radiation, the reported frequency of the development of acute symptoms was slightly higher in those who indicated they had been exposed to rain than in those who did not, both in Hiroshima and Nagasaki. The frequency of many acute symptoms, however, was significantly lower in those who were exposed to rain and to direct radiation of <5mGy than in those who were not exposed to rain but exposed to direct radiation of 100–500 mGy. Thus, it is unlikely that the rain contained uniformly high levels of radiation to produce effects equivalent to those experienced at a level of several hundred mGy.

Odds ratio (OR) was used to evaluate, in this study, the association between exposure to rain and frequency of development of acute symptoms (i.e., what percentage increase), and a larger OR indicates a stronger association. The OR of reporting exposure to rain somewhere in Hiroshima was 1.19 ($p = 0.08$) among those who developed severe epilation (defined as >2/3 of scalp), 1.23 ($p < 0.01$) in cases of at least slight epilation (>1/4 of scalp), 1.48 ($p < 0.01$) for bleeding, and 1.47 ($p < 0.01$) for

oropharyngeal lesions. The ORs in Nagasaki were 1.76 ($p = 0.11$), 2.10 ($p < 0.01$), 2.01 ($p < 0.01$), and 2.46 ($p < 0.01$), respectively. As for survivor location at exposure to rain in Hiroshima, the OR was largest for those who reported exposure to rain in an area southeast of the hypocenter. The ORs for those who indicated they had been exposed to rain in the areas where rainfall was reported, i.e., clockwise from west-southwest to northeast, including the west-southwest area beyond 2 km that included the Koi/Takasu districts where high residual radiation was detected, were similar to the OR for exposure to rain somewhere in Hiroshima. In Nagasaki, the ORs tended to be bigger for those who reported exposure to rain in the western half of the area centered on the hypocenter than for those in the eastern half. The frequency of acute symptoms was not high among those who had reported exposure to rain in the area beyond 2 km from the hypocenter to the east that included the Nishiyama district, where heavy rainfall and high residual radiation were observed soon after the bombing.

Study Significance

The association between radiation exposure and development of acute symptoms was, in general, strongest for severe epilation and weakest for epilation of lesser degrees, as well as bleeding and oropharyngeal lesions, because the latter symptoms contained a larger number of cases not caused by radiation exposure. In this study, reports of exposure to rain were associated with development of symptoms other than severe epilation; this association was similar to, or slightly stronger than, the association with severe epilation. Also, the association tended to be stronger in those who were exposed to rain in areas where there were few reports of rainfall than in those who were exposed to rain in areas where rainfall was frequently reported. The association was not stronger in the areas where ground residual radiation levels were high in post-war surveys than in other areas. This trend in association is thought to be somewhat inconsistent with the hypothesis that acute symptoms developed due to radiation exposure from rain.

Potential reasons for the observed association between exposure to rain and development of acute symptoms included: a strong radioactive fallout contained in the rain and a high radiosensitivity of the individuals exposed to the rain; synergistic effects between radiation and poor hygienic conditions; as well as inaccuracies and recall bias in memories and in reports of locations at the time of the bombings and exposure to rain and timing related to the development of symptoms (recall bias is the tendency for people to believe they might have developed acute symptoms because they had been exposed to rain, or vice versa). Although there may have been some individual cases of development of acute symptoms caused by radioactive fallout in rain, the overall trend in the results is inconsistent with the conclusion that acute symptoms were generally caused by radioactive fallout in rain. Rather, recall bias, and other factors, were thought to be more plausible explanations for the association. However, insufficient data imposed limits on the assessment of whether the reports of rainfall after the A-bombings and development of acute symptoms were attributed to actual radioactive fallout or uncertain memories and other such factors.

Progerin, the protein responsible for the Hutchinson-Gilford Progeria Syndrome, increases the unrepaired DNA damages following exposure to ionizing radiation*

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*This article is based on the following publication:

Asao Noda, Shuji Mishima, Yuko Hirai, Kanya Hamasaki, Reid D. Landes, Hiroshi Mitani, Kei Haga, Tohru Kiyono, Nori Nakamura, Yoshiaki Kodama: Progerin, the protein responsible for the Hutchinson-Gilford Progeria Syndrome, increases the unrepaired DNA damages following exposure to ionizing radiation. *Genes and Environment* 2015 (October): 37(13):1-12 (doi: 10.1186/s41021-015-0018-4)

Study Findings

We conducted a model-based investigation to test the hypothesis that genomic damage induced by radiation contributes to abnormal cell nuclear morphology and premature aging. We identified advanced nuclear envelope abnormalities and the expression of markers of premature aging in cells with unrepaired DNA double strand breaks (DSBs) induced by radiation exposure. We also found increased numbers of unrepaired DSBs in cells from patients with progeria, a genetic disease associated with rapid aging. Such cells express progerin, a mutant form of lamin A protein responsible for progeria in humans, and feature abnormal nuclear envelope structure. We concluded that nuclear lamin A, a protein thought to cause age-associated changes in nuclear envelope structure, is related to the formation of radiation-induced unrepaired DSBs.

Explanation

We attempted to measure unrepaired DSBs as a new biomarker for detecting tissues previously exposed to radiation and for estimating the radiation doses to which such tissues were exposed. In our research, we noticed that cells with unrepaired DSBs developed abnormal nuclear envelope morphology, with signs of premature aging. This led us to investigate whether nuclear lamin A could be involved in DSB repair. Hutchinson-Gilford progeria syndrome (HGPS) is an extreme example of aging caused by abnormal nuclear envelope structure. Cells of HGPS patients express progerin and have a nuclear envelope that is stiffer and more fragile than normal.

1. Objectives

The objectives were to evaluate whether nuclear lamin A, a structural protein in the meshwork of the nuclear envelope, is involved in repairing radiation-induced DSBs and whether the protein acts as a site for repairing or anchoring DSBs that are particularly resistant to repair.

2. Methods

Radiation-induced unrepaired DSBs and structural changes in the nuclear envelope were measured in cells from healthy humans and HGPS patients. Effects of farnesyl transferase inhibitor (FTI), a new class of cancer drug, were also measured, because FTI suppresses the changes in nuclear envelope structure caused by progerin. Finally, unrepaired DSBs and nuclear envelope changes were assessed following telomerase gene induction, as telomerase gene induction has been implicated in rejuvenating cells and making cells immortal.

3. Results

(1) About 1% of radiation-induced DSBs persist in the cell nucleus as unrepaired DSBs (Noda et al., J Cell Science 125:5280, 2012). Unrepaired DSBs inhibit cell division, indefinitely arresting growth and causing premature aging. The numbers of unrepaired DSBs induced by radiation were at least two-fold higher in HGPS cells than in healthy cells. The numbers were even higher in cells with abnormal nuclear envelope structure.

(2) FTI treatment suppressed the anchoring of

progerin to the nuclear membrane, thereby improving the nuclear structure in HGPS cells. The number of unrepaired DSBs consequently decreased. Nuclear structure improved and unrepaired DSBs decreased in HGPS cells with cell division capability restored by telomerase induction. The forced expression of telomerase suppressed progerin expression and induced the expression of nuclear lamin B1, a cousin of lamin A. This expression profile is characteristic of young and undifferentiated cells.

(3) Structural changes in the nuclear envelope and the numbers of unrepaired DSBs were also found to be correlated with radiation-induced premature aging in normal cells.

Study Significance

Previous studies indicated that cells bearing unrepaired DSBs underwent premature senescence, even though this finding was not directly linked to physiological changes in humans. In this study we show that the occurrence and anchoring of unrepaired DSBs caused by radiation exposure depend on nuclear envelope structure.

Creation of mice bearing a partial duplication of HPRT gene marked with a GFP gene and detection of revertant cells in situ as GFP-positive somatic cells*

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*This article is based on the following publication:

Asao Noda, Hirofumi Suemori, Yuko Hirai, Kanya Hamasaki, Yoshiaki Kodama, Hiroshi Mitani, Reid D. Landes, Nori Nakamura: Creation of mice bearing a partial duplication of HPRT gene marked with a GFP gene and detection of revertant cells in situ as GFP-positive somatic cells. *PLOS ONE* (August 21, 2015): 10(8): e0136041. (doi: 10.1371/journal.pone.0136041)

Study Findings

We created transgenic mice that allow *in situ* (i.e., in tissue) visualization of mutations in any cell throughout the body of the animal. The mice are technically called HPRT-dup-GFP knock-in mice. We used this knock-in mouse model to detect mutant cells arising in organs, including the liver, pancreas, small intestine, large intestine, lungs, thyroid, and testes. Large differences among individuals in terms of spontaneous mutation frequencies were observed in somatic cells. Such high spontaneous frequencies impeded detection of mutations induced by radiation. Lowering the background mutation frequency is the next challenge for better use of this system in radiation research.

1. Objectives

One objective was to create mice to assist in the detection of radiation-induced mutations in somatic and germ-line cells. Cells developing a mutation in this mouse model survive and fluoresce green (because they contain green fluorescent protein, or GFP). Another objective was to use this mouse model to observe where radiation-induced mutant cells occur and grow in the body. The final objective was to establish a system for monitoring the genetic effects of radiation in individual organisms.

2. Methods

Embryological engineering techniques were used for manipulating the mouse HPRT gene (a structural gene involved in nucleic acid synthesis) to be partially duplicated in conjunction with the GFP gene on the X chromosome, thereby creating

transgenic mice. Recombination-mediated reversion from the partial duplications of the *HPRT* (i.e., reactivation of gene activity) in the cells of these mice led to expression of the HPRT-GFP fusion protein and caused the affected cells to fluoresce green.

Radiation exposure effects were evaluated using fluorescence to determine mutation frequency in the mouse cells after the mice were exposed to radiation.

3. Results

(1) We successfully created transgenic mice (HPRT-dup-GFP mice) by double gene knock-in (the insertion of a gene in a specific location in a chromosome) in mouse embryonic stem cells (cells from the early embryo that can differentiate into any cell type). On the HPRT-dup-GFP locus of the mice, *in vivo* arising, somatic mutant cells, which are revertants from the partial duplicated allele of the *HPRT* gene, were confirmed as originating from gene deletion via normal homologous recombination repair. Mutant cells in any of the tissues except the brain fluoresced green, but the frequencies of spontaneous mutations differed among tissues.

(2) Large individual differences were seen in the frequency of somatic cell mutations, even in the mice not exposed to radiation. Around 1% of the mice developed mutations too numerous to be countable. We used the term "extreme jackpot mutations" to describe such cases. The large differences in mutation frequency among individual mice may depend on when during development and growth cycles mutant cells arise. The investigation thus can be conceived as a fluctuation test of mutations at the level of the individual.

(3) Somatic cell mutation frequencies were measured in different tissues of mice 3 months after exposure to a dose of 3 Gy as a model of radiation exposure. Mutation frequency was observed to be little changed in certain tissues (pancreas and lymphocytes) but two-fold higher in others (e.g., liver, small intestine).

Study Significance

We successfully created mice whose living cells fluoresce when developing a mutation. Although the model is useful, background noise from spontaneous mutations will have to be reduced for the model to be a reliable indicator of the effects of radiation exposure. Our findings strongly suggest that many of the somatic cells making up our bodies already contain mutations that give us a genetically mosaic appearance.

A Bayesian semiparametric model for radiation dose-response estimation*

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Department of Statistics, Hiroshima, RERF

*This article is based on the following publication:

Kyoji Furukawa, Munechika Misumi, John B. Cologne, Harry M. Cullings: A Bayesian semiparametric model for radiation dose-response estimation. *Risk Analysis* 2016 (June); 36(6): 1211-23 (doi: 10.1111/risa.12513)

Study Findings

This study proposed a new statistical approach using a semiparametric model* to estimate the dose-response relationship under a framework of Bayesian statistics* —one of the primary objectives of radiation risk analysis—with increased accuracy. Without assuming a specific parametric model,* such as the linear non-threshold model,* this approach can estimate various dose-response curves with uncertainty more accurately and therefore is expected to be particularly useful in evaluating the risk associated with low-dose exposure.

*Semiparametric model: falls between a parametric model and a nonparametric model, which assumes no specific form with respect to dose response

*Bayesian statistics: generalizes conventional statistics by introducing a "prior probability" based on common sense or experiences and enables us to conduct data analysis more flexibly. The term "Bayesian semiparametric model" in the title indicates a semiparametric model under this framework of Bayesian statistics.

*Parametric model: describes how risk increases with dose (x) with a set of parameters (β), such as the linear non-threshold dose model (βx)

*Linear non-threshold model: assumes risk to be monotonically increasing in proportion to the increasing dose

Explanation

Characterizing the dose-response relationship and estimating acceptable exposure levels are the primary goals of risk assessment. In analyses of health risks associated with exposure to radiation, while there is clear agreement that moderate to high radiation doses cause harmful effects in humans, information is limited for understanding the possible biological effects at low doses, e.g., less than 100 mGy, which is the dose range relevant to most radiation exposures today. While a simple parametric model, such as the linear non-threshold model, is interpretable and supported by some biological considerations, risk analysis based on a simple parametric structure can be misleading in evaluating the risk and its uncertainty associated with low-dose exposure. In particular, a linear model with a fixed value at the lowest dose (e.g., zero response at zero dose) can only accommodate linear confidence bounds that narrow to a point at the low-dose end. This study proposed a new approach using a semiparametric model that is flexible in regard to the shape of both the mean response and the confidence bounds and evaluated its performance in comparison with the conventional approach of parametric models.

1. Study purpose

The main purpose of this study was to show that a semiparametric dose-response model that assumes no specific parametric function form can be an alternative approach that is appropriate for evaluation of risk associated with radiation exposure, especially at low doses.

2. Study methods

This study considered a semiparametric dose-response model that has a connected, piecewise-linear dose-response function with a correlation structure among the random slope coefficients defined over closely spaced dose categories, which was applied to radiation-dose-response estimation. Using simulations under several plausible dose-response relationships, we evaluated the performance of the proposed approach compared to those of the conventional parametric approach in terms of bias, efficiency, and precision of uncertainty estimation. Also, the proposed approach was applied to analysis of solid cancer incidence

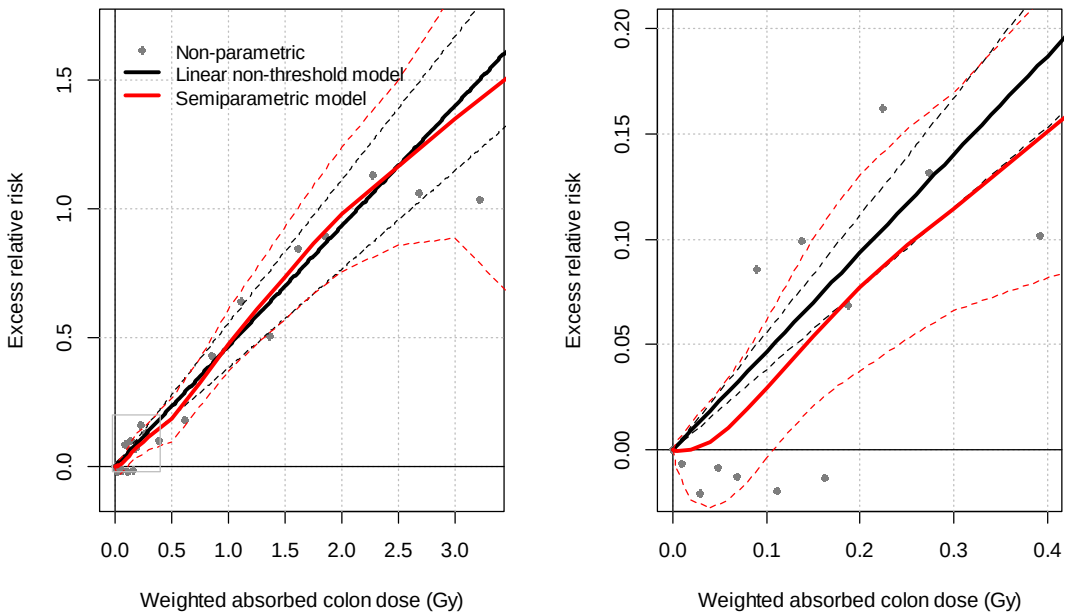

Figure: Excess relative risk (ERR) for all solid cancer in the Life Span Study cohort (1958–1998) in relation to radiation exposure, estimated by the linear non-threshold model (black) and the semiparametric model (red) over the entire dose range (left) and at 0–0.4 Gy (right). Dashed curves are 95% confidence (or credible) intervals. All estimates are gender-averaged ERRs at age 70 after exposure at age 30.

in the Life Span Study (LSS) cohort of atomic-bomb survivors (1958–1998), and the estimated dose-response curves with interval estimates were compared to those obtained by other approaches.

3. Study results

Our simulation study demonstrated that the conventional approach using parametric models could be problematic in bias and underestimation of uncertainty when a non-linearity was assumed in the dose response at a low dose range. In contrast, the proposed approach produced results that were overall less biased and more accurate in uncertainty estimation. In analysis of the LSS data, compared to the conventional linear non-threshold model, the proposed approach estimated smaller risks with wider interval estimates at low doses, which indicated no clear evidence of an increased risk up to 100 mGy of exposure (Figure).

Study Significance

With relatively few assumptions and modeling options to be made by the analyst, the semiparametric model proposed in this study can be flexibly fitted to data generated by various shapes of dose-response curves with uncertainty appropriately handled at any dose range and therefore is expected to be particularly useful in characterizing risk at a low dose range and accurately estimating acceptable exposure levels.

Circulating hematopoietic stem and progenitor cells in aging atomic bomb survivors*

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*This article is based on the following publication:

Seishi Kyoizumi, Yoshiko Kubo, Munechika Misumi, Junko Kajimura, Kengo Yoshida, Tomonori Hayashi, Kazue Imai, Waka Ohishi, Kei Nakachi, Lauren F. Young, Jae-Hung Shieh, Malcolm A. Moore, Marcel R.M. van den Brink, Yoichiro Kusunoki: Circulating hematopoietic stem and progenitor cells in aging atomic bomb survivors. *Radiat Res* 2016 (January): 185(1):69–76 (doi: 10.1667/RR14209.1)

Study Findings

Counts of hematopoietic stem and progenitor cells (HSPCs) in the blood of atomic bomb (A-bomb) survivors decreased with age, but no significant association with radiation dose was found.

Explanation

1. Study purpose

Hematopoietic stem cells (HSCs) are known to be highly radiosensitive. Deterioration in hematopoietic function and decrease in peripheral erythrocytes and leukocytes have been reported as some of the acute effects of radiation observed in A-bomb survivors. However, as a result of the regenerative capacity of HSCs, hematopoiesis among A-bomb survivors was reported to have recovered to a considerable extent about 10 weeks after A-bomb radiation exposure. Nonetheless, gene abnormalities such as mutations persist in the HSCs of A-bomb survivors even now, 70 years after radiation exposure. To determine whether or not effects of radiation persist in the HSC function of A-bomb survivors, this study examined the counts of circulating hematopoietic stem and progenitor cells per unit volume of blood, as well as their proportions vis-à-vis all HPSCs in blood, reviewing whether dose-dependent effects of radiation were observed.

2. Study methods

Peripheral blood was collected from 231 Hiroshima survivors (aged 66–91 years) who had participated in the Adult Health Study (AHS) during the period 2011–2013 and, using a cell sorter, separated CD34-positive/lineage marker-negative ($CD34^+Lin^-$) cells thought to contain HSPCs. The counts of the following types of colony-forming units in this cell population were evaluated using cell culture: cobblestone area-forming cells*; long-term culture-initiating cells*; erythroid burst-forming units*; granulocyte and macrophage colony-

forming units*; and T-cell and natural killer cell progenitors.* Cobblestone area-forming cells and long-term culture-initiating cells reflect the self-renewal and the multilineage differentiation functions of HSCs, respectively. Other colony-forming units reflect lineage-committed hematopoietic progenitor cells.

Cobblestone area-forming cells: Because these cells form an undifferentiated, cobblestone-like colony in the absence of hematopoietic factors and under the presence of stromal cells, they are thought to originate from self-renewable HSCs.

Long-term culture-initiating cells: Because these cells can produce erythroid burst-forming units and granulocyte and macrophage colony-forming units over a prolonged period, they are thought to originate from HSCs with capacity for multi-lineage differentiation.

Erythroid burst-forming units: Hematopoietic progenitors that can produce erythrocytes

Granulocyte and macrophage colony-forming units: Hematopoietic progenitors that can produce granulocytes and macrophages

T-cell and natural killer cell progenitors: Hematopoietic progenitors that can produce T lymphocytes or NK lymphocytes

3. Study results

(1) Association with age

We found that the counts of $CD34^{+}Lin^{-}$ cells, which are thought to include all HPSCs in blood, significantly decreased with age per unit volume of blood ($P = 0.0022$). Furthermore, the counts of respective colony-forming units significantly decreased with age ($P = 0.0001$–0.0047). As for the proportions of respective colony-forming units in the $CD34^{+}Lin^{-}$ cell population, only T-cell progenitors decreased with age ($P = 0.010$), suggesting an aging-related decline in the stem-cell function (capacity) of T-cell differentiation induction, even among subjects aged around 70 and older.

(2) Association with radiation dose

With regard to the $CD34^{+}Lin^{-}$ cell population and colony-forming units, no significant effects of radiation exposure were observed in either the absolute cell numbers per unit volume of blood or in their proportions vis-à-vis all HPSCs in blood.

Study Significance

Our findings showed that aging in HSC function continued, even among subjects aged around 70 and older. Specifically with regard to T cells, it is believed that decline in thymic function induces a decrease in mature peripheral naïve T cells.* This study, however, revealed that decline in the stem-cell function of T-cell differentiation induction due to stem cell aging was one reason for the aforementioned decrease. This study also suggests that the numbers and function of HSPCs overall in living A-bomb survivors have recovered to normal levels even as the survivors aged over the decades since A-bomb radiation exposure (compared to the levels in unexposed individuals of the same ages).

Mature naïve T cells: Different from T-cell progenitors shown in the fifth line of (1) "Association with age" under the section titled "3. Study results," these cells are mature lymphocytes that arise by differentiation from T-cell progenitors in the thymic environment and differentiate into memory T cells in response to antigen stimulation in the periphery. This study suggested the possibility that aging of HSCs decreased production of T-cell progenitors, resulting in a decrease in thymic production of mature naïve T cells.

Memories of My Struggles in England

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The following is a record of my days in England. I stayed in the borough of Colchester in Essex, England for one year starting in April 2015, with my daughters (eight- and four-year olds) and newly born son (seven months). We made the move because my husband, who is engaged in research on administrative law at Himeji Dokkyo University, here in Japan, was appointed to serve as a visiting researcher at the University of Essex.

In August 2014, I gave birth to my third child and first son. Three months later, I returned to work at RERF. Over the next three months, while working on preparations for the Scientific Advisory Committee (SAC) meeting, which takes place each year in March, I had to finish preparations for moving to England, including the handing over of my routine duties to my colleagues. Those preparations were tough and included obtaining visas for five people, late-night house-hunting with a local real-estate agent in England using Skype, finding a school for my daughters, translating vaccination and medical records of the three children, arranging to sign up for national health insurance, and of course, packing.

Unfortunately, we arrived in England during the Easter holidays. All shops were closed, and what was worse, we could not move into the house I had finally found via Skype. Under such circumstances, we had no option but to stay in a hotel for a lengthy 10 days. Upon arriving in England, every day was full of first-time experiences and therefore confusion.

The best example was our attempt to find a school for my daughters. Even primary schools in England do not accept pupils beyond an enrollment limit. Even though I started looking for a school for my daughters before leaving for England, things did not proceed in the desired direction, and I ended up calling the county council every few days for a full month upon arriving in England. After a difficult period, my eldest daughter was accepted into a school. But that was not the end of the story. Finding a school for my second daughter was much harder. Due to a lack of vacancies, my second daughter was assigned to a school 10 kilometers

Dr. Sugiyama, learning how to make mince pie for Christmas at British friend's house

Roast dinner, made with help from British friend

In England, it is said "All swans in England belong to the Queen"

from my first daughter's school. I decided that was enough. I made a phone call to the county council every week but their reaction differed depending on who answered the phone. At last I got to the point where I could not take it anymore and shouted on the phone, "I can't drop off and pick up my two daughters at the same time!" Oddly enough, two days later, my first daughter's school informed me of the second daughter's admission.

Unlike Japan, children can neither travel to school nor play outside by themselves. I thus began the work of dropping them off and picking them up by car with my youngest son in tow, whatever the weather.

Food was also a source of trouble. Since we could barely afford to eat out due to high taxes, I had to cook three meals every day. Contrary to London, Japanese ingredients were not available in Essex, and I had no clue as to what to cook at first. Every day, I searched for recipes on YouTube and cooked different meals using unfamiliar English ingredients. Ingredients grown domestically were suitable for English cooking and both my husband and children enjoyed the fare I managed to come up with.

What troubled me most, however, was the English language. I found it especially hard to make arrangements for my children's sleepovers and playdates with their friends' parents by telephone or text messages in English. Fortunately, both of my daughters' female teachers were exceedingly kind, enabling my daughters to gradually feel at home even though they did not understand English.

Having experienced English at RERF helped me a lot, but I did have difficulties becoming accustomed to British English as well as the unique Essex dialect. For instance, in Essex they greet each other by saying "Hiya," they call dinner "tea," and use "lovely" in place of "good." Also, they always include their postal codes when stating their addresses. The Essex accent is characterized by the dropping of the letters "r" and "t" in the middle of a word and pronouncing "th" as "f." As such, "date of birth," often needed for administrative procedures, sounded like [debaf], "water" like [wɔ:ə˞] and "later" like [leɪə˞].

In such circumstances, English ladies from the women's club of the University of Essex and Japanese women who had permanent residence status warmly taught me about the English lifestyle as well as how to cook British cuisine. Thanks to them, my life in Essex got on track. It was such a blessing that my entire family could live together for one year; before that, my husband and I had a long-distance marriage for 10 years, as we lived apart for reasons related to our work.

In closing, I would like to express my sincere appreciation to everyone at RERF, who agreeably allowed me to leave work for a year in spite of the many extra duties imposed on them, and warmly accepted me back again at work earlier this year.

Report on NEWS (2nd in series)

RERF Epidemiological Study of Health Effects in Fukushima Emergency Workers

Toshiteru Okubo
NEWS Principal Investigator
RERF Senior Consulting Scientist

Compared with other nuclear accidents that the world has experienced, the accident at the Tokyo Electric Power Company (TEPCO) Fukushima Daiichi nuclear power plant (hereinafter referred to as the "Fukushima nuclear accident") was an unprecedented disaster involving the simultaneous meltdown of three nuclear reactors. However, fortunately, no marked acute radiation damage has been observed among those engaged in emergency and recovery work following the accident. As was the case in other accidents in the past, however, prospects for completion of restoration operations such as retrieval of nuclear fuel from the reactors is not at all promising.

This is the second of a series of reports on the Epidemiological Study of Health Effects in Fukushima Emergency Workers (called the NEW Study or NEWS for short, as indicated in the title) subsequent to the first report appearing in the "Facts and Figures" section of the Winter 2015 issue of RERF Update. There is some overlap with the first report, but this new article is expected to provide useful in-depth information about the NEWS program.

Lifelong follow-up of approximately 20,000 emergency workers

With the aim of bringing the Fukushima nuclear

Research coordinator meeting of Epidemiological Study for Health Effects in Fukushima Emergency Workers held in Tokyo. Dr. Toshiteru Okubo, NEWS Principal Investigator (at rear), giving lecture about study policy and medical manual to representatives of collaborating research health organizations

accident under control, the radiation limit for emergency workers was elevated from 100 mSv to 250 mSv between March 14 and December 16, 2011. Those who entered the power plant for any length of time during this relevant period are defined as emergency workers, totaling 19,679 individuals, all of whom are potential NEWS participants.

Pursuant to Japan's Ministry of Health, Labour and Welfare (MHLW) guidelines regarding health management, all these emergency workers were registered in an MHLW database. Registration cards were issued to the workers, and radiation dose data and results of annual general/special health examinations are entered into the relevant database. The aforementioned guidelines also prescribe cataract testing for those exposed to at least 50 mSv and cancer screening for the 174 individuals exposed to more than 100 mSv. The health examinations will be performed over the subjects' lifetimes, and the results will be registered in the aforementioned database. This study was initiated after we were provided with access to the database. The potential study participants are now dispersed in every prefecture throughout Japan.

Even taking into account radiation exposure before and after engaging in emergency operations as well as medical exposure, the subject population consists mostly of those exposed to low-dose radiation. Consequently, such reliable epidemiological research is expected to bring about significant information about health effects from low-dose radiation exposure, specifically in relation to risk assessment of cancer development and its mechanisms.

The lower the radiation dose, the more significant the impact of confounding factors is on the effects of radiation exposure, making difficult the job of specifying the effects of radiation exposure. Consequently, this general study will endeavor to identify confounders such as psychological factors and work on developing a study of psychological effects, which are thought to impart a significant impact on the assessment of health-effect indexes.

Regarding access to the aforementioned MHLW database and provision/receipt of personal information between collaborating research institutes, this study started by undergoing ethical reviews, obtained consent from potential study participants, and finally embarked on health examinations nationwide. In detail, we explained the significance, objectives, supervising agency, and methods of NEWS, advantages and disadvantages from collaborating in the study, and the legal rights of the study participants. We stated that participants are free to decide whether or not to participate in the study and obtained consent for the following items:

a) Consent for receipt of information from other institutes that have existing source materials
b) Consent for participation in the clinical study including in the health examinations
c) Consent for participation in different planned research programs in the future

Regarding radiation dose that the subjects received during the period of emergency operations, actual measurement data are available. Since necessary devices were not available in the initial days after the accident occurred, however, radiation dose exposure for the relevant days must be estimated on the basis of work locations, hours worked, and types of work performed, using radiation exposure-related primary materials including job diaries and measurement data of colleagues and others. Concerning radiation exposure due to radiation-related work before and after engaging in the emergency operations, the Radiation Effects Association-affiliated Central Registration Center will provide data to the NEWS Office.

The breadth of health effects for which the entire subject population will be followed and of health effects to be reviewed in the future in different research plans are shown below:

a) Malignant tumors, specifically leukemia, thyroid cancer, etc.
b) Non-cancer diseases, including circulatory disease, cataract, and thyroid disease
c) Psychological effects, including PTSD, adjustment disorder, and depression
d) Biomarkers to assess mechanisms behind radiation's health effects (immunosenescence and chronic inflammation markers, etc.) and molecular biological markers (SNPs, genome sequencing analysis, and DNA adducts, etc.)
e) And, other items that are shown to be necessary during the course of the study

Explanatory letter sent to the entire NEWS subject population to examine their willingness to participate

NEWS started by sending all subjects a letter to briefly outline the NEWS project and ask their consent for participation.

The study population consists mostly of employees of secondary subcontractors and below that have no direct dealings with TEPCO, with the number of such subcontractors estimated at more than 1,000 but less than 2,000. Under such conditions, company efforts are indispensable in encouraging study subjects to participate in the study, and we therefore decided to utilize the network of corporate groups. First, to contact such subcontractors via the original contractors, a meeting with the original contractors was held on July 6, 2015, with 15 contractors and TEPCO representatives in attendance (a total of 16 companies). At that

meeting, the participating original contractors were requested to encourage their respective subcontractors to participate in the later explanatory sessions held in Tokyo, Fukushima, and Niigata. As a result, 140 persons in charge from such subcontractors participated in a session held on August 6 at the Japan Football Village (J-Village); 229 on August 18 in Tokyo; 111 on August 27 at the J-Village; and 53 on August 28 in Kashiwazaki-Kariwa.

Furthermore, we sent the aforementioned letter on August 17, 2015, to 2,106 people who did not belong to any corporate group, with the aim of examining their willingness to participate in the study.

With regard to emergency workers who belonged to companies at the time of emergency operations, their employers held internal explanatory meetings in response to our request made at the aforementioned explanatory sessions. In synchronized timing, we sent the letter of request to these emergency workers via their respective companies, completing the mailing to 16,743 people by the end of September. The remaining subjects are employees of TEPCO, the cooperative framework with which is currently under review separately.

As a result of the mailing, we received 7,203 responses, or 43% of the total, as of December 2, 2015, with 1,360 address-unknown and 8,180 non-response cases. From among the responses, 1,890 people, or 26.2%, declined to participate in the study or returned a blank form. Consequently, for our FY2016 activities, we decided to contact the remaining 5,313 responders to call for their participation in the health examinations.

The next NEWS article, scheduled to appear in the Winter 2016 issue of Update, will look into such issues as how we handle study participants dispersed in every prefecture throughout Japan.

Research Protocol Approved in November 2015–April 2016

RP 6-15 Epidemiological Study of Health Effects in Fukushima Emergency Workers (Abbreviation: NEW Study)

Toshiteru Okubo, Makoto Akashi, Waka Ohishi, Ryuji Okazaki, Kotaro Ozasa, Fumiyoshi Kasagi, Hiroaki Katayama, Osamu Kurihara, Kazunori Kodama, Hiroshi Sasaki, Jun Shigemura, Yumiko Suto, Tomotaka Sobue, Nobuyuki Taniguchi, Hisanori Hiro, Hokuto Hoshi, Megumi Miyakawa, Takumaro Momose, Shinji Yoshinaga

The emergency radiation exposure dose limit for the workers at the Fukushima Daiichi nuclear power plant of the Tokyo Electric Power Company (TEPCO) was raised from 100 mSv to 250 mSv during the period between March 14 and December 16, 2011. During this period, 174 out of approximately 20,000 emergency workers exceeded the dose limit of 100 mSv imposed for radiation workers in a consecutive five-year period during ordinary circumstances. The objective of this study is to clarify the long-term health effects of radiation on those 20,000 radiation emergency workers. Reliable epidemiological research on the cohort of radiation workers, the majority of whom were exposed to less than 100 mSv, is expected to lead to new findings about the risks of low-dose radiation exposure and its mechanisms. The conventional knowledge about health risks of radiation exposure derives from studies of A-bomb survivors, who were exposed to radiation one time only, while this study involves persistent exposure to mainly low-dose radiation. This study is expected to also bring about new findings on radiation dose and dose-rate effect, and the research results may contribute to establishment of more accurate radiation protection standards. We will also examine the psychological effects of engaging in such emergency work.

Recent Publications

(Japanese): the original article is in Japanese.

Fowke JH et al. (RERF: Ozasa K, Ohishi W, Grant EJ): Associations of body mass index, smoking, and alcohol consumption with prostate cancer mortality in the Asia Cohort Consortium. Am J Epidemiol 2015 (September); 182(5):381-9.

Furukawa K, Misumi M, Cologne JB, Cullings HM: A Bayesian semiparametric model for radiation dose-response estimation. Risk Anal 2016 (June); 36(6):1211-23.

Hirabayashi Y, Tsuboi I, Kuramoto K, Kusunoki Y, Inoue T: Cell cycle of primitive hematopoietic progenitors decelerated in senescent mice is reactively accelerated after 2-Gy whole-body irradiation. Exp Biol Med 2016 (March); 241(5):485-92.

Imaizumi M: Subclinical thyrotoxicosis and heart disease. Nihon Kojosen Gakkai Zasshi [J Jpn Thyroid Assoc] 2015 (October); 6(2):91-4. (Japanese)

Izumi S, Sakata R, Yamada M, Cologne JB: Interaction between a single exposure and age in cohort-based hazard rate models impacted the statistical distribution of age at onset. J Clin Epidemiol 2016 (March); 71:43-50. (RR 5-14)

Joo J, Yoon KA, Hayashi T, Kong SY, Shin HJ, Park B, Kim YM, Hwang SH, Kim J, Shin A, Kim JY: Nucleotide excision repair gene *ERCC2* and *ERCC5* variants increase risk of uterine cervical cancer. Cancer Res Treat 2015 (June):1-7 [Epub ahead of Print].

Kajimura J, Ito R, Manley NR, Hale LP: Optimization of single- and dual-color imunofluorescence protocols for formalin-fixed, paraffin-embedded archival tissues. J Histochem Cytochem 2016 (February); 64(2):112-24. (RR 10-15)

Kerr GD et al. (RERF: Cullings HM, Grant EJ): Workshop report on atomic bomb dosimetry–Review of dose related factors for the evaluation of exposures to residual radiation at Hiroshima and Nagasaki. Health Phys 2015 (December); 109(6):582-600.

Key TJ et al.; Endogenous Hormones and Breast Cancer Collaborative Group (RERF: Grant EJ, Cologne JB, Ohishi W, Hida A): Steroid hormone measurements from different types of assays in relation to body mass index and breast cancer risk in postmenopausal women: Reanalysis of eighteen prospective studies. Steroids 2015 (July); 99(Pt A):49-55.

Kyoizumi S, Kubo Y, Misumi M, Kajimura J, Yoshida K, Hayashi T, Imai K, Ohishi W, Nakachi K, Young LF, Shieh JH, Moore MA, van den Brink MRM, Kusunoki Y: Circulating hematopoietic stem and progenitor cells in aging atomic bomb survivors. Radiat Res 2016 (January); 185(1):69-76. (RR 6-15)

Milder CM, Sakata R, Sugiyama H, Sadakane A, Utada M, Cordova KA, Hida A, Ohishi W, Ozasa K, Grant EJ: Initial report for the Radiation

Effects Research Foundation F1 Mail Survey. Asian Pacific J Cancer Prevent 2016 (April); 17(3):1313-23. (RR 14-15)

Nezu T, Hosomi N, Takahashi T, Anno K, Aoki S, Shimamoto A, Maruyama H, Hayashi T, Matsumoto M, Tahara H: Telomere G-tail length is a promising biomarker related to white matter lesions and endothelial dysfunction in patients with cardiovascular risk: A cross-sectional study. EBioMedicine 2015 (May); 2(8):958-65.

Ozasa K: Epidemiological research on radiation-induced cancer in atomic bomb survivors. J Radiat Res (Tokyo) 2016 (March):1-6. [Epub ahead of Print]

Ozasa K, Sugiyama H, Katayama H, Nakamoto M, Tsumura H, Nagasaki K, Arita K, Yasui W, Kajihara H, Usui S: Japan, Hiroshima. Cancer Incidence in Five Continents Volume X (IARC Scientific Publications No. 164). Lyon: International Agency for Research on Cancer, World Health Organization; 2014, pp 570-1.

Ozasa K, Takahashi I, Grant EJ: Radiation-related risks of non-cancer outcomes in the atomic bomb survivors. Ann ICRP 2016 (March):1-9. [Epub ahead of Print].

Schöllnberger H, Ozasa K, Neff F, Kaiser JC: Cardiovascular disease mortality of A-bomb survivors and the healthy survivor selection effect. Radiat Prot Dosimetry 2015 (May); 166(1-4):320-3.

Seed TM, Xiao S, Manley NR, Nikolich-Zugich J, Pugh J, van den Brink MRM, Hirabayashi Y, Yasutomo K, Iwama A, Koyasu S, Shterev I, Sempowski G, Macchiarini F, Nakachi K, Kunugi KC, Hammer CG, Dewerd LA: An inter-laboratory comparison of dosimetry for a multi-institutional radiobiological research project: Observations, problems, solutions, and lessons learned. Int J Radiat Biol 2016 (February); 92(2): 59–70.

Soda M, Sekine I, Taguchi T, Fukushima K, Ashizawa K, Suyama A: Japan, Nagasaki Prefecture. Cancer Incidence in Five Continents Volume X (IARC Scientific Publications No. 164). Lyon: International Agency for Research on Cancer, World Health Organization; 2014, pp 574-5.

Utada M, Ohno Y, Tamaki T, Sobue T, Endo G: Global and Japanese trends of intrahepatic and extrahepatic bile duct cancer and factors influencing those trends. JACR Monograph 2015 (November); No.21:3-10. (Japanese)

Yamada M, Landes RD, Mimori Y, Nagano Y, Sasaki H: Radiation effects on cognitive function among atomic bomb survivors exposed at or after adolescence. Am J Med 2015 (October):1-6 [Epub ahead of Print]. (RR 8-15)

Publications Using RERF Data

Allodji RS, Schwartz B, Diallo I, Agbovon C, Laurier D, de Vathaire F: Simulation-extrapolation method to address errors in atomic bomb survivor dosimetry on solid cancer and leukaemia mortality risk estimates, 1950-2003. Radiat Environ Biophys 2015 (August); 54(3):273-83.

Hamaoka Y: Reanalysis of data on A-bomb survivors in Hiroshima and Nagasaki. Kagaku [Science] 2015 (September); 85(9):875-88. (Japanese)

Peterson LE, Kovyrshina T: Adjustment of lifetime risks of space radiation-induced cancer by the healthy worker effect and cancer misclassification. Heliyon 2015 (December):1-51.

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