



update

Winter
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News and Views

Radiation Effects Research Foundation Hiroshima and Nagasaki, Japan



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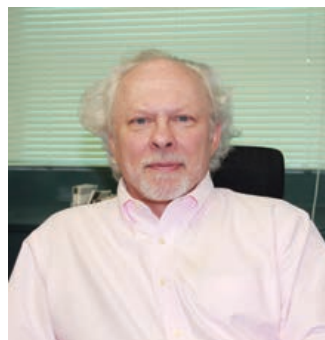
From the Editors

Welcome to the Winter edition of Update for 2015. This has been an unseasonably warm and rainy autumn in Hiroshima, remaining mild enough to walk around in shirtsleeves during the day, into the week of Labor Thanksgiving (Japan) and Thanksgiving (U.S.).

Hiroshima in its downtown has just finished hosting the festival celebrating Ebisu, a deity that symbolizes business prosperity for merchants and people in all occupations, and now the ever-expanding holiday light display along Peace Boulevard has been activated. The display has burgeoned in recent years with the advent of LED lighting, and now stretches from Rijo-dori (the streetcar street near the NHK building) on the west all the way to Ekimae-dori (the street near the shopping center Fuji Grand) on the east.

RERF now has a large temporary office building in the middle of the quadrangle where the tennis court normally sits, due to seismic reinforcement construction underway in the newer “non-Quonset-hut” buildings. In addition, the new robotic freezer is in operation, with its detailed story the subject of an article in this issue.

As mentioned in the last issue, 2015 is a year of major milestones, being the 70th year since the atomic bombings and the 40th since the formation of RERF. We have recently welcomed two new directors at RERF, and said farewell to two others, which is also a topic touched on in this issue. In August again this year, RERF held its two Open House events, in both Hiroshima and Nagasaki—see the article in this issue for a report on this



annual event as well. We have the usual selection of scientific reports, along with three reports on conferences and workshops, and a number of news items on meetings and events related to institutional governance as well as on media relations during the course of the year.

We hope you enjoy this issue!

November 26, 2015

Harry M. Cullings
Editor-in-Chief

Technical Editors

Jeffrey L. Hart
Setsumi Harachi
Tomoe Matsumoto

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

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Editorial Policy

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

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Messages from the Newly Appointed Chairman and Vice Chairman

Ohtsura Niwa, Chairman

Having assumed the role of Chairman of the Radiation Effects Research Foundation (RERF), I would like to discuss in general terms my vision of RERF's future direction.

RERF has studied the health of atomic bomb survivors and their children for more than 60 years, ever since the days of the Atomic Bomb Casualty Commission (ABCC), RERF's predecessor organization. While the studies conducted to date by ABCC-RERF have not detected any genetic effects among the children of A-bomb survivors, they have shown that the frequencies of cancer and non-cancer diseases increase with increased radiation dose in the directly exposed A-bomb survivors. The findings of our studies have been given high marks by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), and are used by the International Commission on Radiological Protection (ICRP) as the basis for establishing its radiation protection standards.

RERF's studies of A-bomb survivors are unrivaled anywhere in the world and follow specific cohorts over nearly the entire course of the study participants' lifetimes. This has been made possible only with the cooperation of A-bomb survivors. RERF's studies have generated numerous clinical and epidemiological findings. RERF recently initiated the Epidemiological Study of Health Effects in Fukushima Emergency Workers, the first application of RERF's accumulated experience to a population other than A-bomb survivors. RERF will further utilize our scientific background in various ways in the 21st century, a time when use of radiation is on the rise.

RERF's clinical and epidemiological studies



New Chairman Ohtsura Niwa

have clearly demonstrated radiation risks, but the underlying mechanisms remain unclear. RERF would do well to work to elucidate such mechanisms, possibly mitigating radiation risks in the process, and to that end, researchers in epidemiology and the basic sciences must work together. Although interdisciplinary collaboration between these two research areas in Europe and the United States has yielded few major achievements, RERF is committed to helping our epidemiology and basic science researchers collaborate toward fulfilling our responsibilities to A-bomb survivors.

RERF's vast supply of biosamples received from A-bomb survivors and their children must be analyzed to better identify radiation health effects and shed light on their mechanisms. For this purpose, RERF will assemble the world's foremost expertise and technology in a form that is accessible to the global community.

As new Chairman of RERF, I am determined to work to develop the direction I have outlined here in my message, and toward that end, I ask for everyone's support.

Robert L. Ullrich, Vice Chairman and Executive Director

As Vice Chairman and Executive Director at the Radiation Effects Research Foundation (RERF), I would like to extend my greetings to all of you. I first arrived at RERF in November of 2013 as Associate Chief of Research. I assumed the position of Vice Chairman and Executive Director in June of 2015.

This is an exciting time to be at RERF. Researchers from all departments are working together as never before with the goal of answering key questions about radiation effects, as well as genetic effects and non-cancer diseases, and unraveling the fundamental mechanisms involved in the onset of cancers. RERF has a wealth of

unique resources that allows us to accomplish this goal, thanks to the generosity of the atomic bomb survivors who have participated in our studies over many years. These resources enable us to conduct cutting-edge research using approaches not possible anywhere else in the world.

RERF has a long and distinguished history. I have been aware of RERF's research for the entirety of my career. Not only did I have the desire to participate in RERF's research when I made the decision to come to Japan; I also felt it important that I participate as an American in efforts to discover radiation effects from the atomic bombings of Hiroshima and Nagasaki in 1945. I thought, and

hoped, my own expertise could help lead the institute to continued growth and development of our research efforts into learning all we can about radiation health effects in the *hibakusha* population.

Our continuing and expanded studies conducted by the RERF Department of Epidemiology are considered the gold standard worldwide for understanding potential risks associated with radiation exposure. The Department of Statistics has been at the forefront in the development of new statistical approaches for the analysis of the vast data coming from RERF studies. Our Department of Clinical Studies monitors the health of *hibakusha* and their children in a supportive caring environment and at the same time provides unique insights into the study of radiation-associated diseases. These epidemiological and clinical studies provide the foundation for the future of RERF as it delves deeper into mechanisms and predictive markers of disease development based on collaborations among epidemiology and clinical sciences, as well as our basic scientists in our newly formed Department of Molecular Biosciences (a result of a merger of the Department of Genetics and the Department of Radiobiology/Molecular Epidemiology). The Department of Information Technology undergirds all the research we do through its careful husbandry of information we receive from *hibakusha* and management of all our databases.



New Vice Chairman Robert Ullrich

Our relatively new Biosample Center houses a new robotic freezer unit that will provide 20 more years of storage space for our precious biosamples (please refer to pages 14–15 for a detailed description of the new system).

We will be expanding our studies and increasing our abilities to conduct this work through active recruitment of first-class scientists worldwide and application of state-of-the-art scientific tools that make it possible to understand the processes involved in disease development as never before.

As I said at the top of my greetings, this is an exciting time to work at RERF. I am delighted and grateful to be a part of this new start, which was made possible by our globally renowned achievements from the past.

Farewell Messages

I retired as Chairman of the Radiation Effects Research Foundation (RERF) at the close of the regular meeting of the Board of Councilors in Washington, D.C., in June 2015. My farewell message here is a reflection of my gratitude for everyone's support through my tenure in that position over the course of 10 years and 3 months.

Since I was initially offered one four-year term of office (I was first hesitant to serve more than that), my tenure continued longer than expected. Before assuming the position of RERF Chairman, I worked for 10 years as Occupational Health Training Center Director, Vice President, and then President at the University of Occupational and Environmental Health, located in the city of Kitakyushu, Fukuoka prefecture. Based on my managerial experience at the university, I immediately realized that RERF was not operated in accordance with many of its established regulations. I therefore began my work by revising and eliminating incongruous regulations to improve operations

Toshiteru Okubo, Senior Consulting Scientist



Former Chairman Toshiteru Okubo

and make them consistent with our regulations to the extent possible.

Ongoing personnel reductions since the transition from the Atomic Bomb Casualty Commission (ABCC) to RERF have left the foundation with an older workforce and reduced organizational viability. For us to fall behind on scientific and technological progress, however, would have made

it difficult to maintain our high research standards. We therefore had to improve at the very least the existing systems used by our research scientists, as well as to introduce new ones.

Looking back, I realize how many new proposals I made in response to these needs. I began, for instance, developing future plans for RERF as internal guidelines. The many proactive opinions proposed for the future plans helped this evolve into a groundbreaking project. I also worked on other major projects to shore up RERF's future, including creation of the Biosample Center to effectively utilize RERF's precious biosamples col-

lected from A-bomb survivors, and introduction of a large robotic biorepository with the capacity to store our growing collection of biosamples.

The past 10 years went by very quickly as I addressed these and other matters to keep RERF viable. But there is one large project that remains uncompleted, namely our epidemiological study of emergency workers who engaged in clean-up work following the Fukushima nuclear power plant accident. This study started last year and will likely become a major RERF research project at some point in the future. I thus intend to continue working at RERF until this project gets on track.

Roy E. Shore, Former Vice Chairman and Executive Director

As an epidemiologist, I came to the Radiation Effects Research Foundation (RERF) in 2006 attracted by its epidemiological radiation studies that form the primary basis for radiation-risk assessment. My goal was to play a role in stimulating and shaping the research program. While that did occur in the decade that followed, the researchers of course deserve primary credit for the changes that came about due to their ideas, hard work, and cooperation.

The new developments during that decade have been gratifying—the following represent a few highlights of departmental research advances: The Department of Genetics transitioned to much more comprehensive, whole-genome studies of radiation-induced heritable genetic effects using high-density microarrays and genomic sequencing. The Department of Radiobiology/Molecular Epidemiology initiated a research program studying radiation effects on immunosenescence (the aging of the human immune system) and its health implications, with collaboration by some of the leading immunologic investigators from Japan and the U.S. The Department of Clinical Studies is carrying out a multifaceted program of prediagnostic assessments for cardiovascular disease in relation to radiation based on biomarkers and physiological markers. That department also began a unique program to study radiation and late-life neurocognitive deficits among those exposed prenatally or in early childhood. The Department of Epidemiology published a landmark paper on the link of radiation to cardiovascular and cerebrovascular disease mortality, whose results stimulated many other studies on the subject worldwide. Their work on radiation and cancer mortality in the Life Span Study of A-bomb survivors also has received considerable international attention. Updates that are nearing completion on cancer incidence among A-bomb survivors and mortality among the F1 offspring of the survivors will be influential as well. The



Former Vice Chairman Roy Shore

department found no evidence that fallout (“black rain”) exposures had significant health impacts or biased the radiation risk estimates. The Department of Statistics has conducted dosimetry research, such as implementing much improved estimates of dose attenuation by terrain shielding and publishing papers on the relative biological effectiveness (RBE) of neutrons and an improved estimation method for dose uncertainties. Statistical developments include a potentially important new semi-parametric method to estimate low-dose effects and increased integration of the Department into research in all RERF departments.

All in all, the past decade has been a period of scientific growth and new developments in which I was privileged to play a role. I believe the next decade at RERF will build on those scientific advances and produce new insights on radiation effects and their biological bases that will be significant for radiation protection and risk assessment.

On a personal note, many scientists and staff at RERF were a great pleasure to work with. Their helpfulness, kindness, and friendship will long be remembered. I especially enjoyed helping to mentor younger scientists and seeing their scientific initiatives and maturation. Working at RERF in Japan was an unforgettable experience for me.

Fifth Board of Councilors Meeting Held in U.S. Capital, Washington, D.C.

The fifth meeting of the Radiation Effects Research Foundation (RERF) Board of Councilors (BOC) took place on June 18–19 (June 18–20, Japan time) at the National Academy of Sciences (NAS) in Washington, D.C. The meeting was attended by seven councilors, as well as RERF directors and auditors. Representatives of the U.S. and Japanese governments and NAS also attended as observers. Executive Councilor Hiroo Dohy served as the moderator. In their remarks at the beginning of the meeting, the government representatives stated that RERF's research findings serve as the basis for radiation protection standards worldwide as well as for atomic bomb survivors' relief policies in Japan, and have thus gained the trust of the international community. They also expressed their appreciation to atomic bomb survivors for their dedicated cooperation in the studies.

The meeting's major agenda items and discussions are summarized below: the FY2014 activities, settlement of accounts, and audit results were reported and approved as proposed. Regarding the FY2015 activity plans, as in the previous year, reports were made on research projects related to the health of A-bomb survivors and their children; research to review individual radiation doses and elucidate radiation's effects on risk estimates; projects to release research results to the public and to collaborate with other scientific organizations; training programs for Japanese and overseas specialists; public information programs; activities necessary to carry out these projects; and budget estimates for all activities. A description of FY2014 activities and FY2015 activity plans for the Epidemiological Study of Health Effects in Fukushima Emergency



Scene inside fifth Board of Councilors meeting

Workers, initiated in FY2014, was also presented.

Scientific Advisor Anatoly Dritschilo reported on the 42nd Scientific Advisory Committee's recommendations made at the meeting held earlier in the year at the Hiroshima Laboratory March 2–4, 2015, which included a focused review of the activities of the Departments of Genetics and Radiobiology/Molecular Epidemiology. General recommendations included the committee's hope for long-term results from the merger of the basic research departments, advice to RERF to explore the possibility of gaining access to advanced technology through collaboration with external researchers, and emphasis that RERF forge collaborative relationships with bioinformatics experts outside of RERF.

Next, two councilors, three directors, two scientific advisors, and two local advisors were appointed. Dr. Ohtsura Niwa, Specially Appointed Professor at Fukushima Medical University, and Dr. Robert L. Ullrich, RERF Associate Chief of Research, who were appointed as directors by decision of the BOC, were designated as Chairman



Participants of RERF fifth Board of Councilors meeting

(representative director) and Vice Chairman (Chief of Research), respectively, at an ad hoc Board of Directors meeting convened after the BOC meeting.

Finally, it was decided that next year's BOC

meeting would be held at the RERF Hiroshima Laboratory June 16–17, 2016. On June 15, an informal meeting of councilors will take place prior to the BOC meeting, as was the case this year.

Local Liaison Councils Meet in Nagasaki and Hiroshima

Meetings of the Local Liaison Council (LLC), composed of local advisors, took place in Nagasaki on September 9, 2015, and two days later in Hiroshima on September 11, 2015. The Nagasaki LLC held its 24th meeting, and the Hiroshima LLC marked its 21st meeting.

The Nagasaki LLC meeting, attended by 12 of the 20 Council members, was opened by the Radiation Effects Research Foundation (RERF)'s Chief of Secretariat Eiji Akimoto, who introduced the new Council members. After greetings from RERF Chairman Ohtsura Niwa, the proceedings got underway, with Nagasaki LLC Chairman Shigeru Katamine (President of Nagasaki University) presiding over the meeting.

Dr. Niwa first reported on the current status of RERF, followed by Vice Chairman and Executive Director Robert L. Ullrich, who spoke about recent progress in research. Acting Chief of the Department of Nagasaki Clinical Studies Ayumi Hida then reported on the Clinical Study of the F₁ Offspring of A-bomb Survivors. Vice Director of the Nagasaki Biosample Center Kunio Yamaguchi described advances at the Biosample Center, followed by a report from the Department Chief of Radiobiology/Molecular Epidemiology Yoichiro Kusunoki on progress in the collaborative study with the U.S. National Institute of Allergy and Infectious Diseases (NIAID). Chief Scientist Kazunori Kodama then spoke about the epidemiological study of health effects in Fukushima emergency workers, followed by a report from Executive Director Takanobu Teramoto, who explained RERF's public relations activities.

At the Hiroshima LLC meeting, 13 of the 15

members attended, including three proxies. The meeting was chaired by Hiroshima LLC Chairman Mitsuo Ochi (President of Hiroshima University). As at the Nagasaki meeting, reports were presented by Dr. Niwa on RERF's present status; Dr. Ullrich on recent research; Chief of the Department of Hiroshima Clinical Studies Waka Ohishi on the Clinical Study of the F₁ Offspring of A-bomb Survivors; and Director of the Biosample Center Yoshiaki Kodama on progress at the Biosample Center.

The account of the Clinical Study of the F₁ Offspring of A-bomb Survivors indicated that during the second four-year cycle, about 10,000 participants underwent health examinations, nearly meeting the 80% target for participation. The report also explained that collected examination data will be aggregated to analyze and evaluate the prevalence and occurrence of diseases among children of A-bomb survivors.

Views were actively exchanged about RERF's data and study results at both meetings, and we were able to hear valuable opinions from the local communities. At the Hiroshima LLC meeting, a participant suggested establishing a system to allow RERF to centrally archive biosamples of A-bomb survivors that are currently stored by medical institutions in Hiroshima City. There was also a request for early relocation of Hiroshima RERF.

The objective of these Councils is to compile ideas from local communities and see them reflected in RERF's operations. We take the opinions and requests presented during these meetings seriously, review them fully, and utilize them in planning RERF's future operations.



Local Liaison Council meeting held at Nagasaki RERF



Local Liaison Council meeting held at Hiroshima RERF

Open House 2015 Held at Hiroshima and Nagasaki RERF

The Radiation Effects Research Foundation (RERF) Hiroshima and Nagasaki Laboratories held their 21st and 19th Open House events on August 5–6 and August 8–9, 2015, respectively, under the theme “Learning about RERF 70 years after the atomic bombings.”

At Hiroshima RERF, in addition to presentations of the newest results from RERF research, which continues thanks to the understanding and cooperation of A-bomb survivors and numerous others, a special exhibit titled “Considering the health effects of low-dose radiation exposure based on atomic bomb radiation studies” and a feature exhibit based on the theme “History of the Radiation Effects Research Foundation over the course of 70 years since the A-bombings” were displayed. At the “Science Corner,” several ‘hands-on’ events such as a liquid-nitrogen show and a presentation of vegetable DNA extraction were held. Also set up were a “Children’s Hospital,” at which the many young people who attended the Open House could try their hand at simulated medical work, and a quiz/stamp rally, which allowed people to engage in the contest while strolling around the facilities.

On August 5, the first day of the event, Dr. Kyoji Furukawa, Associate Senior Scientist, Department of Statistics, gave a lecture titled “Statistics could be fun—From radiation risk to the likelihood of the Carp winning a championship,” introducing statistics in a general sense. Using various measures, Dr. Furukawa also talked about the chances of the local Hiroshima Carp winning the baseball pennant this season, making for a fun time shared with many guests. On August 6, the second day, Dr. Kazunori Kodama, Chief Scientist, lectured on the “Health effects of A-bomb radiation—Considering what we do and don’t know at this juncture 70 years later,” describing RERF’s research results to this point in time as well as issues to be addressed in the future. After the lecture, Dr. Kodama turned to English to explain the same information to non-Japanese guests.

At Nagasaki RERF, in addition to a feature



Participation by many children made for lively Hiroshima Open House



Children trying their hand at the Science Corner

exhibit, information on RERF’s research and results, and a special exhibit, Dr. Kodama lectured on the same theme as in Hiroshima. ‘Hands-on’ areas—including experiments with liquid nitrogen, observations using electron and other microscopes, and commemorative photographs taken while wearing white lab coats—were a big hit with children. The adult visitors seemed to be most interested in arteriosclerosis testing, bone mineral density measurements, body fat monitoring, urinalysis, and other health tests. A lasting impression of the event was the sight of both children and adults enjoying interaction with RERF staff.

With the weather clear during the two-day events in the cities, a total of 1,046 people visited the Hiroshima Laboratory and 678 the Nagasaki Laboratory. This year’s lively Open House featured lots of communication between visitors and RERF staff, and prominent throughout the facilities were families with children, one of the focal points of this year’s events.

The Open House this year provided a good opportunity for the public to become more familiar with RERF at this juncture 70 years after the atomic bombings.



Nagasaki RERF Open House lecture

Regional Television Crew Revisits RERF to Film Additional Educational Program about Radiation

Two episodes of the popular educational television program “Let’s see...,” hosted by comic duo Daisuke and Hanako Miyagawa, were filmed at the Hiroshima Laboratory of the Radiation Effects Research Foundation (RERF) during the summer, on June 30, 2015. The film crew returned to RERF to record these episodes in response to requests for more information from people watching the previous episodes broadcast in February 2015 (for more on the previous episodes, refer to our Update Summer 2015 edition, page 11). In the most recent episodes, the question posed to RERF was “What is radiation?”

Dr. Norio Takahashi, Consultant to the RERF Associate Chief of Research’s Office and guest in both the first film session in February and the recent session, addressed the question by first touching on the difference between radiation and radioactivity. He explained that the effects of radiation on the human body depend on dose (measured in a unit called the sievert [Sv]), which is the energy amount deposited by radiation in tissue. He also used a dosimeter to demonstrate that a smaller dose is received the more distant one is from the source of radiation and that radiation can be blocked by water or concrete and similar materials.

Hiroshima was added to the viewing area for the “Let’s see...” program in mid-October 2015, but the latest two episodes on radioactivity were aired earlier, on September 27 and October 4, 2015, and were thus limited to Japan’s San-in region (on the Japan Sea side of the main island of Honshu). We truly hope the general public was able to deepen its understanding about radiation.



Dr. Norio Takahashi (right), Consultant, Associate Chief of Research Office, appears for second time with TV variety program comic duo hosts Daisuke (left) and Hanako Miyagawa

Marking of 70th Year Since A-bombings Draws Considerable Media Attention

The Radiation Effects Research Foundation (RERF) typically goes about its business without expecting much in the way of media fanfare. This year, the 70th since the atomic bombings in 1945



CBS Asia Bureau team interviews Dr. Harry Cullings, Chief, Statistics Dept., about GIS mapping technology

and the 40th since the founding of RERF in 1975, the media spotlight shone more brightly on our institute in Hiroshima and Nagasaki. As we reflected this many years later on the A-bombings of Hiroshima and Nagasaki, news organizations across the globe took up the banner, helping to share important stories of the survivors and our research.

International media in particular showed intense interest. In the spring, for example, Tokyo Productions, a company comprised of freelance French journalists based in Tokyo, visited Hiroshima RERF to film a documentary for RMC Decouverte, a French broadcaster. The original one-hour program, which was broadcast in France on the evening of September 8, delves into examples of World War II historical traces that remain in Japan today—from naval wreckage off Okinawa’s coast to medical records of A-bomb survivors archived at RERF. Please check out the September 15 entry on the timeline of our Facebook page (Radiation

Effects Research Foundation) for the video portion of the program that speaks specifically to RERF's A-bomb survivor records.

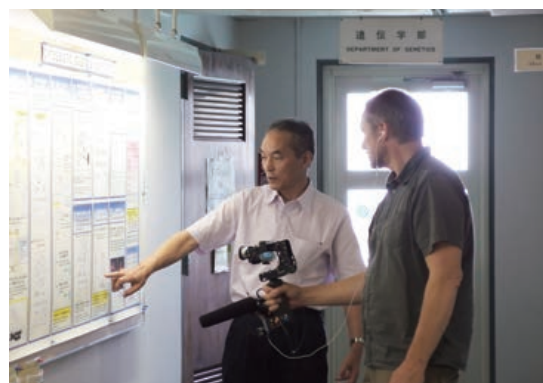
In June, the same Tokyo production group of French freelance journalists in Tokyo visited RERF to produce an August 6 program for France 24, a French TV channel broadcast in three languages (French, English, and Arabic) in Europe, Africa, the Middle East, and the U.S. The link indicated below was sent to us by the team at Tokyo production and is the English-language version of the news program: <http://www.france24.com/en/20150806-japan-hiroshima-70-years-survivors-medical-scrutiny-cancers-radiations>.

In late July, RERF was visited by the Asia Bureau of CBS for that organization's story on RERF efforts to understand radiation health effects in survivors of the Hiroshima and Nagasaki A-bombings, which took place on August 6 and 9, 1945, respectively. The CBS story aired August 9 on CBS Evening News. The story should still be accessible at: <http://www.cbsnews.com/videos/the-health-effects-of-the-hiroshima-and-nagasaki-atomic-bombs-70-years-later/>.

In early August, Inside Science published an article that discussed the radiation health research that began at the Atomic Bomb Casualty Commission (ABCC), RERF's predecessor organization, in the 1940s and continues to this day. The article describes RERF's research in detail, the contributions the organization has made to low-dose radiation research, and the future direction radiation research must take to produce a more complete picture of how radiation impacts human beings exposed to sources besides atomic bombs. For the full article, please check out the link indicated below: <https://www.insidescience.org/content/seventy-years-later-atomic-bombs-still-influence-health-research/3086>.

By way of comparison, in fiscal 2014, there was not one report on RERF that was broadcast by overseas media. As outlined above, fiscal 2015 has had considerably more impact from that perspective.

The media in Japan were also focused on RERF at this 70th-year juncture. The annual RERF media gathering, held this year in late-April in both Hiroshima and Nagasaki, touched on the topic of RERF's new epidemiological study of emergency workers engaged in the cleanup after the *tsunami*-caused accident at the Fukushima Daiichi nuclear power plant. The study at RERF to investigate health effects in Fukushima emergency workers as well as research conducted elsewhere will highlight long-term, persistent exposures of smaller amounts



Dr. Asao Noda, Assistant Chief, Genetics Dept., interviewed by French journalist

of radiation, information that will complement RERF's longstanding research into the instantaneous exposures experienced by A-bomb survivors. The theme of Fukushima, a topic of great interest in Japan and throughout the world, drew a sizeable delegation of local and national media representatives. The session also included discussion of RERF plans and projects scheduled for fiscal 2015.

Later in the year, in October, a press explanatory session attended by a large contingent of print and broadcast media representatives was held for the recently published paper "Risk of Death among Children of Atomic Bomb Survivors after 62 Years of Follow-up: A Cohort Study." RERF invited the media to attend with the aim of explaining results from the updated study, which found no increased mortality in the children of A-bomb survivors (please see the Science Articles piece of the same title for a summary explanation of the paper in this Update on page 21). The health effects in this second generation represent a study area of great interest to the public and therefore the media.

Overall, it was a busy year for RERF, with journalists from the U.S., Germany, several groups from France, Brazil and, naturally, local and national journalists in Japan producing reports on the A-bombings of Hiroshima and Nagasaki, as well as on our efforts to understand radiation health effects in A-bomb survivors, in this 70th year after the bombings.

Worldwide radiation protection standards have been established in large part from RERF's research on the health effects of the bombings, and in that and other senses, the work deserves considerable recognition. We are gratified that the media paid RERF and its research so much attention in 2015; we invite them to continue in 2016 and beyond.

Staff of U.S. Congressional Study Group on Japan Visit Hiroshima RERF

On the morning of Monday, May 25, 2015, senior staff of the U.S. Congressional Study Group on Japan and members of the Sasakawa Peace Foundation, a total of 11 people, visited the Hiroshima Radiation Effects Research Foundation (RERF).

After then RERF Chairman Toshiteru Okubo welcomed the group, Dr. Eric J. Grant, Assistant Chief, Department of Epidemiology, gave a general overview of RERF that included a description of the Life Span Study (LSS) cohort and findings. Dr. Waka Ohishi, Chief, Department of Clinical Studies, then spoke on the Adult Health Study (AHS), its significance, and some of the findings in the many years since that study's inception.

Dr. Yoshiaki Kodama, then Director of the RERF Biosample Center, introduced the visitors to the freezers and nitrogen tanks used for the storage of RERF's more than 900,000 biosamples. The group next viewed the then-empty space at which the Biosample Center's robotic freezer system was to begin operations later this year. At the end of their visit, the visitors passed by RERF's photographic exhibit and looked over the historical photographs of well-known political figures who had visited RERF in the past.

The group had an ambitious schedule. On Sunday, May 24, after arriving in Hiroshima, they visited the Hiroshima Peace Memorial Museum. On the morning of May 25, before arriving at RERF, they paid a courtesy visit to Hiroshima Governor Hidehiko Yuzaki. During their RERF tour, the group mentioned they were scheduled to visit the Satake Corporation, a multinational grain-sorting equipment manufacturer located in Higashi-Hiroshima, before flying to Tokyo the



U.S. Congressional study group takes in historical photographs exhibited at Hiroshima RERF

same day. They then visited Fukushima to gather information on the area affected by the Great East Japan Earthquake and by the continuing radiation leak from the Fukushima Daiichi (No. 1) nuclear power plant. Given their itinerary, the group expressed great interest in RERF's involvement in Fukushima, especially our new health survey of the roughly 20,000 emergency workers who labored at the Fukushima nuclear power plant during the first nine months following the accident in March 2011 (please refer to page 31 of this Update).

According to the Congressional Study Group on Japan's website at <http://usafmc.org/international-programs/congressional-study-groups/congressional-study-group-on-japan/>, the Study Group is an independent and non-partisan organization that promotes legislative exchange between the U.S. Congress and the Japanese Diet. The group was conceived in 1993 and has served as an ongoing forum for dialogue about important issues concerning the U.S.-Japan relationship.

As the website states, "Bipartisan pairs of current members of Congress chair the Congressional Study Group on Japan in each Chamber of Congress. Rep. Diana DeGette (D-CO) and Rep. Billy Long (R-MO) serve as co-chairs in the House. Senator Mazie Hirono (D-HI) and Senator Lisa Murkowski (R-AK) lead the Study Group in the Senate.... The Study Group's activities are supported in part by a generous grant from the Sasakawa Peace Foundation USA..."

The Sasakawa Peace Foundation is a private Japanese foundation that works to strengthen cooperation at all levels among nations in terms of issues facing societies as well as natural and social crises. For more information, see the Foundation's website at: <https://www.spf.org/e/>.



Dr. Eric Grant, Assistant Chief, Epidemiology Dept., speaks to group of U.S. Congressional aides who were in Japan on study tour

RERF Welcomes Japan Studies Association Delegation to Hiroshima Laboratory



Dr. Eric Grant, Assistant Chief, Epidemiology Dept., lectures Japan Studies Association delegation about RERF research

Summer was busy for the Radiation Effects Research Foundation (RERF), given that 2015 was the 70th year since the atomic bombings of Hiroshima and Nagasaki in 1945, as well as the 40th anniversary of RERF's founding. While RERF strives to convey information from Hiroshima and Nagasaki about its research by reaching out to the public using multiple platforms, sometimes we are fortunate to have the public visit RERF in an effort to learn directly from us.

On the morning of July 1, RERF welcomed a delegation from the Japan Studies Association (JSA), an organization established in 1994 that assists its members—primarily teachers from U.S. two- and four-year colleges and universities—to acquire first-hand knowledge about Japan and incorporate it into their curricula through workshops and study-tours. According to its website, the association enables JSA members to engage in Japan-related curriculum development, to design study-abroad programs, and to initiate comparative research. The 2015 study tour to Japan was titled “Remembering Hiroshima and Nagasaki 1945–2015” and brought the group to the two A-bombed cities from June 28 to July 5, 2015.

During its four-day visit to Hiroshima, the group met with Hiroshima Peace Memorial Museum representatives and A-bomb survivors and toured Hiroshima Peace Memorial Park. On July 1, about 25 members from the group came to Hiroshima RERF to learn about the scientific aspects of the bombings of the two cities. Other members of the group traveling to Japan signed up for an optional tour of Hiroshima Castle, Shukkeien Garden, or other activity on that day.

At RERF, Mr. Takanobu Teramoto, Executive

Director, led off the series of presentations with an overview of RERF and its research; next was a showing of RERF's introductory video. Mr. Douglas C. Solvie, Associate Chief, Secretariat, spoke on ABCC-RERF history and government involvement in the organization; Dr. Eric J. Grant, Assistant Chief, Epidemiology Department, spoke on RERF research results, with a particular focus on the RERF Life Span Study (LSS). After an extensive Q&A session, Mr. Jeffrey L. Hart, Chief, Public Relations and Publications Office, took the group on a facility tour, touching on historical aspects of ABCC-RERF and details about some of RERF's research efforts.

Some in the visitors group were science educators, including one radiation physicist, who engaged in conversation at length with Dr. Grant after his lecture. The diverse group included those from the University of Wisconsin River Falls, Kapi'olani Community College of the University of Hawaii, and Antioch College in Ohio, among others.

During its three days in Nagasaki at the tail-end of its Japan visit, the group visited Nagasaki Peace Memorial Park, the Nagai Museum, Urakami Cathedral, and Glover Garden.

Ms. Fay Beauchamp, JSA Vice President for Special Projects, later wrote that everyone thought the trip to Japan was a meaningful experience that would affect the faculty in terms of teaching students in many different colleges and arranging plans to return to Japan with different groups. She closed the message with the following words: “Thank you very much for arranging the visit to RERF. The Japan Studies Association participants thought that was a key event, and for some it was a main reason for coming to Hiroshima.”



JSA delegation given tour of Hiroshima RERF facilities

Staff News

The Radiation Effects Research Foundation (RERF) Chairman Toshiteru Okubo and RERF Vice Chairman Roy E. Shore resigned on June 20, 2015, when their terms expired. On the same day, Ohtsura Niwa, Specially Appointed Professor of Fukushima Medical University, assumed the position of Chairman, and Robert L. Ullrich, RERF Associate Chief of Research, became Vice Chairman. Together with Executive Director Takanobu Teramoto, Dr. Niwa and Dr. Ullrich have assumed guidance of operations at RERF. Upon resigning as RERF Chairman, Dr. Okubo was appointed Senior Consulting Scientist to lead the Epidemiological Study of Health Effects in Fukushima Emergency Workers, beginning July 1. Greetings from the newly appointed Chairman and Vice Chairman and messages from the outgoing officers are on pages 2–4.

Eiji Nakashima, Assistant Chief of the Depart-

ment of Statistics, retired June 30, under the mandatory age limit, but will continue research as Research Scientist (adjunct specialist) in the same department. Reid D. Landes, Senior Scientist in the Department of Statistics (fixed-term research scientist), and Seishi Kyoizumi, NIAID Project Research Scientist in the Laboratory of Immunology, Department of Radiobiology/Molecular Epidemiology, resigned as their terms expired on June 30 and September 30, respectively. Jun-ichi Asakawa, Senior Scientist (fixed-term research scientist) in the Laboratory of Biochemical Genetics, Department of Genetics, also retired under the mandatory age limit on June 30, but will continue his engagement with RERF research as a consultant to the same department.

Kismet A. Cordova newly joined the Department of Statistics on July 13. She introduces herself below.

Kismet A. Cordova, MS

On July 13, 2015, I joined RERF as a research scientist in the Department of Statistics. My undergraduate degree in psychology with an emphasis on research methodology and statistics was awarded in 2011 from the University of Colorado Boulder. From then, I spent four years as a research assistant at CU-Boulder studying psychosocial factors and cognitive impacts associated with long-term marijuana use. In May 2015, I completed my Master's degree in applied biostatistics and bioinformatics from the Colorado School of Public Health.

I have always felt a great kinship and adoration for Japanese culture, ever since I visited as a child. This was amplified when I met my husband Damien, as we bonded over a mutual love for Japanese history and aesthetics. When we married in 2013, we folded 1,000 cranes together as a blessing and prayer for the happiness and longevity of our marriage. Last summer, we spent our honeymoon in Japan, traveling from Tokyo to Kagoshima and back. When I saw the job opening at RERF, I was anxious for the opportunity to expand my statistical consulting skills while living in Japan for an extended period of time.

During my time at RERF, I look forward to learning more about the history, current status, and



Ms. Kismet Cordova, research scientist, Statistics Dept., in her office

future of this important organization. As a consulting statistician, I love to work on a wide variety of projects spanning diverse topics, problems, and types of data. Clear communication and dissemination of information to non-statisticians is a passion of mine, and I look forward to honing this skill even further at RERF as I begin to learn Japanese. Ultimately, I hope to have the opportunity to work with RERF researchers on the research topics that are important to them, and to help bring those ideas to life. I appreciate your support and guidance as I learn more about RERF and living in Japan.

Receiving the Journal of Radiation Research Award at ICRR 2015

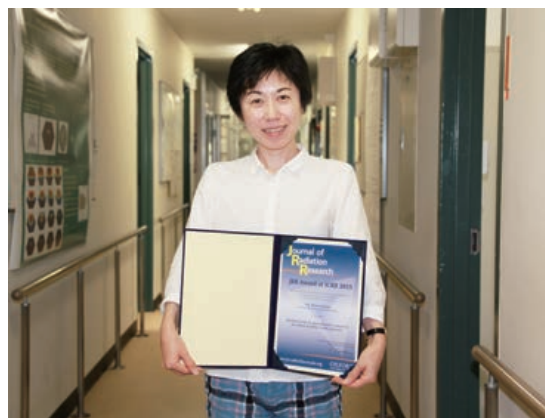
**Ritsu Sakata, Associate Senior Scientist
Department of Epidemiology, Hiroshima**

At the 15th International Congress of Radiation Research (ICRR), held in Kyoto, Japan, May 25–29, 2015, I was happy to receive the Journal of Radiation Research Award for my presentation titled “Radiation risks of upper digestive cancers in the cohort of atomic-bomb survivors.”

In my presentation, I discussed the findings of a study on radiation effects in upper gastrointestinal cancers (of the mouth, esophagus, and stomach) in a series of collaborative studies that the Radiation Effects Research Foundation (RERF) conducts with the U.S. National Cancer Institute (NCI) based on cancer incidence data through 2009.

In these ongoing cancer incidence studies, non-radiation factors for cancer, such as smoking and drinking, are adjusted for using lifestyle data obtained through mail surveys and other sources. Oral and esophageal cancers are known to be strongly associated with smoking and drinking. Although findings on an association between smoking and drinking and stomach cancer are inconsistent, many studies have found some kind of relationship. Stomach cancer is the most common type of cancer in the RERF Life Span Study (LSS) cohort, accounting for about one-quarter of all cancers observed. This prevalence enables detailed analyses of dose-response relationships and effect modifiers, making the stomach an interesting site for study.

I reported at the meeting that the study showed upper gastrointestinal cancers to be related to smoking and drinking but with no confounding



Dr. Ritsu Sakata, Associate Senior Scientist, Epidemiology Dept., displays Journal of Radiation Research Award

between radiation and these lifestyle factors. I also reported that, for esophageal cancer, a model that included the time since exposure as an effect modifier provided a better fit than a model that included attained age and age at exposure as effect modifiers. I have since conducted more analyses and am writing a manuscript explaining my findings.

I believe that the award reflects international recognition of RERF's epidemiological research on radiation health effects. Credit must go to the senior researchers who guided me, my colleagues who advised me, and collaborative investigators at the NCI who assisted me. I look forward to your continued guidance and encouragement.

RERF's "BioStore"—Ticket to the Future

Yoshiaki Kodama, Director
Ayako Ishibe, Vice Director, Biosample Center

A robotic biorepository installed in October 2015 at the Radiation Effects Research Foundation (RERF) Biosample Center in Hiroshima is about to start full operations. Herein, we look back on what led to the largest equipment purchase in RERF history.

Concern surfaces and grows about the future of RERF's biosamples

The mission of RERF is to investigate the effects of radiation on human health. The data and samples RERF has accumulated over more than 60 years make this possible. They are truly valuable and unique to the world, treasures, as has already been described.

Long ago, nurses and technicians responsible for storing biosamples in freezers started wondering what would happen if samples kept being added at such a rapid pace.

The RERF Committee on Biological Samples and others previously reviewed some stored samples and discussed how samples should be managed. But the findings of these reviews and discussions did not prompt any action, since the samples were individually managed by research departments and RERF had nothing but their own individual freezers in which to store them. The nurses and technicians who inspected the samples likely understood the situation best.

Also concerned was then RERF Chairman Toshiteru Okubo. On many occasions he explained that input from A-bomb survivors and society in general was needed to decide when, by whom, and for what RERF's samples would be used.

In 2009, RERF collaborated in an international project on age-related decline in immune function funded by the U.S. National Institute of Allergy and Infectious Diseases (NIAID). The project required Dr. Okubo to devote himself to fully informing relevant local communities about how the samples would be used. This called the foundation's attention to serious consideration of the use of RERF's biological assets.

This major project took three years of planning

RERF created its first Future Plans in 2011, collecting opinions from all RERF staff. The plans included many comments on biosample storage, such as: "We will run out of space for freezers in a few years."

"We don't have enough employees to properly

operate the freezers."

"We should centrally manage the samples, which are now scattered among the departments."

"Our existing emergency generators may not be able to supply enough power for the freezers."

We wish we could say that to resolve these problems, RERF equipped its "ships" representing Hiroshima and Nagasaki with an "engine" called the Biosample Center and "sailed out full steam ahead" for the purchase of a robotic biorepository. But it was not that simple.

Dr. Waka Ohishi, Chief of the Hiroshima Department of Clinical Studies, and Mr. Takeshi Kishi, Senior Technician in that department, introduced a robotic biorepository vendor to Dr. Okubo, who was intrigued by the idea. Later, Dr. Ohishi and Dr. Tomonori Hayashi, Assistant Chief of the Department of Radiology/Molecular Epidemiology, identified other companies' models as candidates, and RERF personnel including Dr. Okubo and Chief Scientist Kazunori Kodama, who was serving as the Biosample Center Director at the time, went to see some models in operation. After obtaining approval from the U.S. and Japan governmental funding agencies and the Board of Councilors, RERF secured a budget and arranged for the purchase of a BioStore II (Brooks Automation, Inc., USA) through a public call for proposals, technical review, and bidding. This major project took RERF three years to complete since inception. It is invigorating to now have an operational BioStore II before us.

Determining how to minimize damage to biosamples

The comments indicated in the Future Plans document motivated Dr. Okubo to make a decision but



Workers erect framework for new robotic biorepository

were just the beginning. Employees discussing the future of epidemiological research—RERF’s core competency—considered how stored samples could be managed efficiently and removed without unnecessary damage. Dr. Okubo repeatedly raised these as practical issues in discussions about research.

Removing dozens of samples collected, say, four, eight, or 12 years ago requires the freezers to be opened and closed and other samples on the same trays to be removed. Sample handlers became concerned that this could damage the samples. Sample damage of this type is not a concern in robotic biorepositories because evaporators set to minus 80 degrees centigrade are located right above the samples; trays are stationed in an insulated four-compartment storage space; and samples are quickly removed and returned in a freezer complete with a dehumidification system to minimize condensation and sample warming. In addition, people no longer need to move cartridges weighing nearly 10 kilograms to and from deep freezers. Other important advantages include more effective use of space and increased energy efficiency.

Engineers who built a world of -80 C°

With preparatory work completed, the robotic biorepository was delivered and assembled starting on June 17, 2015. As we watched the multinational engineers from Brooks take turns assembling the equipment in groups of four or five workers, we became increasingly convinced this was a worthwhile investment.

The engineers showed their professionalism during construction and during a particular incident. In the morning of August 26, other workers excavating a nearby road inadvertently severed cable carrying electricity to RERF, shutting down power throughout the RERF facility. The accident happened just when the equipment had been dehumidified with an air compressor and eight evaporators were being sequentially started. A newly installed second emergency generator, by ill for-



RERF Biosample Center staff try their hand at tray removal

tune, was not connected yet, and therefore all work completed to that point came to nothing. Spending no time being despondent, the engineers inspected the damage and carried out recovery work throughout the night. Their enthusiasm seemed to say, “The BioStore is our baby!” Prompting their effort was their understanding of the value of RERF’s samples to the world and their pride in being assigned this important task. The smiles on the faces of the departing engineers, who built a world of -80 C° , spoke volumes about how satisfied they were to have helped protect the samples.

Biosample Center has more work to do

The Brooks BioStore II was inspected and turned over to RERF on October 5. But we still must determine exactly how we will use this “ticket to the future” that RERF employees envisioned in the Future Plans.

The robotic biorepository will help RERF conduct studies possible only with RERF samples. The Biosample Center has more work to do as it takes stock of the samples and addresses the remaining tasks, which include assessing the impact of the freezing and thawing of frozen samples on components. Viewing the magnificent BioStore robotic freezer through the tour window reminds us of all we have mentioned here.



RERF Biosample Center staff, along with Brooks workers, pose for photo at initial stage of work

Fifth Meeting of the Scientific and Ethics Committee for Offspring Study

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

The fifth meeting of the Scientific and Ethics Committee for the Clinical Study of the F₁ Offspring of A-bomb Survivors was held in the Hiroshima Radiation Effects Research Foundation (RERF) Auditorium on May 14, 2015. The purpose of the meeting was to discuss the progress of the Longitudinal Clinical Study of the F₁ Offspring of A-bomb Survivors and report on the preliminary data of the study.

The initial Clinical Study of the F₁ Offspring of A-bomb Survivors (the so-called “first cycle,” which had a cross-sectional design) was conducted during 2002–2006 to study associations between parental exposure and prevalence of multifactorial diseases (hypertension, hypercholesterolemia, diabetes mellitus, angina pectoris, myocardial infarction, and stroke) in the offspring of atomic bomb survivors. Prevalence was analyzed for all diseases and for each of the diseases independently. In neither case was evidence obtained showing an increased risk associated with parental exposure. This study of prevalence, however, may have had a participation bias (by which study results become non-representative because disproportionate participation in the study of subjects possessing certain traits affects the outcome) in the health examinations, and the average age of the participants was relatively young, at about 49 years. For these and other reasons, it was recommended that a long-term study be conducted. As recommended, the Longitudinal Clinical Study of the F₁ Offspring of A-bomb Survivors (the so-called “second cycle”) was initiated on November 24, 2010, with approxi-

mately 12,000 study participants.

The meeting began with RERF Vice Chairman Roy E. Shore’s opening remarks, which were followed by RERF Chief Scientist Kazunori Kodama’s introduction of the committee members. Subsequently, Committee Chairman Tadao Shimao, Consultant, Japan Anti-Tuberculosis Association, addressed the audience. Dr. Waka Ohishi, Chief, Department of Clinical Studies, reported on the progress made over the four years since initiation of the second cycle. She noted that during this period about 10,000 participants underwent health examinations, nearly meeting the targeted 80% participation rate and keeping the study moving steadily forward toward the third cycle. Dr. Ohishi added that approximately 99% of the participants had consented to the storage and use of their blood and urine samples for non-genome/gene analysis, 97% to the storage and use of these samples for genome/gene analysis, and 99.7% to continued participation in the clinical study, indications of the participants’ high level of understanding and cooperation.

Dr. Yoshimi Tatsukawa, Associate Senior Scientist, Division of Health Examinations, Department of Clinical Studies, next presented preliminary calculations of participant data from the first three years of the second cycle of the Longitudinal Clinical Study of the F₁ Offspring of A-bomb Survivors. Attendees engaged in an active question-and-answer session, moderated by Committee Vice Chairman Hiraku Takebe, Fellow, Kinki University Atomic Energy Research Institute, about the



Fifth meeting of Scientific and Ethics Committee for Clinical Study of the F₁ Offspring of A-bomb Survivors held at Hiroshima RERF

prevalence and incidence of multifactorial diseases, comparisons of lifestyles and disease prevalences between those who participated in the second cycle and those who did not based on information obtained in the first cycle, and plans for future statistical analyses based on the results of these comparisons. The committee eagerly provided valuable comments. The latest participation data indicate that the vast majority of those eligible for the second cycle of the study would have undergone health examinations by the end of October 2015. It was explained that the full-scale calculations include participants projected to undergo

examinations within that timeframe and that statistical plans for upcoming analyses will be further scrutinized. Dr. Shimao wrapped up the meeting with a summary, and Dr. Kodama provided closing remarks, expressing his appreciation to the committee members.

We will continue to advocate the significance of the study to obtain understanding and cooperation from as many study participants as possible. We will also further improve our health examination program to allow earlier disease detection and better treatment and care for the health of the participants.

Members of the Scientific and Ethics Committee for the Clinical Study of the F₁ Offspring of A-bomb Survivors

Dr. Tadao Shimao (Chairman), Consultant, Japan Anti-Tuberculosis Association

Dr. Hiraku Takebe (Vice-Chairman), Professor Emeritus, Kyoto University

Dr. Hirotosugu Ueshima, Special Contract Professor, Center for Epidemiologic Research in Asia, Shiga University of Medical Science

Dr. Takashi Kawamoto, Professor, Division of Philosophy and Religion, College of Liberal Arts, International Christian University

Mr. Shinsuke Kimura, Attorney, Kimura Shinsuke Law Office

Dr. Hideo Sasaki, Professor, Department of Nutritional Sciences, Faculty of Human Ecology, Yasuda Women's University

Dr. Steve Wing, Associate Professor, Department of Epidemiology, School of Public Health, University of North Carolina

Dr. Kazuo Tajima, Advisor to Director of Mie University Hospital

Dr. Masao Tomonaga, Professor Emeritus, Nagasaki University

Dr. Taisei Nomura, Professor Emeritus, Osaka University

Dr. Norihiko Hayakawa, Professor Emeritus, Hiroshima University

Dr. Yoshimitsu Fukushima, Professor and Head, Department of Medical Genetics, Shinshu University School of Medicine

Dr. Katsumi Furitsu, Assistant Professor, Department of Genetics, Hyogo College of Medicine

Dr. Eiji Maruyama, Professor, Graduate School of Law, Kobe University

RERF

Dr. Toshiteru Okubo, Chairman

Dr. Roy E. Shore, Vice Chairman

Mr. Takanobu Teramoto, Executive Director

Dr. Robert L. Ullrich, Associate Chief of Research

Dr. Kazunori Kodama, Chief Scientist

Mr. Eiji Akimoto, Chief of Secretariat

Mr. Douglas C. Solvie, Associate Chief of Secretariat

Members, Working Group for the Clinical Study of the F₁ Offspring of A-bomb Survivors

Research Scientists, Department of Clinical Studies

Press Explanatory Session

“Risk of Death among Children of Atomic Bomb Survivors after 62 years of Follow-up: A Cohort Study”

Interest among the public has always been high in the Radiation Effects Research Foundation (RERF)’s findings regarding morbidity and mortality in the children of directly exposed atomic bomb survivors, in particular among members of the media.

With that in mind, on October 5, 2015, RERF convened an explanatory session for the media concerning a paper recently published online in London-based *The Lancet Oncology*. The paper, “Risk of Death among Children of Atomic Bomb Survivors after 62 years of Follow-up: A Cohort Study,” reported the latest results from RERF’s long-term study of atomic bomb radiation effects in the offspring of atomic bomb survivors in Hiroshima and Nagasaki.

The media session was held at Hiroshima RERF and connected to Nagasaki RERF by teleconferencing. Attending media members in both cities totaled around 15 representatives of major news publications and broadcasters, including local news organizations from Hiroshima and Nagasaki, as well as national media. Several of their reports describing what was reported at the meeting were broadcast and published in the following days.

Dr. Kotaro Ozasa, Chief, Department of Epidemiology, opened the session with a general explanation of the study’s findings and significance (please see the Science Articles piece of the same title in this Update on page 21).

Dr. Eric J. Grant, Assistant Chief, Department

of Epidemiology, responded to the questions following the brief description, explaining the technical details and nuances of the study as its lead author. Diverse questions from the media included those regarding what level of hazard ratio represents statistical significance, as well as why genetic effects in the offspring generation have not been seen in humans despite such effects being apparent in many other species.

Given intense interest expressed by the media, the entire session went considerably longer than usual.

The study’s 75,327 participants were born between 1946 and 1984, being conceived after the 1945 atomic bombings of Hiroshima and Nagasaki, and followed up until December 31, 2009. The study, which was the latest in a series of RERF research into the same topic, showed no increased mortality from cancer or non-cancer diseases with larger parental exposure in children of atomic bomb survivors. Thus, children of people exposed to the atomic bombs in Hiroshima and Nagasaki have so far had no indications of deleterious health effects even after 62 years.

Dr. Grant was careful to point out to the media, however, that such epidemiological studies must be complemented by sensitive molecular techniques in the future to fully understand the overall effects of preconception exposure to ionizing radiation in human beings.



Press explanatory session held for paper “Risk of Death among Children of Atomic Bomb Survivors after 62 years of Follow-up: A Cohort Study”

Sixth Epidemiological Training Workshop for Biologists

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

The sixth Epidemiological Training Workshop for Biologists, sponsored by the Council of Radiation Effects Research Organizations,* was held August 24–25, 2015, and 49 people (six from the Radiation Effects Research Foundation [RERF]) attended. Although past workshops were held in RERF's Auditorium, this year's workshop took place in the Hiroshima RERF Laboratory's Hijiyama Hall. Many Epidemiology Department staff helped to move tables from the Auditorium up to Hijiyama Hall. The heavy lifting we did served as a reminder again of how much RERF's workforce has aged.

On the first day of the workshop, I gave a talk titled "Epidemiology for non-specialists" about epidemiological terminology and methods. Dr. Kotaro Ozasa, Chief, RERF Department of Epidemiology, presented RERF research results in a lecture titled "Recent results from the Life Span Study (LSS)." Dr. Atsuko Sadakane, Acting Chief, Pathology Laboratory, Associate Senior Scientist, from the same department, shared tips for reading and understanding epidemiological papers in her talk "Risk of childhood cancer from CT scans." Dr. Misa Imaizumi, Chief, Divisions of Radiology and Clinical Laboratories, Department of Clinical Studies, Nagasaki RERF, spoke about "Radiation exposure and thyroid cancer," covering the thyroid gland and its association with radiation. Subsequent talks titled "Radiation effects on the fetus" (Dr. Nori Nakamura, Consultant, Department of Genetics) and "Combined effects of radiation exposure and estradiol on postmenopausal breast cancer" (Dr. Eric J. Grant, Assistant Chief, Department of Epidemiology) attracted participants' interest as each touched on both epidemiological

and biological findings. In the last session of the first day, RERF Chairman Ohtsura Niwa gave the presentation "Summary of the ICRP tissue stem cell report." This report was a reason why many of the participants, who listened intently, decided to attend. Following this presentation, Dr. Kazuo Yoshida, Director, Radiation Safety Research Center, Central Research Institute of Electric Power Industry, talked about a model for integrating biology and epidemiology in his presentation titled "Simulation of dose-rate effects with stem-cell competition." This presentation marked the end of the first day of the workshop.

Almost all participants attend the reception every year. This year's reception began with greetings by RERF Vice Chairman Robert L. Ullrich and Chief Scientist Kazunori Kodama. The participants shared information with each other throughout the reception.

A typhoon was forecast to pass near Hiroshima around noon on the second day, when the workshop was scheduled to conclude. Concerned that the approaching typhoon might halt westbound train service, some of the participants, particularly those from Kyushu, had to cut short their visit and leave early. However, most participants stayed through until the end of the workshop despite the storm. Dr. Nori Nakamura gave a talk titled "Observing mouse experiments from the perspective of epidemiology," which served as a bridge between the two fields of epidemiology and biology. Dr. Kazutaka Doi, a researcher from the National Institute of Radiological Sciences, gave a presentation titled "Can epidemiology markers be generated with data from animal experiments?" about the development of an R extension pack-



Sixth Epidemiological Training Workshop for Biologists held at Hijiyama Hall, Hiroshima RERF

age for calculating excess relative and other risks. Some participants requested that they be able to use the package. Lastly, there was a general discussion about a paper by Tomasetti et al., titled "Variation in cancer risk among tissues can be explained by the number of stem cell divisions." The research described in the paper looks at changes in number of mutations, rather than at individual genes as conventional studies have done. Understanding the explanation was a challenge for many of the participants.

We were worried about the participants' journey home through the approaching typhoon. Fortunately, those from the east were able to return as scheduled via eastbound *Shinkansen* train service, which was not affected.

In this year's workshop, less time was spent introducing RERF's research to allow more time for presentations bridging epidemiological and biological research. New this year were presentations by researchers from the Central Research Institute of Electric Power Industry and the National Institute of Radiological Sciences.

Participants were asked to complete a question-

naire at the end of the workshop. Some told us what they plan to present next year, responses that will help with planning for the next workshop. A participant reported finding the workshop educational because it helped him remember the many things he had learned at previous workshops and subsequently forgotten. His comment reminded us why we must keep holding the workshop. In response to demands to restore the theme "Radiation biology for non-biologists," employed at the fourth workshop, we will include this session in next year's program.

On the next day, after the storm had passed, we began moving the tables from Hijiyama Hall back to the Auditorium, only to find that the elevator was out of service due to a power outage. But despite this and other unexpected events, we successfully wrapped up the workshop, the importance of which we became well aware. I would like to express my sincere appreciation to the participants, the presenters, and the staff from the General Affairs Section and the Department of Epidemiology, who helped make this workshop possible.

*The Council of Radiation Effects Research Organizations, consisting of the Institute for Environmental Sciences, Kyoto University, Nagasaki University, Hirosaki University, Hiroshima University, Fukushima Medical University, National Institute of Radiological Sciences, and Radiation Effects Research Foundation (order of above institutes arranged according to the Japanese syllabary), was established to develop understanding among radiation research organizations and strengthen their alliance.

Risk of Death among Children of Atomic Bomb Survivors after 62 Years of Follow-up: A Cohort Study*

Eric. J. Grant

Department of Epidemiology, Hiroshima, RERF

*This article is based on the following publication:

Eric J. Grant, Kyoji Furukawa, Ritsu Sakata, Hiromi Sugiyama, Atsuko Sadakane, Ikuno Takahashi, Mai Utada, Yukiko Shimizu, Kotaro Ozasa: Risk of Death among Children of Atomic Bomb Survivors after 62 Years of Follow-up: A Cohort Study. *Lancet Oncol* 2015 (October); 16(13):1316–23 (doi:10.1016/S1470-2045(15)00209-0)

Study Findings

We did not observe any association of mortality in the children of the atomic bomb survivors with parental (either paternal or maternal) radiation exposure from the atomic bombings.

Explanation

We conducted a study of the relationship between parental radiation exposure and the patterns of cancer and non-cancer deaths among children conceived after the bombings in the F1 mortality cohort of the Radiation Effects Research Foundation (RERF).

1. Study purpose

Radiation-induced hereditary effects have been detected in many species, but no clear epidemiological effects have been demonstrated in humans. This mortality study of children conceived by the survivors of the atomic bombings includes follow-up data since 1946, serving as an important resource in the search for hereditary effects of radiation exposure in humans.

2. Study methods

In this prospective cohort study (a follow-up study of a fixed population), we assessed 75,327 children of atomic bomb survivors in Hiroshima and Nagasaki and unexposed controls who were born between 1946 and 1984 and followed up until December 31, 2009. Analyses were conducted using parental gonadal radiation doses from the atomic bombings. The primary health effects endpoint was death due to cancer or non-cancer disease, based on death certificates. We analyzed deaths over the full follow-up period, divided into the period between birth and until age 20 years and the period at and after age 20. Analyses were

performed using *Cox proportional hazards regression, and *hazard ratios (HR) were reported.

*Cox proportional hazards regression: Is a statistical methodology, developed by Sir David Cox in the 1970s, to estimate the risk (or hazard) of the occurrence of an event. In this case, we estimated the hazard of death. The word “proportional” in the title is used because the hazard of those exposed to an agent is assumed to be proportional to those unexposed to the agent.

*hazard ratios (HR): The hazards are compared as a mathematical ratio. In this study, if the ratio is 1.0, then the hazard of death is not associated with parental radiation exposure.

3. Study results

(1) Demographics:

Median follow-up was 54.3 years (*inter-quartile range: 45.4–59.3). A total of 5,183 participants died from disease. The mean age of the 68,689 surviving children at the end of follow-up was 53.1 years (SD 7.9) with 15,623 (23%) older than age 60 years. For parents who were exposed to a non-zero gonadal dose of radiation, the mean gonadal dose was 264 mGy (*SD 463).

*inter-quartile range: The inter-quartile range describes the range from the 25th percentile to the 75th percentile. This statistic is often reported in combination with the ‘median’ (50th percentile).

*SD: The standard deviation (SD) is a measure of the spread of the data and is often used in combination with the mean value.

(2) Relationship between mortality and parental exposure:

No association was detected between maternal gonadal radiation exposure and risk of death

caused by cancer in the children (HR for 1 Gy change in exposure 0.891 [95% CI: 0.693–1.145]; $p = 0.36$) or risk of death caused by non-cancer diseases (HR: 0.973 [0.849–1.115]; $p = 0.69$). Similarly, paternal exposure had no effect on deaths caused by cancer (HR: 0.815 [0.614–1.083]; $p = 0.14$) or deaths caused by non-cancer disease (HR: 1.103 [0.979–1.241]; $p = 0.12$). Analyses of the period birth until age 20, and the period at and after age 20 also showed no association between parental exposure and mortality in the children.

*Confidence interval (95% CI): The confidence interval means that if the experiment were repeated 100 times, the “true value” of the hazard ratio would be within each experiment’s reported confidence interval 95% of the time. Or stated another way, if the confidence interval that we derived from our data does not contain the “true” value, then an event has occurred that had a 5% probability of happening by chance.

(3) Other findings:

Those born in the decade immediately after the

bombings had higher non-cancer death rates than those born in later decades regardless of parental exposure, but parental age at exposure or time between parental exposure and childbirth had no effect on risk of death.

Study Significance

Based on RERF research results, late effects of ionizing radiation exposure include increased mortality risks in those exposed directly to the atomic bombs. Theoretical models of the transgenerational effects of radiation exposure predict more disease based on genetic alterations in the children of people exposed to radiation. However, children of people directly exposed to the atomic bombs in Hiroshima and Nagasaki had no indications of deleterious health effects after 62 years of follow-up. Epidemiological studies complemented by sensitive molecular biologic techniques are needed to understand the overall effects of preconception parental exposure to ionizing radiation on children and are being pursued at RERF.

Radiation Effects on Cognitive Function among Atomic Bomb Survivors Exposed at or after Adolescence*

Michiko Yamada

Department of Clinical Studies, Hiroshima, RERF

*This article is based on the following publication:

Michiko Yamada, Reid D. Landes, Yasuyo Mimori, Yoshito Nagano, Hideo Sasaki: Radiation Effects on Cognitive Function among Atomic Bomb Survivors Exposed at or after Adolescence. *The American Journal of Medicine*; 1–6, 2015 [ONLINE AHEAD OF PRINT] (doi: 10.1016/j.amjmed.2015.09.002)

Study Findings

We analyzed longitudinal cognitive decline data spanning two decades from atomic bomb survivors exposed in or after adolescence. Radiation exposure was not significantly associated with late-life pre-dementia cognition level or age-associated cognitive decline.

Explanation

Cognitive function was evaluated in medical examinations performed every other year from 1992 through 2011. The effects of radiation exposure on longitudinal pre-dementia cognitive decline were estimated after adjustment for age, sex, education level, and occurrence of dementia during follow-up.

1. Study purpose

The objective was to investigate what effects radiation exposure in or after adolescence has on late-life cognitive function by estimating longitudinal cognitive decline in the participants who did and in those who did not develop dementia during follow-up.

2. Study methods

To observe longitudinal pre-dementia cognitive decline, cognitive function was assessed in medical examinations of 1,844 participants in the Hiroshima Adult Health Study (AHS) who were exposed to atomic bomb radiation at or after the age of 13 and, in 1992, were between 60 and 80 years of age and free of dementia. The Cognitive Abilities Screening Instrument (CASI), a standardized survey of cognitive ability, was used to evaluate cognitive function. Of that total, 313 participants developed dementia during follow-up from 1992 through 2011. A mixed-effects* model was used to analyze changes over time in pre-dementia cognitive scores.

*Mixed-effects model: This statistical model is useful for analyzing repeated measurements over time. It factors in both fixed and random

effects (hence its name).

3. Study results

- (1) Cognition level was significantly lower in participants who were older, had a low level of education, or developed dementia but was unrelated to radiation dose or sex.
- (2) Cognitive decline accelerated with age, dropping particularly rapidly in participants who had developed dementia. Tendencies in age-associated cognitive decline were unrelated to radiation or education.
- (3) Radiation dose did not significantly affect cognition level or tendencies in age-related cognitive decline in the participants who did and in those who did not develop dementia.

Study Significance

Interest is growing in the effects of radiation exposure on cognitive function as more patients survive malignancies. Research on survivors of cancer radiation therapy has shown cognitive decline many years after exposure in younger patients exposed to high doses. But the effects of high radiation therapy doses for cancer treatment are not easily distinguished from the effects of the underlying cancer and chemotherapy. The effects of moderate and lower radiation doses or in patients undergoing radiation therapy at relatively older ages, moreover, have not been sufficiently studied. In this study, we evaluated cognitive function in elderly atomic bomb survivors exposed once to a moderate or lower dose (≤ 4 Gy) in or after adolescence. We did not find that radiation exposure significantly affected cognition. A similar cognitive study has been carried out since 2011 of AHS participants who were 12 years or younger at the time of the A-bombings. Upon completion of the four-year cross-sectional study, those data will be analyzed.

Long-Term Effects of the Rain Exposure Shortly after the Atomic Bombings in Hiroshima and Nagasaki*

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*This article is based on the following publication:

Ritsu Sakata, Eric J. Grant, Kyoji Furukawa, Munechika Misumi, Harry M. Cullings, Kotaro Ozasa, and Roy E. Shore: Long-Term Effects of the Rain Exposure Shortly after the Atomic Bombings in Hiroshima and Nagasaki. *Radiat Res* 2014 (November); 182(6):599–606

Study Findings

Using a population of individuals responding to surveys from 1949 to 1961, we compared mortality and cancer incidence between those reporting rain exposure shortly after the atomic bombing and those reporting no such rain exposure. No increase in mortality or cancer incidence was observed in those reporting rain exposure.

Explanation

1. Objectives

The objective of the study was to determine whether mortality or cancer incidence was higher among individuals reporting rain exposure shortly after the atomic bombing than individuals reporting no such rain exposure.

2. Methods

The study included 86,609 Life Span Study cohort members who had an estimated Dosimetry System 2002 (DS02) radiation dose. The Atomic Bomb Casualty Commission, the predecessor to the Radiation Effects Research Foundation, conducted surveys through personal interviews from 1949 to 1961. Based on these survey results, the respondents were categorized into three groups according to their response to the question on rain exposure (i.e., “Yes,” “No,” “Unknown”). The excess relative risks (ERRs) of mortality between 1950 and 2005 and cancer incidence between 1958 and 2005 were estimated among those reporting rain exposure relative to those reporting no rain exposure. The data were adjusted for city, sex, year of birth, attained age, and individual DS02 dose estimates from direct radiation exposure.

3. Results

➤ Of the individuals interviewed, 42,050 (72%) in Hiroshima and 25,064 (89%) in Nagasaki

responded to the question on rain exposure. Of these, 11,661 (20%) in Hiroshima and 733 (2.6%) in Nagasaki reported rain exposure.

- The ERR of all-cause mortality from 1950 to 2005 among those who reported rain exposure in Hiroshima was 0.01 (95% confidence interval (CI): -0.02, 0.04). The ERRs of mortality for solid cancer and leukemia for the same period were -0.02 (95% CI: -0.06, 0.04) and 0.06 (95% CI: -0.15, 0.32), respectively. No significant increase in risk was observed.
- A weak association was observed between all-cause mortality and rain exposure in Nagasaki (ERR = 0.08, 95% CI: 0.00006, 0.17) for the entire period of observation (1950 to 2005). However, the association was not statistically significant for the period after all surveys had been completed (1962 to 2005). The ERRs of mortality for solid cancer and leukemia between 1950 and 2005 were 0.14 (95% CI: -0.01, 0.33) and -0.03 (95% CI: -0.07, 0.02), respectively, suggesting no significant increase in risk.
- No increase in cancer incidence in those who reported rain exposure was observed in either city.

The individuals reporting rain exposure in Hiroshima were not at significantly higher risk of mortality from all cause, solid cancer, or leukemia or of developing solid cancer or leukemia. The findings, however, were inconsistent for those reporting rain exposure in Nagasaki; all-cause mortality risk was higher for certain observation periods and statistical models but not others. In addition, risk estimates for cancer mortality and incidence were inconsistent with each other. These inconsistencies could be attributable to the low number of individuals who reported rain exposure in Nagasaki (733), which is too small to provide reliable statistical inference. In addition, answers to

the question on rain exposure would more likely be “unknown” when the 1949–1961 surveys, including the question on rain exposure, were conducted after individuals died and questions were answered by their proxies who had no knowledge regarding whether or not that individual had been caught in rain (outcome-dependent bias). It was also possible when the surveys were conducted after individuals had developed cancer or died that the respondents might have associated this health outcome with their rain-exposure experience (recall bias). For the observation period after completion of the surveys (i.e., starting in 1962), analysis results were probably less affected by these biases. For this observation period, therefore, no significant increase in

risk was observed in Nagasaki. No increased risk was observed in either city for mortality from or the occurrence of leukemia, which is often taken to be a “sentinel” indicator of radiation effects. For these reasons, the association observed in Nagasaki is unlikely to be attributable to exposure to radiation from rain. In this study, a large percentage of individuals have missing data on rain exposure. In addition, we did not obtain any information on rain exposure from a considerable proportion of the subjects and no details were available on the circumstances surrounding the rainfall and how individuals experienced the rain from those providing the information on rain exposure. The results should thus be interpreted with caution.

Prognostic significance of premature ventricular contractions without obvious heart diseases determined by standard 12-lead electrocardiography considering their morphology*

Daisuke Haruta

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*This article is based on the following publication:

Daisuke Haruta, Masazumi Akahoshi, Ayumi Hida, Nobuko Sera, Misa Imaizumi, Shinichiro Ichimaru, Eiji Nakashima, Ikuno Takahashi, Waka Ohishi, Satoki Fukae, Koji Maemura: Prognostic significance of premature ventricular contractions without obvious heart diseases determined by standard 12-lead electrocardiography considering their morphology. *Ann Noninvasive Electrocardiol* :1–10, 2015 (online ahead of print) (doi: 10.1111/anec.12275)

Study Findings

Premature ventricular contraction (PVC) (a type of arrhythmia characterized by premature heart contractions originating in one of the ventricles) in patients with no overt underlying heart disease did not increase the risk of all-cause death, death from heart disease, or death from ischemic heart disease (angina pectoris and myocardial infarction). Analysis by underlying morphology, however, showed the possibility that PVC with left bundle branch block morphology (which has impulses arising in the right ventricle and resembles a left bundle branch conduction abnormality) increased the risk of death from ischemic heart disease.

Explanation

PVC—a common arrhythmia triggered by impulses arising outside the normal conduction pathway of the heart—occurs even in people with no underlying heart disease (pre-existing heart condition, including angina pectoris, valve disease, or myocardial disease). No consensus has been reached on the prognosis (mortality) of PVC with no underlying heart disease, and the effects of disease morphology on outcome are not well characterized. We evaluated the outcomes of PVC in Adult Health Study participants, analyzing the data according to disease morphology.

1. Objectives

This study was designed to evaluate the outcomes of PVC in Adult Health Study participants according to disease morphology and to review the association between PVC prevalence and radiation dose.

2. Methods

First, all 6685 Hiroshima and Nagasaki atomic-

bomb survivors who were examined during the two-year base period from January 1990 to December 1991 (period of case entry) were selected as candidates for analysis. Next, the 1000 participants with an overt underlying heart disease or EKG abnormality noted in the examination were excluded for an analysis population of 5685 participants, 67.1% of whom were women. One hundred thirty-one participants with PVC reported in 12-lead EKG performed at the examination were then identified. These participants with PVC were classified according to EKG morphology: left bundle branch block (74), right bundle branch block (21), and other (36). They were followed through December 2008 for the endpoints of all-cause death, cardiac death, and death from ischemic heart disease. Cause of death was based on information obtained from death certificates. The data were tested with the multivariate Cox proportional hazards model to calculate the risk (hazard ratio) of the endpoints.

3. Results

No PVC morphology (overall, left bundle branch block, right bundle branch block, other) was associated with increased all-cause death or cardiac death. Participants with PVC of left bundle branch block morphology, however, were at significantly higher risk of death from ischemic heart disease (hazard ratio, 2.73; 95% confidence interval, 1.11–6.73). Our analyses revealed no significant correlation between radiation dose and the incidence of PVC in the examination period.

The study data suggest that PVC with no overt underlying heart disease could be a risk factor for death from ischemic heart disease. Morphological classification of PVC may therefore inform risk evaluations for ischemic heart disease performed in health examinations.

Bioinformatics Sabbatical in Hawaii

**John B. Cologne, Senior Scientist
Department of Statistics**

I had the fortunate opportunity to spend two months (May–June 2015) at the University of Hawaii Cancer Center (UHCC) in Honolulu, Hawaii (first photo) to study methods of high-dimensional “omics” data analysis and collaborate in the analysis of cellular pathway and network genetic markers using genomic data. Motivating my trip was encouragement that the Radiation Effects Research Foundation (RERF) Statistics Department received in 2014 from the Scientific Advisory Committee (SAC) to undertake continued training and development of “big data” and genomic data analysis skills and to establish relationships with external experts and organizations with the aim of accelerating work on machine learning and related methods for analysis of gene-environment interaction.

I was eager to take up this challenge because of my interest in bioinformatics and my yearning to obtain hands-on experience with true high-dimensional data. I had already learned some basics of genome-wide association (GWA) analysis using Harvard PLINK software through a six-month collaboration with Dr. Kenji Shimizu, Department of Molecular Genetics, Okayama University Graduate School of Medicine and Dentistry, several years ago, and had studied on my own to learn the use of kernel logistic regression methods of testing genomic association and gene-environment inter-

action in case-control data. (Kernel logistic regression is based on support vector machine learning and implemented in the SKAT and iSKAT packages in R software.)

Having been introduced to UHCC by former RERF visiting research scientist Dr. Marc Troup Goodman, Director, Cancer Prevention and Genetics, Cedars-Sinai Medical Center, Los Angeles, I knew UHCC had a joint biostatistics/informatics group, biologists collaborating closely with their cancer epidemiology program, and heavy involvement in studies of gene-environment interaction in cancers based on high-dimensional molecular data. UHCC therefore offered a unique opportunity for me to gain experience with high-dimensional data and to practice genomic analysis based on cellular pathways/networks (gene sets, which are based on combining single nucleotide polymorphisms—SNPs—that are related through common disease pathways) in a rich environment of collaborating statisticians, epidemiologists, biologists, and informaticians (specialists in the field of informatics).

The Biostatistics Group at UHCC collaborates with the Department of Preventive Medicine at the University of Southern California (USC) Keck School of Medicine on the Multi-Ethnic Cohort (MEC) study of interaction between genomic and lifestyle/dietary factors as well as genetic susceptibility in relation to causation of cancer. RERF Con-



University of Hawaii's Cancer Center, where Dr. John Cologne, Senior Scientist, Statistics Dept., studied on sabbatical

sultant Dr. Dan Stram, Associate Professor of Preventive Medicine, Division of Biostatistics, USC Keck School of Medicine, is intimately involved in that program, and he introduced me to Dr. Lynne Wilkins, Co-Director, Biostatistics & Informatics Shared Resource, UHCC. The MEC includes a sub-population of people of Japanese descent that may facilitate validation studies (which are sorely needed in genomic research because of small sample sizes and many non-reproducible false-positive findings).

While at UHCC I had access to data from both genome-wide and targeted SNP arrays: the latter was the “MetaboChip,” designed for studying metabolic, cardiovascular, and anthropometric traits and their relationship to disease. GWA data were available on more than 300,000 SNPs which, with imputation based on linkage disequilibrium (LD) using data from the 1000 Genomes Project (an international consortium launched in 2008 to establish a catalog of human genomic variation in diverse ethnic groups), produced genotypes on over four million variants for the Japanese sub-population of the MEC.

The anonymized MetaboChip data, which I was provided through a data-sharing agreement between UHCC and RERF and was able to bring back to Japan with me, includes about 200,000 SNPs from about 8,000 persons of Japanese ancestry with 676 cases of colorectal cancer. I am currently analyzing those data for association between colorectal cancer and various cell-signaling pathways related to cancer risk. Because there is no radiation exposure in the MEC, I am unable to test for gene-radiation interaction in those data. However, given the relatively small size of available data and limited number of colorectal cancer cases in the RERF data, results from the MEC Japanese data should be useful in terms of focusing RERF analyses on potential risk variants (statistical power is greater in GWA studies than in RERF’s if the numbers of non-informative SNPs can be minimized).

Finally, while at UHCC I met with a group of informaticians and mathematicians who are doing cutting-edge research on statistical methods of analysis of integrated omics data. Because any one level of omics gives an incomplete picture of the complex mechanisms of cancer risk (for example, a risk variant cannot confer a risk if not expressed), these researchers are implementing mathemati-

cal procedures to combine multivariate outcomes (e.g., genotype, expression, and methylation) and to search for common patterns. Among the procedures they use are methods of sparse principal components analysis, which is described in the book “Analysis of Multivariate and High-Dimensional Data” by Inge Koch, Associate Professor, School of Mathematical Sciences, University of Adelaide, Australia, who previously visited Hiroshima and presented her high-dimensional results to the Hiroshima Statistics Study Group in January of 2015 (please see the Summer 2015 edition of Update, page 23).

It is not possible to describe in a brief news article all of the experience and knowledge I gained during my two months in Hawaii. However, as “a picture is worth a thousand words,” I will share with readers the view from my office at UHCC (photo below), from which I hope they can sense the refreshment and renewed vigor I felt. I also had the opportunity to interact with statisticians in other fields at the University of Hawaii during my two seminars: one describing my research into methods of sampling from cohorts, the other on my study of bias arising from omitting covariates from excess relative risk models for binary outcome data. No photo can capture the stimulation of new research ideas I was treated to by Dr. Wilkins and the many other kind and knowledgeable researchers at UHCC through numerous meetings and discussions, but that should become apparent as I now focus on finding ways to integrate my newly gained skills and knowledge in my various projects at RERF.



View from Dr. Cologne’s office

My Starting Point

**Kyoji Furukawa, Associate Senior Scientist
Department of Statistics**

I flew to Sri Lanka in late July 2015 after a presentation I gave at a scientific meeting in Singapore. Sri Lanka is a tropical island nation a bit smaller than Hokkaido and located in the Indian Ocean. The island is known for its tea, jewels, ancient ruins (many of which are World Heritage sites), and stunning beaches.

My connection with the country goes back 20 years.

Aspiring to see as many countries as possible while young, I quit my job in my mid-20s and applied for an overseas volunteer position at the Japan International Cooperation Agency (JICA). After successfully passing the screening and undergoing three months of training in Japan, I was sent to Sri Lanka in April 1995. I spent two-and-a-half years as an instructor at the Department of Computer Science and Engineering at the University of Moratuwa near the capital city of Colombo. I felt more worried than excited flying into Sri Lanka, which was then in a state of civil war due to ethnic tensions. There were nightly curfews and travel restrictions as well as frequent terrorist bombings. Once I arrived, though, I felt safe so long as I stayed in the faculty residence on campus in the suburbs. All the friendly assistance I received allowed me to live in peace and security. (The civil war, which began in 1983, ended finally in 2009.)

Students of the fewer than 10 universities in the entire country, which had a population of 20 million, represented the nation's elites. My job was mainly to teach students how to develop artificial intelligence and applications for such tech-

nologies, as well as to provide guidance for their projects. When I lectured, I always marveled at how engaged all the competent and hardworking students were. Giving over 150 hours of classes in English taught me so much. I spent long hours in preparation to make up for my limited expertise and English ability. I tried to make my lectures simple but fun, using intriguing examples. This experience molded my present style of research and presentation. I also learned through teaching at the university the importance of statistics, which is my specialty today.

I treasure all I did with my students: I celebrated with a student group when they won a research competition, and had beach parties, traveled, and played cricket with them. I learned a lot watching the students in Sri Lanka strive for limited opportunities with a can-do attitude even though the country was not nearly as blessed as Japan in many aspects. Wanting to be a better teacher, I decided to pursue a doctorate in the United States. In this way, Sri Lanka was the starting point of my research career.

The purpose of my most recent visit to Sri Lanka in July 2015 was to give a lecture at the ESOFTE College of Engineering & Technology in Moratuwa at the invitation of a friend of mine, who was a colleague when I was working as an instructor. As with many developing countries, Sri Lanka has a high demand for engineers and information technology workers to support economic growth. In my lecture titled "Risk and statistical decision-making," I talked to promising engineer-



Dr. Furukawa teaching in classroom, 20 years ago



Dr. Kyoji Furukawa in Sri Lanka, then

ing students about how risks are analyzed and utilized for decision-making, citing radiation research and environmental risk assessments as examples. Although the atomic bombings of Hiroshima and Nagasaki are well known in Sri Lanka, the students seemed to know little about the prolonged health effects from radiation exposure. Surrounded as they are by extensive damage from the earthquake in the Indian Ocean off Sumatra and the ensuing *tsunami* in 2004, the students showed great interest in the damage from the *tsunami* in Tohoku, Japan, and the accident at the Fukushima Daiichi nuclear power plant.

During my stay, I also met up with old colleagues I had not seen in several decades and

enjoyed short trips such as to tea fields up in the hills. Leaving the fast-changing urban area, I was reunited with rice fields and palm trees in the countryside. Local people were still friendly, speaking to me wherever I went. Speaking Sinhala, the local language that I thought I had forgotten, eating curry with my fingers, and watching from the beach as the sun set into the Indian Ocean, I returned to my younger days 20 years ago. Back then, about to turn 30, I was optimistically following my intuition to try to build a future for myself despite any clear sense of purpose. My recent trip to Sri Lanka made me realize that those young days are the foundation of who I am today.



Dr. Furukawa, in classroom 20 years later

RERF Epidemiological Study of Health Effects in Fukushima Emergency Workers

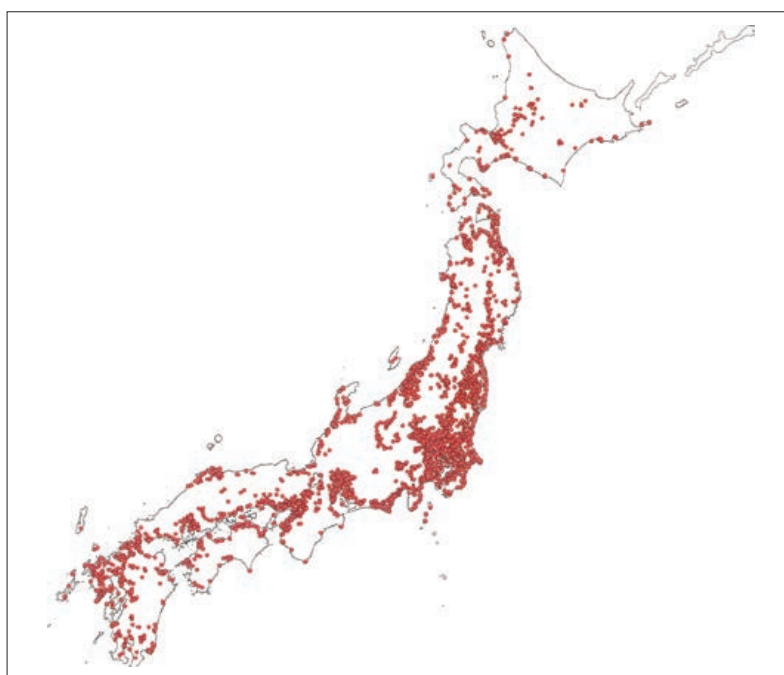
The Radiation Effects Research Foundation (RERF) has commenced preparations for the conduct of a first-time study of radiation health effects in a population different from the atomic bomb survivors: nuclear emergency workers who were involved in the response to the accident at the Fukushima Daiichi (No. 1) nuclear power plant between March 14 and December 16, 2011. During this period, the Japanese national government raised the exposure limit for such emergency countermeasure workers from 100 millisievert (mSv) to 250 mSv in order to contain as best as possible a situation that looked close to being out of control.

The roughly 20,000 total workers, who are now scattered in every one of Japan's 47 prefectures, received doses that were generally low and low-dose rate (protracted, i.e., received over an extended period of time, as opposed to the A-bomb survivors' doses, which were received almost instantaneously). RERF started health surveys of around 5,000 such workers still resident in Fukushima prefecture at the initiation of the study in the early spring of 2015. For this initial portion of the study, RERF sent letters around the end of January to those workers living in the pre-

fecture requesting their participation in the study, but many of the letters were returned because the addressee could not be located. By the reply deadline at the end of February, only around 1,000 people had responded. From August 17 to the end of September 2015, letters had been sent to about 17,000 workers, with 7,000 responding (8,000 not responding), and 74% of that number agreeing to participate. A study cohort is planned to be established within the first five years, and the greatest challenge for the study administrators appears to be improving this participation rate.

A-bomb survivors have doses that range up into the tens of gray (or, Gy) in a few cases, although doses above 4 Gy are generally truncated to 4 Gy for use in RERF analyses. Workers in the Fukushima study, abbreviated as the NEW Study, mostly have received doses <0.1 Sv (100 mSv), with only 174 workers having doses >0.1 Sv and an estimated nine workers with doses >0.2 Sv (200 mSv). The greatest radiation exposure for any of the workers during this timeframe has been reported as being 679 mSv.

The first period of the NEW Study contract will be for five years, although it is expected that the



Current location of the nearly 20,000 Fukushima emergency workers, who are spread throughout all 47 prefectures of Japan, including Okinawa (not shown on map; as of December 2014)

study will be renewed every five years, with the participants followed throughout their lifetimes. The RERF Life Span Study (LSS), in contrast, has been following survivors for 65 years to this point in time for mortality and 57 years for cancer incidence. The RERF Adult Health Study (AHS), which is more like the NEW Study in that it involves medical examinations of the participants, has been continued for 57 years.

Participants in the NEW Study will receive repeated medical examinations at clinics throughout Japan, with at least one clinic in each of the 47 prefectures. The study will be led by Dr. Toshiro Okubo, former RERF Chairman, and will involve

investigators from RERF along with collaborating investigators from at least 12 other research organizations in Japan.

According to Dr. Okubo, “The study will gauge whether low-dose exposure to radiation, including internal exposure or accumulation of a daily dose, affects health. It is also highly significant in that the results will be compared with those of studies of A-bomb survivors.” As of March 2015, the estimated cost for the health survey through fiscal 2018 is expected to reach about 2.3 billion yen, including the amount to be distributed to the external collaborators.

Note: Sievert is used as the dose unit here for the nuclear workers, as it is the unit for radiation *dose equivalent* used in radiation protection and associated regulations. For the atomic bomb survivors, RERF uses dose units of weighted *absorbed dose* in gray with a particular, specified weight for neutrons, rather than the energy-dependent neutron weights recommended by international advisory bodies for converting *absorbed dose* in gray to *dose equivalent* in sievert. The two units are essentially equivalent in this particular context.

Research Protocols Approved in May–October 2015

RP 2-15 Histopathological evaluation of human thymus architecture changes following radiation exposure and aging (An addendum to RP-B-48-09 and RP-P2-11)

Reiko Ito, Junko Kajimura, Kengo Yoshida, Seishi Kyoizumi, Kotaro Ozasa, Tomonori Hayashi, Koji Arihiro, Susan M. Geyer, Laura P. Hale, Gregory D. Sempowski, Nancy R. Manley, Marcel R. M. van den Brink, Munechika Misumi, Kei Nakachi, Yoichiro Kusunoki

Preliminary studies under RP-B-48-09 and RP-P2-11 have thus far found that thymus autopsy specimens from a total of 205 Life Span Study (LSS) cases were available at the Radiation Effects Research Foundation (RERF) for investigating the effects of radiation exposure and aging on human thymus architecture. A subset of 76 cases selected from all available specimens were examined by histochemical staining; these analyses revealed sufficient quality for conventional histopathological analyses. In this proposed study, we will develop a scoring system for selected pathological endpoints related to thymus tissue morphology using healthy normal, unexposed thymus specimens, and utilize this system to score the 205 LSS autopsy cases with thymus specimens. Differences in human thymus architecture based on radiation exposure and aging will be evaluated in terms of this histological scoring system to be established. We will also validate Multitaper Circularly Averaged Spectral Analysis (MiCASA) approach for evaluating thymus architecture and assess how these endpoints may differ based on radiation exposure and age. Through these histological approaches, we will test the hypothesis that radiation exposure and aging reduce active thymopoiesis by altering the thymic microenvironment in conjunction with shrinkage of the thymic epithelial area.

RP 3-15 Research protocol for collection and transfer of samples and information by the Biosample Center at the Radiation Effects Research Foundation

Misa Imaizumi, Tomonori Hayashi, Atsuko Sadakane, Kotaro Ozasa, Harry M. Cullings, Waka Ohishi, Ayumi Hida, Yoichiro Kusunoki, Hiroaki Katayama, Yoshiaki Kodama

Multifactorial diseases are the result of complex interactions among lifestyle, environment, individual sensitivity, genetic components, and other factors. In recent years, researchers of these diseases comprehensively perform clinical and epidemiological analysis to identify contributing lifestyle and environmental factors in conjunction

with basic research using biological samples. This comprehensive approach not only elucidates causes of specific diseases but leads to the establishment of methods for their early detection and prevention. To be useful for research, biological samples must be of adequate quality, volume and number and must satisfy ethical criteria based on the informed consent of sample donors. Additionally, high-quality clinical, epidemiological, and pathological information must be available for samples. Thus, to satisfy these conditions, the importance of infrastructural development for “biobanks” that support large-scale research using human samples is on the rise.

The Atomic Bomb Casualty Commission (ABCC) and Radiation Effects Research Foundation (RERF) have long retained biological samples provided by A-bomb survivors and their children, such as blood, urine, pathological specimens, and teeth. But, until this time, individual researchers and departments were entrusted to select sample storage methods and manage sample information. Realizing the need to indefinitely preserve our valuable biological sample collection in good condition and promote research that uses these samples, the integrated management of samples, and the establishment of sample information databases, RERF established the Biosample Center (hereinafter: “the Center”) in April 2013.

Samples and related information kept at individual departments will be transferred to the Center when it begins operating, and samples collected after the start of operations will be handled and stored in the Center according to written procedures. Sample information will be integrally managed in RERF databases. Quality control of stored samples will be conducted periodically in accordance with a “Quality Control Manual” to be created for the Center. The Center will collaborate with the Committee on Biological Samples to formulate detailed regulations governing the use of RERF biological samples. Researchers and other employees involved in the activities of the Center will be required to observe the “Radiation Effects Research Foundation Regulations for Protection of Personal Information” as well as all applicable laws, regulations, and guidelines, including Japanese government ethical guidelines pertaining to biomedical research involving human subjects and human genome and genetic analysis. Informed consent information will be stored in the databases and associated with the samples. Every sample provided will be appropriately anonymized.

Thus, the Center aims to integrally manage RERF’s biological samples and sample information to ensure that they can be stored and used properly to further elucidate the role of radiation in diseases and biological and molecular changes in

A-bomb survivors and their children.

RP 4-15 Two-dimensional speckle-tracking strain analysis in the Adult Health Study subjects (Addendum to RP 2-14)

Ikuno Takahashi, Daisuke Haruta, Takayuki Hidaka, Akira Tsuneto, Junko Kajimura, Tomonori Hayashi, Kyoji Furukawa, Misa Imaizumi, Ayumi Hida, Waka Ohishi, Masaaki Takeuchi, Yasuki Kihara

We propose this research protocol as an addendum for RP 2-14 with the aim of investigating the association between atomic bomb radiation and various kinds of cardiac dysfunction using the echocardiographic speckle-tracking analysis technique. This addendum will be based on RP 2-14 with regard to the study period and participants, which total 2,700 Adult Health Study (AHS) participants aged 15 years or younger at the time of bombings. The primary endpoint will be longitudinal/circumferential global strain acquired using speckle-tracking analyses. Other measurements of integrated backscatter (IBS) will be measured as our sub-endpoints. These measurements are thought to be involved in valvular function and cardiac fibrosis. The stored images already collected since June 2014 will be quantified on the basis of informed consent we have already obtained from the participants for future studies.

RP 5-15 Ophthalmological Study of A-bomb Survivors Using a New Ophthalmic Camera

Ayumi Hida, Misa Imaizumi, Daisuke Haruta, Yoshimi Tatsukawa, Fukiko Mitsui, Waka Ohishi, Kyoji Furukawa, Hiroaki Katayama, Yoshiaki Kiuchi, Takashi Kitaoka, Hiroshi Sasaki

Previous ophthalmological studies have shown significant association between A-bomb radiation and posterior subcapsular opacities. However, significant association between A-bomb radiation and cortical opacities was observed only in the 2000–2002 ophthalmological study, involving 837 A-bomb survivors. Due to inconsistent photographic methods, re-analyses of the lens images stored from this study were not possible.

In this research, we will conduct a cataract study among Adult Health Study (AHS) participants (including *in utero* survivors) who were exposed to A-bomb radiation at the age of 15 or younger, using a standard epidemiological study method now widely employed for investigating cataract. Under the supervision of experts in relevant fields, we will photograph and store digital images of the lenses, using a new, well-suited photographic device under appropriate, controlled photographic conditions. Subsequently, cataract specialists will collectively evaluate stored images for lens opacity and analyze association with radiation exposure.

Recent Publications

(*Japanese*): the original article is in Japanese.

Åsvold BO et al. (RERF: Imaizumi M): Thyroid function within the normal range and risk of coronary heart disease: An individual participant data analysis of 14 cohorts. *JAMA Intern Med* 2015 (June); 175(6):1037–47.

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